Elevated nitric oxide/peroxynitrite neurochemical mechanism of multiple chemical sensitivity.
Pall, ML M. Fukunaga Journal/Neurochemistry.
The elevated nitric oxide/peroxynitrite and the neural sensitization theories of multiple chemical sensitivity (MCS) are extended here to propose a central mechanism for the exquisite sensitivity to organic solvents apparently induced by previous chemical exposure in MCS. This mechanism is centered on the activation of N-methyl-D-aspartate (NMDA) receptors by organic solvents producing elevated nitric oxide and peroxynitrite, leading in turn to increased stimulating of and hypersensitivity of NMDA receptors. In this way, organic solvent exposure may produce progressive sensitivity to organic solvents. Pesticides such as organophosphates and carbamates may act via muscarinic stimulation to produce a similar biochemical and sensitivity response. Accessory mechanisms of sensitivity may involve both increased blood-brain barrier permeability, induced by peroxynitrite, and cytochrome P450 inhibition by nitric oxide. The NMDA hyperactivity/hypersensitivity and excessive nitric oxide/peroxynitrite view of MCS provides answers to many of the most puzzling aspects of MCS while building on previous studies and views of this condition.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12948884

Muscarinic receptor-independent activation of cyclic adenosine monophosphate-dependent protein kinase in rostral ventrolateral medulla underlies the sympathoexcitatory phase of cardiovascular responses during mevinphos intoxication in the rat.
Tsai, CY, Wu, CH, Chan, SH and Chang, AY Journal/Shock. 27: 559-564.

As inhibitors of acetylcholinesterase, clinical presentations of poisoning from organophosphate compounds are generally believed to entail overstimulation by the accumulated acetylcholine on muscarinic receptors at peripheral and central synapses. That some patients still yielded to acute organophosphate poisoning despite repeated dosing of atropine suggests that cellular mechanisms that are independent of muscarinic receptor activation may also be engaged in organophosphate poisoning. The present study was undertaken to test the hypothesis that muscarinic receptor-independent activation of cyclic adenosine monophosphate-dependent protein kinase A (PKA) in rostral ventrolateral medulla (RVLM), a medullary site where sympathetic vasomotor tone originates and where the organophosphate poison mevinphos (Mev) acts, is involved in the cardiovascular responses exhibited during organophosphate intoxication. In Sprague-Dawley rats, microinjection bilaterally of Mev (10 nmol) into the RVLM significantly augmented PKA activity in ventrolateral medulla that was not antagonized by coadministration of an equimolar concentration (1 nmol) of atropine or selective muscarinic receptor type M1 (pirenzepine), M2 (methoctramine), M3 (4-diphenyl-acetoxy-N-dimethylpiperidinium), or M4 (tropicamide) inhibitor. Comicroinjection of two selective PKA antagonists (100 pmol),
N-[2-(p-bromocinnamylamino)ethyl]-5-isoquinolinesulfonamide and (9R,10S,12S)-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-9,12-epoxy-1H-diindolo[1,2,3-fg;3',2',1'-kl]pyrrolo[3,4-1][1,6]benzodiazocine-10-carboxylic acid, significantly blunted the initial sympathoexcitatory cardiovascular response and the accompanying augmentation of nitric oxide synthase (NOS I) expression in the ventrolateral medulla exhibited during Mev intoxication; the secondary sympathoinhibitory phase and associated elevation in NOS II expression were unaffected. We conclude that whereas a muscarinic receptor-independent augmentation of PKA activity in the ventrolateral medulla was manifested throughout acute Mev intoxication, this activation was preferentially involved in the sympathoexcitatory phase by an upregulation of NOS I expression.


We investigated the effects of red pepper (Capsicum annuum Lin.) extracts (capsicum extract) and its main pungent capsaicin on T helper 1 (Th1) and 2 (Th2) cytokine production in cultured murine Peyer's patch (PP) cells in vitro and ex vivo. Direct administration of capsicum extract (1 and 10 μg/ml) and capsaicin (3 and 30 μM) resulted in suppression of interleukin (IL)-2, interferon (IFN)-gamma, IL-4 and IL-5 production. In an ex vivo experiment using PP cells removed from the mice after oral administration of capsicum extract (10 mg/kg/day for 4 consecutive days), IL-2, IFN-gamma and IL-5 increased in response to concanavalin A (Con A). Oral administration of 3 mg/kg/day capsaicin, one active constituent of the extract, also enhanced IL-2, INF-gamma and IL-4 production in response to Con A stimulation but did not influence the production of IL-5. Orally administered capsazepine (3 mg/kg day), a selective transient receptor potential vanilloid 1 (TRPV1) antagonist, slightly enhanced IL-2 production also irrespective of Con A stimulation. The capsaicin-induced enhancement of both IL-2 and IFN-gamma production was not reduced by oral administration of capsazepine (3 mg/kg/day), suggesting a TRPV1 receptor-independent mechanism. Flow cytometric analysis revealed that the population of CD3(+) cells in the PP cells was significantly reduced while CD19(+) cells increased after oral administration of capsicum extract (1 and 10 mg/kg/day) and capsaicin (0.3 and 3 mg/kg/day). Capsazepine (3 mg/kg/day) weakly but significantly reversed these effects. Orally administered capsicum extract and capsaicin did not change the T cell subset (CD4(+) and CD8(+) cell-immune responses, and their immunomodulatory effects on murine PP cells are partly due to both TRPV1-dependent and -independent pathway.

BACKGROUND: Idiopathic environmental intolerance (IEI) is a descriptor for nonspecific complaints that are attributed to environmental exposure. METHODS: The Minnesota Multiphasic Personality Inventory 2 (MMPI-2) was administered to 50 female and 20 male personal injury litigants alleging IEI. RESULTS: The validity scales indicated no overreporting of psychopathology. Half of the cases had elevated scores on validity scales suggesting defensiveness, and a large number had elevations on Fake Bad Scale (FBS) suggesting overreporting of unauthenticated symptoms. The average T-score profile for females was defined by the two-point code type 3-1 (Hysteria-Hypochondriasis), and the average T-score profile for males was defined by the three-point code type 3-1-2 (Hysteria, Hypochondriasis-Depression). On the content scales, Health Concerns (HEA) scale was significantly elevated.

CONCLUSION: Idiopathic environmental intolerance litigants (a) are more defensive about expressing psychopathology, (b) express distress through somatization, (c) use a self-serving misrepresentation of exaggerated health concerns, and (d) may exaggerate unauthenticated symptoms suggesting malingering.


BACKGROUND: N-acetyltransferases (NAT) and glutathione S-transferases (GST) are involved in the metabolism of several ubiquitous chemical substances leading to the activation and detoxification of carcinogenic heterocyclic and aromatic amines. Since polymorphisms within these genes are described to influence the metabolism of ubiquitous chemicals, we conducted the present study to determine if individuals with self-reported chemical-related sensitivity differed from controls without self-reported chemical-related sensitivity with regard to the distribution of genotype frequencies of NAT2, GSTM1, GSTT1, and GSTP1 polymorphisms. METHODS: Out of 800 subjects who answered a questionnaire of ten items with regard to their severity of chemical sensitivity 521 unrelated individuals agreed to participate in the study. Subsequently, genetic variants of the NAT2, GSTM1, GSTT1, and GSTP1 genes were analyzed. RESULTS: The results show significant differences between individuals with and without self-reported chemical-related sensitivity with regard to the distribution of NAT2, GSTM1, and GSTT1 gene variants. Cases with self-reported chemical-related
sensitivity were significantly more frequently NAT2 slow acetylators (controlled OR = 1.81, 95% CI = 1.27-2.59, P = 0.001). GSTM1 and GSTT1 genes were significantly more often homozygously deleted in those individuals reporting sensitivity to chemicals compared to controls (GSTM1: controlled OR 2.08, 95% CI = 1.46-2.96, P = 0.0001; GSTT1: controlled OR = 2.80, 95% CI = 1.65-4.75, P = 0.0001). Effects for GSTP1 gene variants were observed in conjunction with GSTM1, GSTT1 and NAT2 gene.

CONCLUSION: The results from our study population show that individuals being slow acetylators and/or harbouring a homozygous GSTM1 and/or GSTT1 deletion reported chemical-related hypersensitivity more frequently.

The aim of this article was to re-evaluate and possibly modify the standardized Environmental Worry Scale (EWS) by Hodapp et al. [1996. Evaluation eines Fragebogens zur Erfassung von Umweltbesorgnis. Z. Gesundheitspsychologie IV(1), 22-36] with regard to its content and structure. In order to do this, 161 participants were chosen as a reference group to take part in a survey. The data were analyzed and a factor analysis yielded two instead of one component of worry, namely "personal" and "general" environmental worry, leading to a new evaluation method. This revised evaluation method was then applied to patients (n=227) with or without self-reported multiple chemical sensitivity (MCS) and thus used in the context of reported health complaints. The outlined results indicate that the assessment of worry as proposed by Hodapp et al. [1996. Evaluation eines Fragebogens zur Erfassung von Umweltbesorgnis. Z. Gesundheitspsychologie IV(1), 22-36] should be elaborated by the newly developed evaluation method with which a ratio determined by "personal" and "general" worry can be calculated. In addition to analyzing the absolute quantity of worry, the calculated ratio allows to draw conclusions on the structure of worry. It will be discussed to what extent the results present new insights into the role of worry among patients suffering from environmental diseases.

Pall, ML  Haworth Press.
Pacher, P, Beckman, JS and Liaudet, L Journal/Physiol Rev. 87: 315-424.

The discovery that mammalian cells have the ability to synthesize the free radical nitric oxide (NO) has stimulated an extraordinary impetus for scientific research in all the fields of biology and medicine. Since its early description as an endothelial-derived relaxing factor, NO has emerged as a fundamental signaling device regulating virtually every critical cellular function, as well as a potent mediator of cellular damage in a wide range of conditions. Recent evidence indicates that most of the cytotoxicity attributed to NO is rather due to peroxynitrite, produced from the diffusion-controlled reaction between NO and another free radical, the superoxide anion. Peroxynitrite interacts with lipids, DNA, and proteins via direct oxidative reactions or via indirect, radical-mediated mechanisms. These reactions trigger cellular responses ranging from subtle modulations of cell signaling to overwhelming oxidative injury, committing cells to necrosis or apoptosis. In vivo, peroxynitrite generation represents a crucial pathogenic mechanism in conditions such as stroke, myocardial infarction, chronic heart failure, diabetes, circulatory shock, chronic inflammatory diseases, cancer, and neurodegenerative disorders. Hence, novel pharmacological strategies aimed at removing peroxynitrite might represent powerful therapeutic tools in the future. Evidence supporting these novel roles of NO and peroxynitrite is presented in detail in this review.

---------------------------------------------------------------


Multiple chemical sensitivity (MCS) is characterized by somatic distress upon exposure to odors. As in other idiopathic environmental intolerances, the mechanisms behind the reported hypersensitivity are unknown. Using the advantage of the well-defined trigger (odor), we investigated whether subjects with MCS could have an increased odor-signal response in the odor-processing neuronal circuits. Positron emission tomography (PET) activation studies with several different odorants were carried out in 12 MCS females and 12 female controls. Activation was defined as a significant increase in regional cerebral blood flow (rCBF) during smelling of the respective odorant compared to smelling of odorless air. The study also included online measurements of respiratory frequency and amplitude and heart rate variations by recording of R wave intervals (RR) on the surface electrocardiogram. The MCS subjects activated odor-processing brain regions less than controls, despite the reported, and physiologically indicated (decreased RR interval) distress. In parallel, they showed an odorant-related increase in activation of the anterior cingulate cortex and cuneus-precuneus. Notably, the baseline rCBF was normal. Thus, the abnormal patterns were observed only in response to odor signals. Subjects with MCS process odors differently from controls, however, without signs of neuronal sensitization. One
possible explanation for the observed pattern of activation in MCS is a top-down regulation of odor-response via cingulate cortex.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16767766


Volatile organic compounds are the main substances causing multiple chemical sensitivity reactions in human. Our laboratory has previously showed that the exposure of low-level formaldehyde causes immunogenic and neurogenic inflammatory responses in mice. The aim of the present study was to investigate the effect of long-term, low-level toluene exposure on airway inflammatory responses in mice lung. We exposed female C3H mice to filtered air (0ppm) or 50ppm of toluene for 6h/day on 5days/week for 6 or 12 weeks in the whole body exposure chamber. One day following the last toluene exposure, we collected bronchoalveolar lavage fluid from each mouse and examined cellular infiltration and production of cytokines, chemokines, neurotrophins and substance P by using ELISA method. We found that the number of total cells and macrophages increased significantly in both 6 and 12-week-exposed mice. In addition, the production of interferon-gamma and substance P were decreased significantly and nerve growth factor was not affected in both 6 and 12-week-exposed mice. In contrast, neurotrophin-3 production in bronchoalveolar lavage fluid was significantly increased only in 12-week-exposed mice. Our findings suggest that long-term (12-week) exposure of mice to low-level toluene modulates airway inflammatory response via neurological signaling.


OBJECTIVE: The aim of this study was to look at the impact of a multidisciplinary approach to treatment of individuals with multiple chemical sensitivity (MCS) and to present preliminary results which compare health care utilization pre- and postmanagement of individuals with MCS. STUDY DESIGN: The design for this study was that for a cohort study. SETTINGS/LOCATION: The setting for this study was the Nova Scotia Environmental Health Centre (NSEHC; Fall River, Nova Scotia, Canada).
PATIENTS AND METHODS: Following ethical approval, individuals who had filled a detailed-symptoms questionnaire and had agreed to participate in research activities were linked to their medical insurance records, using encrypted numbers and a blind procedure for confidentiality. Diagnosis by the NSEHC; physicians followed the consensus criteria for multiple chemical sensitivity (MCS). A total of 563 patients formed 3 cohorts (145 in 1998; 181 in 1999; and 237 in 2000). RESULTS: Physicians’ visits by general practitioner and by specialists, emergency and hospital separations, and associated costs showed a relative decrease in the years following the consultation at the NSEHC. The overall yearly decline in consultations between the years before the initial consultation until 2002, for each cohort, was: 9.1% for the 1998 cohort; 8% for the 1999 cohort; and 10.6% for the 2000 cohort; compared with 1.3% for the overall Nova Scotia population. Relative to the provincial utilization costs, the standardized average yearly decrease in utilization costs for the 3 cohorts combined was 8.7%, or a total savings of $77,440. The 1998 cohort showed a sustained decrease up to 2002, reaching a level similar to the overall Nova Scotia population. Those with high symptom scores had the highest reduction in mean physician visits (31% for the 1998 cohort) in the following years. CONCLUSIONS: Presented in this paper are the preliminary results of the health care utilization costs in the management of individuals with MCS. Despite the limitations of our study design, the initial findings from this study are encouraging and warrant further exploration. These results indicate a possible impact on the long-term health care utilization from the NSEHC’s management strategies, although a further controlled study, with a longer follow-up, may be necessary to confirm these findings.


Multiple chemical sensitivity (MCS) is a condition in which people experience a broad array of symptoms in reaction to exposure to trace amounts of common chemicals. Symptoms are most often triggered by odors, typically affect many systems, and can range from a runny nose to difficulty breathing and heart palpitations. The cause of this condition is unclear and there is no universal consensus on how to diagnose or treat it. MCS afflicts millions of Americans, although its prevalence is difficult to establish reliably. Theories of causation include both the physical and the psychogenic. This article begins with a case study, describes the current research on MCS, and offers recommendations to guide nurses when treating these patients in the hospital.

Multiple Chemical Sensitivity in the Clinical Setting: Although the cause and diagnosis of this condition remain controversial, the patient's concerns should be heeded.


OVERVIEW: Multiple chemical sensitivity (MCS) is a condition in which people experience a broad array of symptoms in reaction to exposure to trace amounts of common chemicals. Symptoms are most often triggered by odors, typically affect many systems, and can range from a runny nose to difficulty breathing and heart palpitations. The cause of this condition is unclear and there is no universal consensus on how to diagnose or treat it. MCS afflicts millions of Americans, although its prevalence is difficult to establish reliably. Theories of causation include both the physical and the psychogenic. This article begins with a case study, describes the current research on MCS, and offers recommendations to guide nurses when treating these patients in the hospital.

Transcriptional upregulation of nitric oxide synthase II by nuclear factor-(kappa)B at rostral ventrolateral medulla in mevinphos intoxication model of brain stem death.


As the origin of a "life-and-death" signal that reflects central cardiovascular regulatory failure during brain stem death, the rostral ventrolateral medulla (RVLM) is a suitable neural substrate for mechanistic delineation of this vital phenomenon. Using a clinically relevant animal model that employed the organophosphate pesticide mevinphos (Mev) as the experimental insult, we evaluated the hypothesis that transcriptional upregulation of nitric oxide synthase I or II (NOS I or II) gene expression by nuclear factor-kappaB (NF-kappaB) on activation of muscarinic receptors in the RVLM underlies brain stem death. In Sprague-Dawley rats maintained under propofol anesthesia, co-microinjection of muscarinic M2R (methoctramine) or M4R (tropicamide), but not M1R (pirenzepine) or M3R (4-diphenylacetoxy-N-dimethylpiperidinium) antagonist significantly reduced the enhanced NOS I/protein kinase G signaling "pro-life" phase) or augmented NOS II peroxynitrite cascade "pro-death" phase) in ventrolateral medulla, blunted the biphasic increase and decrease in baroreceptor reflex-mediated sympathetic vasomotor tone that reflect the transition from life to death, and diminished the elevated DNA binding activity or nucleus-bound translocation of NF-kappaB in RVLM neurons induced by microinjection of Mev into the bilateral RVLM. However, NF-kappaB inhibitors (diethyldithiocarbamate or pyrrolidine dithiocarbamate) or double-stranded kappaB decoy DNA preferentially antagonized the augmented NOS II/peroxynitrite cascade and the associated cardiovascular depression exhibited during the "pro-death" phase. We conclude that transcriptional upregulation of NOS II gene expression by activation
of NF-kappaB on selective stimulation of muscarinic M2 or M4 subtype receptors in the RVLM underlies the elicited cardiovascular depression during the "pro-death" phase in our Mev intoxication model of brain stem death.

(2007) Ethanol inhibits cold-menthol receptor TRPM8 by modulating its interaction with membrane phosphatidylinositol 4,5-bisphosphate.

Ethanol has opposite effects on two members of the transient receptor potential (TRP) family of ion channels: it inhibits the cold-menthol receptor TRPM8, whereas it potentiates the activity of the heat- and capsaicin-gated vanilloid receptor TRPV1. Both thermosensitive cation channels are critically regulated by the membrane lipid, phosphatidylinositol 4,5-bisphosphate (PIP(2)). The effects of this phospholipid on TRPM8 and TRPV1 are also functionally opposite: PIP(2) is necessary for the activation of TRPM8 but it constitutively inhibits TRPV1. This parallel led us to investigate the possible role of PIP(2) in the ethanol-induced modulation of rat TRPM8, heterologously expressed in HEK293T cells. In this study, we characterize the effects of ethanol (0.1-10%) on whole-cell currents produced by menthol and by low temperature (< 17 degrees C). We show that the inclusion of PIP(2) in the intracellular solution results in a strong reduction in the ethanol-induced inhibition of menthol-evoked responses. Conversely, intracellular dialysis with anti-PIP(2) antibody or with the PIP(2) scavenger, poly L-lysine, enhanced the ethanol-induced inhibition of TRPM8. A 20 min pre-incubation with wortmannin caused a modest decrease in inhibition produced by 1% ethanol, indicating that the ethanol-induced inhibition is not mediated by lipid kinases. These findings suggest that ethanol inhibits TRPM8 by weakening the PIP(2)-TRPM8 channel interaction; a similar mechanism may contribute to the ethanol-mediated modulation of some other PIP(2)-sensitive TRP channels.

(2006) Our recent experiences with sarin poisoning cases in Japan and pesticide users with references to some selected chemicals.
Yokoyama, K Journal/Neurotoxicology.
Attention has been paid to neurobehavioral effects of occupational and environmental exposures to chemicals such as pesticides, heavy metals and organic solvents. The area of research that includes neurobehavioral methods and effects in occupational and environmental health has been called "Occupational and Environmental Neurology and Behavioral Medicine." The methods, by which early changes in neurological, cognitive and behavioral function can be assessed, include neurobehavioral test battery, neurophysiological methods, questionnaires and structured interview, biochemical markers and imaging techniques. The author presents his observations of
neurobehavioral and neurophysiological effects in Tokyo subway sarin poisoning cases as well as in pesticide users (tobacco farmers) in Malaysia in relation to Green Tobacco Sickness (GTS). In sarin cases, a variety effects were observed 6-8 months after exposure, suggesting delayed neurological effects. Studies on pesticide users revealed that organophosphorus and dithiocarbamate affected peripheral nerve conduction and postural balance; subjective symptoms related to GTS were also observed, indicating the effects of nicotine absorbed from wet tobacco leaves. In addition, non-neurological effects of pesticides and other chemicals are presented, in relation to genetic polymorphism and oxidative stress.

(2006) Selective attention, memory bias, and symptom perception in idiopathic environmental intolerance and somatoform disorders.

Idiopathic environmental intolerance (IEI) refers to a polysymptomatic condition, similar to somatoform disorders. Various processes seem to contribute to its yet unknown etiology. Attention and memory for somatic symptom and IEI-trigger words was compared among participants with IEI (n = 54), somatoform disorders (SFD; n = 44) and control participants (n = 54). Groups did not differ in a dot-probe task. However, in an emotional Stroop task, attention was biased in IEI and SFD groups toward symptom words but not toward IEI-trigger words. Only the IEI group rated trigger words as more unpleasant and more arousing, and participants remembered them better in a recognition task. These implicit and explicit cognitive abnormalities in IEI and SFD may maintain processes of somatosensory amplification.

Wilson, HD, Wilson, JR and Fuchs, PN Journal/Brain Res. 1098: 126-8.

Hyperbaric oxygen therapy has been used to treat a variety of ailments from carbon monoxide poisoning to fibromyalgia. The purpose of this experiment was to explore the effect of hyperbaric oxygen treatment on carrageenan-induced inflammation and pain in rats. Hyperbaric oxygen treatment significantly decreased inflammation and pain following carrageenan injection. Clinically hyperbaric oxygen may be used in situations where NSAIDS are contraindicated or in persistent cases of inflammation.
(2006) Screening for depressive symptoms in patients with chronic spinal pain using the SF-36 Health Survey.

BACKGROUND DATA: Depression is a common co-morbidity for patients with complaints of spinal pain, yet often goes undiagnosed in clinical practice. Depressed patients who are not identified do not receive a referral or recommendation for treatments that may help ease their total illness burden. Relative to the total outcomes of spine care this may increase costs, decrease overall functional outcomes, and limit patient satisfaction. Some spine care settings track functional outcomes using a general health status survey. Although a specific and reliable survey to detect depression could be employed, an additional survey would unnecessarily increase responder and analyst burdens if the general health status survey could be used instead. OBJECTIVE: To identify the Mental Component Summary (MCS) cutoff score from the Short Form 36-item Health Survey (SF-36) that best predicts a positive depression score as measured by the Center for Epidemiological Study-Depression Survey (CES-D). STUDY DESIGN: An analysis of the diagnostic properties of the SF-36 MCS Scale as a predictor of depressive symptoms as measured by the CES-D. OUTCOME MEASURES: The SF-36 is a general health survey that contains a MCS score that represents the psychological well-being and general health perception of the respondent. This composite score is norm-based (mean = 50, SD = 10) with lower scores representing poorer health. The CES-D has been well-studied in patients with chronic pain complaints and was used as the gold standard for determining the MCS cutoff score. A CES-D score of 19 or greater was considered positive for depressive symptoms. PATIENT SAMPLE: All patients entering our facility routinely complete the SF-36. Between February 2002 and October 2002, all patients scoring 30 or less on the MCS (MCS < or = 30) also completed the CES-D. Patients who scored 2 standard deviations below the mean (MCS = 30 or less) were considered most at risk for depression. Patients scoring above 30 on their MCS (MCS > 30) were considered less likely to have depressive symptoms and were randomly chosen to complete the CES-D. There were 420 patients who completed both surveys of which there were 99 MCS < or = 30 patients and 321 MCS > 30 patients. METHODS: Receiver operating characteristic (ROC) curves were used to assess the sensitivity and specificity of the SF-36 as a screening tool for detecting depressive symptoms. RESULTS: An MCS score of 35 has a sensitivity of 80% (76-83; 95% confidence interval), a specificity of 90% (87-93), an ROC area of 0.8517 (0.81-0.89), and correctly identified 87% of the sample. CONCLUSION: The SF-36 provides the benefits of a general functional health status measure and additionally appears to provide a screening tool for depressive symptoms. A cutoff score of 35 or less on the MCS scale has a high degree of sensitivity and specificity and is able to identify depressive symptoms in patients with back pain, which can help identify patients who will benefit from mental health treatments.

The catalytic properties of organophosphate hydrolase (OPH) containing a hexahistidine tag His6 (His6-OPH) and purified to 98% homogeneity were investigated. The pH optimum of enzymatic activity and isoelectric point of His6-OPH, which were shown to be 10.5 and 8.5, respectively, are shifted to the alkaline range as compared to the same parameters of the native OPH. The recombinant enzyme possessed improved catalytic activity towards S-containing substrates: the catalytic efficiency of methylparathion hydrolysis by His6-OPH is $4.2 \times 10^6$ M$^{-1}$ x sec$^{-1}$, whereas by native OPH it is $3.5 \times 10^5$ M$^{-1}$ x sec$^{-1}$.

---------------------------------------------------------------

(2006) [Multiple chemical sensitivity, a well-defined illness?]

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16768910

---------------------------------------------------------------

(2006) Sensitization of transient receptor potential vanilloid 1 by the prokineticin receptor agonist Bv8.

Small mammalian proteins called the prokineticins [prokineticin 1 (PK1) and PK2] and two corresponding G-protein-coupled receptors [prokineticin receptor 1 (PKR1) and PKR2] have been identified recently, but the physiological role of the PK/PKR system remains mostly unexplored. Bv8, a protein extracted from frog skin, is a convenient and potent agonist for both PKR1 and PKR2, and injection of Bv8 in vivo causes a potent and long-lasting hyperalgesia. Here, we investigate the cellular basis of hyperalgesia caused by activation of PKRs. Bv8 caused increases in [Ca$^+$]i in a population of isolated dorsal root ganglion (DRG) neurons, which we identified as nociceptors, or sensors for painful stimuli, from their responses to capsaicin, bradykinin, mustard oil, or proteases. Bv8 enhanced the inward current carried by the heat and capsaicin receptor, transient receptor potential vanilloid 1 (TRPV1) via a pathway involving activation of protein kinase Cepsilon (PKCepsilon), because Bv8 caused translocation of PKCepsilon to the neuronal membrane and because PKC antagonists reduced both the enhancement of current carried by TRPV1 and behavioral hyperalgesia in rodents. The neuronal population expressing PKRs consisted partly of small peptidergic neurons and partly of
neurons expressing the N52 marker for myelinated fibers. Using single-cell reverse transcriptase-PCR, we found that mRNA for PKR1 was mainly expressed in small DRG neurons. Exposure to GDNF (glial cell line-derived neurotrophic factor) induced de novo expression of functional receptors for Bv8 in a nonpeptidergic population of neurons. These results show that prokineticin receptors are expressed in nociceptors and cause heat hyperalgesia by sensitizing TRPV1 through activation of PKCepsilon. The results suggest a role for prokineticins in physiological inflammation and hyperalgesia.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16687502


OBJECTIVES: Chronic toxic encephalopathy (CTE) caused by long term occupational exposure to organic solvents is still a controversial disorder. Neuropsychological testing is the cornerstone for diagnosing the syndrome, but can be negatively influenced by motivational problems. In this nationwide study, we investigated the neuropsychological functioning and psychological symptoms of a large group of patients with suspected CTE, and ruled out alternative explanations for their complaints, including suboptimal performance due to insufficient effort. METHODS: We studied participants with suspected CTE (n = 386) who were referred for further diagnosis to the Netherlands Centre of Occupational Diseases in the period 1998-2003 and who had completed the entire diagnostic protocol. Patients were excluded if there was the slightest suspicion that test performance had been negatively influenced by insufficient effort (n = 221), or if comprehensive assessment identified an alternative diagnosis (n = 80). Insufficient effort was defined by a combination of three indices. The neuropsychological test scores of the patient group (n = 85) were compared with those of a control group of building trade workers matched for sex, age, and educational level (n = 35). RESULTS: The patient group had significantly more psychological complaints and performed significantly worse than the control group on tests of speed of information processing and memory and learning. However, only a small percentage of the patients had clearly abnormal scores for cognitive speed (9%) or memory (8%). Attention, verbal abilities, and constructional functions were not disturbed. Exposure duration and cognitive complaints were significantly correlated, whereas the correlation between exposure duration and neuropsychological domain scores was not significant. CONCLUSIONS: Insufficient effort was present in a substantial part of the patient group. After minimising the likelihood that insufficient effort negatively influenced neuropsychological scores, we still found neuropsychological deficits in speed of cognitive processing and memory; however, these scores were clearly abnormal only
in a minority of patients with suspected CTE. Screening instruments should focus on these domains.


PURPOSE: This study was designed to clarify the definition of sick house syndrome (SHS). METHODS: SHS was defined based on the disease related to habitation as follows. 1. The cause of the onset of a disease relates to house. 2. Symptoms appear within house. 3. Symptoms will be less serious or disappear if patient away from house. 4. If patient goes into house, symptoms will appear repeatedly. When it corresponded to all above, it was defined to SHS, and it classified as MCS (multiple chemical sensitivities) without above conditions. Even if SHS is isolated from similar disease completely, characteristic symptoms of MCS are hard to be detected because MCS are combination of two or more diseases. Based on this working hypothesis, the logistic regression by setting MCS as reference was performed so that characteristic symptoms of SHS show odds ratios with exceeding one. RESULTS: The odds ratios with more than two of characteristic symptoms in SHS were "nausea or vomiting" "Troublesome in everything" and the causative substances to which symptoms get worse was "The smell of a perfume and cosmetics". Characteristic symptoms of an allergy disease were detected by comparison with the allergic conjunctivitis, allergic rhinitis, and bronchial asthma, respectively. CONCLUSION: These results showed that the classification method was appropriate. This definition is not fundamentally differed from the definition of the sick-building syndrome of WHO.


Background. Gulf War veterans have a number of health complaints. We therefore decided to carry out a systematic review to identify and summarize the findings from studies that have assessed multi-symptom conditions in Gulf War veterans and in an unexposed comparison group.

Method. Studies published between January 1990 and May 2004 were identified by searching a large number of electronic databases. Reference lists and websites were also searched and key researchers were contacted. Studies were included if they compared the prevalence of chronic fatigue syndrome, multiple chemical sensitivity, CDC-defined chronic multi-symptom illness, fibromyalgia, or symptoms of either fatigue or numbness and tingling in Gulf War veterans and non-Gulf veterans. A total of 2401 abstracts were independently reviewed by two authors.

Results. Twenty-three publications fulfilled the inclusion criteria. Gulf deployment was most strongly associated with chronic fatigue syndrome (OR 3.8, 95% CI 2.2-6.7). Gulf War veterans were also approximately three and a half times more likely than non-Gulf veterans to report multiple chemical sensitivity or chronic multi-symptom illness as defined by CDC. The methodological quality of the studies varied but the later and larger studies were of a high methodological standard with robust sampling strategies, adequate response rates and good adjustment for confounders.

Conclusions. The results support the hypothesis that deployment to the Gulf War is associated with greater reporting of multi-symptom conditions.


BACKGROUND: Veterans of the Persian Gulf War of 1991 have reported a range of adverse health symptoms. This systematic review aims to identify all studies that have compared the prevalence of symptoms of pain in veterans of the Gulf War to that in a non-Gulf military comparison group, and to determine whether Gulf War veterans are at increased risk of reporting pain. METHODS: Studies published between January 1990 and May 2004 were identified by searching a large number of electronic databases. Reference lists and websites were also searched and key researchers were contacted. Studies were included if they reported the prevalence of any symptom or condition that included the word "pain" in Gulf War veterans and in a comparison group of non-Gulf veterans. 2401 abstracts were independently reviewed by two authors. RESULTS: Twenty studies fulfilled the inclusion criteria. Five main sites of pain were identified (muscle, joint, chest/heart, back and abdominal pain) and separate meta-analyses were performed to summarise the results related to each site. A greater proportion of Gulf veterans reported symptoms at each site of pain when compared to a non-Gulf military group. Gulf deployment was most strongly associated with abdominal pain, with Gulf veterans being more than three times more likely to report
such pain than a comparison group (OR 3.23; 95% CI 2.31-4.51). Statistical heterogeneity between study estimates was significant, probably due to variation in measured periods of prevalence and symptom measurement methods.

CONCLUSION: A higher proportion of veterans of the Persian Gulf War of 1991 reported symptoms of pain than military comparison groups. This is consistent with previously demonstrated increased reporting of more general symptoms (fatigue, multiple chemical sensitivity, post traumatic stress disorder) in these veterans compared with non-Gulf military groups. However, the primary studies were heterogeneous and varied greatly in quality.

(2006) [Questionable procedures in environmental medicine using an example of "multiple chemical sensitivity"].
Rottgers, HR and Nedjat, S Journal/Versicherungsmedizin. 58: 126-32.

"Multiple Chemical Sensitivity" (MCS) has to be regarded as a merely subjective concept without etiological and pathological background or objective criteria for diagnosis. Most of the "MCS" patients suffer from various psychiatric disorders; in a small minority somatic diseases can be found. The data recently won in the German multicenter study on MCS underline this point of view. The informal German "MCS network" consisting of patients' self-help groups, "therapists" with or without medical background and law firms specialised in compensation claims nevertheless strictly denies any psychogenic model. They do, however, propose a whole range of diagnostic and therapeutic procedures based on different theoretical concepts. Some of the procedures are derived from scientifically based medicine, others have an unconventional and esoteric background. Most of them are logically incompatible; however, they are applied in a polypragmatic manner. None of these so-called diagnostic or therapeutic procedures or health technologies can be regarded as evidence-based. Some of them, however, are extremely expensive and/or pose significant risks for patients' health. In any case, wrong subjective disease concepts are perpetuated iatrogenically. Additionally, those procedures make effective help for the real underlying medical and/or psychiatric conditions impossible.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17002176

Our prospective cohort study of nonsmoking African-American and Dominican mothers and children in New York City is evaluating the role of prenatal exposure to urban pollutants, including polycyclic aromatic hydrocarbons (PAHs), environmental tobacco smoke (ETS), and pesticides, in the pathogenesis of neurobehavioral disorders. We used the Bayley Scales of Infant Development to evaluate the effects on child mental and psychomotor development of prenatal exposure to airborne PAHs monitored during pregnancy by personal air sampling. Behavioral development was assessed by the Child Behavior Checklist. We adjusted for potential confounders including sociodemographic factors and prenatal exposure to ETS and chlorpyrifos. Prenatal exposure to PAHs was not associated with psychomotor development index or behavioral problems. However, high prenatal exposure to PAHs (upper quartile) was associated with lower mental development index at age 3 [beta=-5.69; 95% confidence interval (CI), -9.05 to -2.33; p<0.01]. The odds of cognitive developmental delay were also significantly greater for children with high prenatal exposure (odds ratio=2.89; 95% CI, 1.33 to 6.25; p=0.01). General estimated equation analysis showed a significant age times PAH effect on mental development (p=0.01), confirming the age-specific regression findings. Further adjustment for lead did not alter the relationships. There were no differences in effect sizes by ethnicity. The results require confirmation but suggest that environmental PAHs at levels recently encountered in New York City air may adversely affect children's cognitive development at 3 years of age, with implications for school performance.


OBJECTIVE: We addressed the question if patients with multiple chemical sensitivity (MCS) differ from participants with self-reported odor sensitivity without MCS and asymptomatic controls in terms of chemosensory, cognitive, and clinical psychological endpoints. METHODS: In a clinical study 23 MCS patients, 21 participants with self-reported odor sensitivity, and 23 controls were investigated using electrophysiological and psychophysical olfactometric tests [chemosensory-event-related potentials (CSERP), olfactory thresholds, odor identification, trigeminal sensitivity]. The participants filled in a mood list, a list of complaints (BL), a Symptom Check List, a State-Trait Anxiety Inventory (STAI), and an MCS questionnaire. RESULTS: The olfactometric investigations revealed no significant differences between the groups. The MCS group reached significantly higher scores on negative mood states following odorant exposure, on health complaints, global indices, and the somatization subscale of the Symptom Check List, trait and state anxiety and symptoms, and triggering matters of the MCS questionnaire. CONCLUSIONS: Our findings reveal that neither olfactory functions, nor chemosensory or cognitive olfactory
information processing are impaired in MCS patients. They rather support findings of altered psychological profile and moderate psychopathology.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16439274


The increasing rate of the idiopathic environmental intolerance (IEI) has been observed for the last decade. The aim of this report was to analyse the allergic component of the disease in particular relation to drug intolerance. Six patients with diagnosed IEI showed a positive skin test reaction to several commonly used antibiotics, nonsteroidal anti-inflammatory drugs, myorelaxants, verapamil, etc. In three cases, the thorough diagnosis of sensitivity to anaesthetic agents enabled to perform necessary surgical treatment, in others - facilitated the proper treatment of headaches and hypertension. Symptoms related to allergy contributed to the deterioration of IEI. Thus, a consultation of IEI patients by an allergologist seems to be of a substantial importance.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16787439


Given the widespread use of insecticides in the environment, it is important to perform studies evaluating their potential effects on humans. Organophosphate insecticides, such as chlorpyrifos, are being phased out; however, the use of pyrethroids in household pest control is increasing. While chlorpyrifos is relatively well studied, much less is known about the potential neurotoxicity of cyfluthrin and other pyrethroids. To gain insights into the neurotoxicity of cyfluthrin, we compared and evaluated the toxicity
profiles of chlorpyrifos and cyfluthrin in primary human fetal astrocytes. We found that at the same concentrations, cyfluthrin exerts as great as, or greater toxic effects on the growth, survival, and proper functioning of human astrocytes. By using microarray gene expression profiling, we systematically identified and compared the potential molecular targets of chlorpyrifos and cyfluthrin, at a genome-wide scale. We found that chlorpyrifos and cyfluthrin affect a similar number of transcripts. These targets include molecular chaperones, signal transducers, transcriptional regulators, transporters, and those involved in behavior and development. Further computational and biochemical analyses show that cyfluthrin and chlorpyrifos upregulate certain targets of the interferon-gamma and insulin-signaling pathways and that they increase the protein levels of activated extracellular signal-regulated kinase 1/2, a key component of insulin signaling; interleukin 6, a key inflammatory mediator; and glial fibrillary acidic protein, a marker of inflammatory astrocyte activation. These results suggest that inflammatory activation of astrocytes might be an important mechanism underlying neurotoxicity of both chlorpyrifos and cyfluthrin.

---------------------------------------------------------------


Preliminary clinical evidence obtained in Gulf War veterans and patients suffering multiple chemical sensitivity points to the existence of a potential link between environmental exposure to organophosphates (OPs) and the emergence of unspecific sickness syndromes in which associative Pavlovian conditioning might be partly involved. A laboratory animal model might be a useful tool for analyzing the involvement of conditioning in sickness syndromes potentially linked to OP poisoning. The first objective in the present study was to determine if paraoxon (PX), the neuroactive metabolite of the OP parathion, elicits a conditioned avoidance response to a novel stimulus (a taste-odor compound) in a conditioned flavor aversion procedure. Data obtained in Experiment 1 show conditioned flavor avoidance, demonstrative of the associative nature of the sickness properties of PX. The second objective was to characterize the nature of the specific physiological cue serving as the unconditioned stimulus in PX-induced conditioned avoidance. Despite PX administration did induce cholinergic hyperactivity, as measured by body hypothermia and increased jaw movements, lesions of the lateral parabrachial area (lPB) disrupted PX-elicited flavor avoidance responses, indicating that cholinergic signs were not sufficient as unconditioned stimuli supporting avoidance responses. Given that IPB neural integrity is necessary to process aversive interoceptive information, disruption of conditioned flavor avoidance as a result of IPB lesions is consistent with a central interruption of interoceptive processing in PX-poisoned animals. Data are discussed under the light of the hypothesis claiming the importance of associative processes and noncholinesterase targets in sickness syndromes potentially induced by OP exposure.
Lipson, JG and Doiron, N Journal/Health Care Women Int. 27: 571-84.

Multiple chemical sensitivities (MCS) is an acquired condition in which exposure to low levels of chemicals causes symptoms in multiple organ systems. Some 12%-16% of the U.S. population has some level of chemical sensitivity, 80% of whom are women. Attempts to reduce chemical exposures leads to enormous life difficulties at home, school, and workplace. We base our article on an ethnographic study of MCS in the United States and Canada. We describe here themes related to work issues in terms of a general trajectory of becoming sick from work exposures, coping with toxic physical environments and dealing with coworkers and, when unable to continue working, applying for workers' compensation, or disability status, or both.


(2006) Structural requirements of acetylcholinesterase reactivators.

Nerve agents (sarin, soman, cyclosarin, tabun and VX agent) and pesticides (paraoxon, chlorpyrifos, TEPP) represent extremely toxic group of organophosphorus compounds (OPCs). These compounds inhibit enzyme acetylcholinesterase (AChE, EC 3.1.1.7) via its phosphorylation or phosphonylation at the serine hydroxy group in its active site. Afterwards, AChE is not able to serve its physiological function and intoxicated organism is died due to overstimulation of cholinergic nervous system. The current standard treatment of poisoning with highly toxic OPCs usually consists of the combined administration of anticholinergic drugs (preferably atropine) and AChE reactivators (called "oximes"). Anticholinergic drugs block effects of accumulated neurotransmitter acetylcholine at nicotinic and muscarinic receptor sites, while oximes reactivate AChE inhibited by OPCs. Unfortunately, none from the currently used oximes is sufficiently effective against all known nerve agents and pesticides. Therefore, to find new oximes able to sufficiently reactivate inhibited AChE (regardless of the type of OPCs) is still very important task for medicinal chemistry with the aim to improve the efficacy of antidotal treatment of the acute poisonings mentioned. In this paper, the relationship between chemical structure of AChE reactivators and their ability to reactivate AChE inhibited by several nerve agents and pesticides is summarized. It is shown that there are several structural fragments possibly involving in the structure of proposed AChE reactivators. Finally, an attempt of a future course of new AChE reactivators development is discussed.
Some people react to smells or chemicals at levels far below toxicological thresholds with nonspecific symptoms, fear and social isolation. They may be diagnosed with multiple chemical sensitivity. There is no empirical evidence indicating that this condition is explained by toxicological mechanisms, even though a number of theories have been proposed. The authors of this review conclude that this is a functional condition. These patients need information and treatment in accordance with this fact. Instead of being advised how to avoid exposure to chemicals, they should be properly trained in appropriate confrontation with the chemicals encountered in everyday life.


OBJECTIVE: To assess posttraumatic stress (PTS) symptoms in adolescents with and without asthma and their parents and the relationship between PTS symptoms and asthma morbidity. METHOD: Three groups of adolescents (12-18 years) participated: adolescents who had experienced a life-threatening asthma episode (n=49), asthma controls (n=71), and healthy controls (n=80). Adolescents completed the UCLA PTSD Reaction Index, Multidimensional Anxiety Scale for Children, and Reynolds Depression Inventory. Parents completed the Impact of Events Scale-Revised, Brief Symptom Inventory, and Asthma Functional Morbidity Scale. RESULTS: Twenty percent of adolescents with life-threatening asthma met criteria for PTSD compared with 11% of the asthma controls and 8% of the normal controls. Twenty-nine percent of parents of adolescents with life-threatening asthma met criteria for PTSD compared with 14% of parents of asthma controls and 2% of normal controls. Adolescent PTS symptoms accounted for 5% of the variance in functional asthma morbidity even after controlling for disease severity and other anxiety and depressive symptoms (beta=.26). CONCLUSIONS: Adolescents with asthma and their parents, particularly those who have experienced a life-threatening event, have high levels of PTS symptoms that are linked to asthma morbidity. Interventions to improve asthma outcomes should include assessment and treatment of trauma and PTS symptoms.
(2006) Changes in immunological and hematological parameters of female residents exposed to volatile organic compounds in the city of Kaohsiung, Taiwan.

The objective of this study was to assess the effects, if any, of volatile organic compounds (VOCs) in the ambient air of Kaohsiung, Taiwan, on certain hematological and immunological parameters of 153 female study participants. The major source of VOCs was vehicle emissions. The participants were selected from three areas, each area at a different distance from a freeway. Results indicated that total concentrations of VOCs and a subgroup of 25 VOCs (VOC25) ranged from 250 to 335 ppb and 89 to 113 ppb, respectively. The distribution of VOC concentrations did not correlate with distance from the freeway. The participants living in the area with higher VOC concentrations had significantly higher abnormalities of white blood cells (WBC) and hemoglobin (Hb). In addition, IgG and IgA counts were significantly lower for the participants in the area with higher VOCs than for participants in the area with lower VOCs. This finding indicates that VOCs in ambient air may suppress immunological variables.

(2006) [Medicine without scientific reasoning].

(2006) Multiple chemical sensitivities following intolerance to azo dye in sweets in a 5-year-old girl.

BACKGROUND: Cases of multiple chemical sensitivities (MCS) have been reported predominantly in adult patients, but pediatric cases have rarely been reported. METHODS: We present a 5-year-old girl who suffered from recurrent reactions accompanied by urticaria, angioedema, headaches, dyspnea, loss of consciousness,
and abdominal pain that were not eradicated, but were instead exacerbated, by various treatments with antihistamines and intravenous corticosteroids. Her diet diary revealed that symptoms occurred after ingestion of colorful sweets such as candies and jellybeans. Open challenge tests with food additives and nonsteroidal anti-inflammatory drugs (NSAIDs) were performed after elimination of these items. Skin prick tests using additives and NSAIDs, which were dissolved in saline, and prick-prick tests using candies and jellybeans, were carried out. RESULTS: Open challenge tests with Tartrazine, aspirin and acetaminophen were positive, whereas skin prick tests using additives and NSAIDs and prick-prick tests using candies and jellybeans were all negative. Consequently, intolerance to azo dyes and NSAIDs such as aspirin was diagnosed. However, she appeared to react to multiple chemical odors such as those of cigarette smoke, disinfectant, detergent, cleaning compounds, perfume, and hairdressing, all while avoiding additives and NSAIDs. On the basis of her history and the neuro-ophthalmological abnormalities, a diagnosis of severe MCS was made and she was prescribed multiple vitamins and glutathione. CONCLUSIONS: The present results suggest that in pediatric MCS, food and drug additives containing azo dyes might play important roles as elicitors.


Hillert, L, Musabasic, V, Berglund, H, Ciumas, C and Savic, I Journal/Hum Brain Mapp.
Multiple chemical sensitivity (MCS) is characterized by somatic distress upon exposure to odors. As in other idiopathic environmental intolerances, the mechanisms behind the reported hypersensitivity are unknown. Using the advantage of the well-defined trigger (odor), we investigated whether subjects with MCS could have an increased odor-signal response in the odor-processing neuronal circuits. Positron emission tomography (PET) activation studies with several different odorants were carried out in 12 MCS females and 12 female controls. Activation was defined as a significant increase in regional cerebral blood flow (rCBF) during smelling of the respective odorant compared to smelling of odorless air. The study also included online measurements of respiratory frequency and amplitude and heart rate variations by recording of R wave intervals (RR) on the surface electrocardiogram. The MCS subjects activated odor-processing brain regions less than controls, despite the reported, and physiologically indicated (decreased RR interval) distress. In parallel, they showed an odorant-related increase in activation of the anterior cingulate cortex and cuneus-precuneus. Notably, the baseline rCBF was normal. Thus, the abnormal patterns were observed only in response to odor signals. Subjects with MCS process odors differently from controls, however, without signs of neuronal sensitization. One possible explanation for the observed pattern of activation in MCS is a top-down regulation of odor-response via cingulate cortex. Hum. Brain Mapping 2006. (c) 2006 Wiley-Liss, Inc.

OBJECTIVE: To understand idiopathic environmental intolerances (IEI)-formerly multiple chemical sensitivities (MCS)-it is helpful to outline its characteristic psychiatric morbidity. METHOD: We applied a standardized interview according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (SCID) to 305 environmental patients with and without IEI. RESULTS: Somatoform, affective and anxiety disorders were the most frequent diagnoses but only slightly differed between patients with or without IEI. In both groups, current substance-related disorders were rare. We found a clearly higher prevalence of psychotic, especially current delusional disorders, in IEI. CONCLUSION: Somatization, depression, and anxiety are frequent in IEI but nonspecific. Psychotic disorders are more common in IEI than in other types of environmental illness. It appears worthwhile to study personality and cognitive style to explain the pivotal features of IEI.


Traumatic stress symptoms were assessed for 218 children ages 5 to 13 following exposure to intimate partner violence: 33% of Caucasian and 17% of minority children were diagnosed with posttraumatic stress disorder. A risk and protective factors model was used to predict traumatic stress symptoms. For Caucasian children, the best predictors were mothers' mental health and low self-esteem. For minority children, the amount of violence, mothers' low self-esteem, and low income predicted traumatic stress. Social support to the mother, inclusive of friends, relatives, and religion, was a protective element. Implications for assessment and intervention are discussed in light of each group's experiences.


OBJECTIVES: Consumption of alcoholic beverages reduces the risk of coronary artery disease (CAD), and epidemiological studies have shown that ethanol per se is protective. However, the mechanism by which ethanol exerts protection is not fully known. Ethanol can stimulate neuropeptide-containing primary sensory neurons via the activation of transient receptor potential vanilloid 1 (TRPV1). Here, we have studied whether ethanol-mediated TRPV1 activation causes the release of calcitonin gene-related peptide (CGRP) that, via dilatation of coronary arteries and other mechanisms, may protect the heart from CAD. METHODS AND RESULTS: Ethanol caused a marked relaxation of small-sized porcine isolated coronary (0.008-2.37%, w/v) and human isolated gastro-epiploic (0.0008-2.37%, w/v) arteries in vitro, an effect that was abolished by capsaicin-desensitization, the TRPV1 antagonist capsazepine, and the CGRP receptor antagonist, CGRP(8-37). In guinea-pig isolated and perfused hearts, ethanol (0.079-0.79%, w/v) increased baseline coronary flow in a concentration-dependent manner: 0.237% ethanol doubled baseline coronary flow. This effect was also abolished by capsaicin-desensitization, capsazepine, and CGRP((8-37)). Finally, the ethanol-induced increase in CGRP release from guinea-pig isolated and perfused hearts and from slices of porcine coronary arteries was abolished by capsaicin-desensitization and by capsazepine. Similar functional and neurochemical results were obtained in all preparations with capsaicin.
CONCLUSIONS: Ethanol, at low concentrations not dissimilar from those found in blood following low to moderate consumption of alcoholic beverages, releases CGRP within coronary arteries via stimulation of TRPV1 on perivascular sensory nerve terminals. Ethanol-induced release of CGRP may contribute to the reduction in the risk of CAD associated with alcohol consumption by various mechanisms, including the increase in coronary flow and arterial dilatation.


Poor indoor air quality has been implicated in the increase in allergic and respiratory diseases seen in industrialized countries in recent decades. Although air pollution in the workplace is well studied, much less is known about the consequences of poor air quality in homes. In an attempt to halt or slow down the increase in allergic and respiratory diseases, the European Federation of Allergy and Airways Diseases Patients Associations (EFA) carried out the EU-funded project entitled 'Towards Healthy Air in Dwellings in Europe' (THADE). The aims were to: compile an overview of evidence-based data about exposure to indoor air pollution and its health effects,
particularly in relation to allergies, asthma and other respiratory diseases such as chronic obstructive pulmonary disease; review cost-effective measures and technology to improve indoor air quality; review legislation and guidelines on indoor air pollution; produce maps of pollutants in dwellings; and recommend an integrated strategy that defines appropriate indoor air quality policies for implementation in Europe. This paper summarizes the information about air quality in dwellings and indoor environment-related diseases collected by expert consultants within the framework of THADE and terminates with recommendations for actions aimed at improving air quality in homes. The results of this project confirmed that air pollution in dwellings is a relevant health problem. It is a complex problem that must be addressed at European and international levels, and it involves the medical profession, scientific societies, patients' organizations, lawmakers, architects and the building industry. The complete THADE report is available at http://www.efanet.org/activities/documents THADEReport.pdf.


P-glycoprotein (P-gp), the most extensively studied ATP-binding transporter, functions as a biological barrier by extruding toxic substances and xenobiotics out of the cell. This study was carried out to determine the effect of N,N-diethyl-m-toluamide (DEET) and pyridostigmine bromide (PB), alone and in combination, on P-gp expression using Escherichia coli leaky mutant transformed with Mdr1 gene (pT5-7/mdr1), which codes for P-gp or lactose permease (pT5-7/lacY) as negative control. Also, daunomycin (a known P-gp sustrate) was used as a positive control and reserpine (a known P-gp inhibitor) served as a negative control. An in vitro cell-resistant assay was used to monitor the potential of test compounds to interact with P-gp. Following exposure of the cells to pyridostigmine bromide or daunomycin, P-gp conferred significant resistance against both compounds, while reserpine and DEET significantly inhibited the glycoprotein. Cells were grown in the presence of noncytotoxic concentrations of daunomycin, pyridostigmine bromide, reserpine, or DEET, and membrane fractions were examined by Western immunoblotting for expression of P-gp. Daunomycin induced P-gp expression quantitatively more than pyridostigmine bromide, while reserpine and DEET significantly inhibited P-gp expression in cells harboring mdr1. Photoaffinity labeling experiment performed with the P-gp ligand [125I]iodoarylazidoprazosin demonstrated that compounds that induced or inhibited P-gp transport activity also bound to P-gp. DEET was also found to be a potent inhibitor of P-gp-mediated ATPase activity, whereas pyridostigmine bromide increased P-gp ATPase activity. Cells expressing P-gp or lac permease were exposed to
pyridostigmine bromide and DEET, alone and in combination. Noncytotoxic concentrations of DEET significantly inhibited P-gp-mediated resistance against pyridostigmine bromide, resulting in a reduction of the number of effective drug interactions with biological targets. An explanation of these results might be that DEET is a third-generation inhibitor of P-gp; it has high potency and specificity for P-gp, it inhibits hydrolysis of ATP, it exerts no appreciable impact on cytochrome P-450 3A4, and it prevents transport of xenobiotics, such as pyridostigmine bromide, out of the cell. This conclusion explains, at least in part, the increased toxicity and bioavailability of pyridostigmine bromide following combined administration with DEET. This study improves our understanding of the basis of chemical interactions with DEET by defining the ability of drugs to interact with P-gp either as inhibitors or substrates, which may in turn lead to altered efficacy or toxicity.


BACKGROUND: Volatile organic compounds (VOCs) are present in much higher concentrations indoors, where people spend most of their time, than outdoors and may have adverse health effects. VOCs have been associated with respiratory symptoms, but few studies address objective respiratory end points such as pulmonary function. Blood levels of VOCs may be more indicative of personal exposures than are air concentrations; no studies have addressed their relationship with respiratory outcomes. OBJECTIVE: We examined whether concentrations of 11 VOCs that were commonly identified in blood from a sample of the U.S. population were associated with pulmonary function. METHODS: We used data from 953 adult participants (20-59 years of age) in the Third National Health and Nutrition Examination Survey (1988-1994) who had VOC blood measures as well as pulmonary function measures. Linear regression models were used to evaluate the relationship between 11 VOCs and measures of pulmonary function. RESULTS: After adjustment for smoking, only 1,4-dichlorobenzene (1,4-DCB) was associated with reduced pulmonary function. Participants in the highest decile of 1,4-DCB concentration had decrements of -153 mL [95% confidence interval (CI), -297 to -8] in forced expiratory volume in 1 sec and -346 mL/sec (95% CI, -667 to -24) in maximum mid-expiratory flow rate, compared with participants in the lowest decile. CONCLUSIONS: Exposure to 1,4-DCB, a VOC related to the use of air fresheners, toilet bowl deodorants, and mothballs, at levels found in the U.S. general population, may result in reduced pulmonary function. This common exposure may have long-term adverse effects on respiratory health.
Elberling, J, Dirksen, A, Johansen, JD and Mosbech, H Journal/Contact Dermatitis. 54: 158-64.

Respiratory symptoms elicited by perfume are common in the population but have unclear pathophysiology. Increased capsaicin cough responsiveness has been associated with the symptoms, but it is unknown whether the site of the symptoms in the airways influences this association. The aim of this study was to investigate the association between the site of airway symptoms elicited by perfume and cough responsiveness to bronchial challenge with capsaicin. 21 eczema patients with respiratory symptoms elicited by perfume were compared with 21 healthy volunteers in a sex- and age-matched case control study. The participants completed a symptom questionnaire and underwent a bronchial challenge with capsaicin. Lower, but not upper, respiratory symptoms elicited by perfume were associated with increased capsaicin cough responsiveness. Having severe symptoms to perfume (n=11) did not relate to the site of the symptoms in the airways and was not associated with increased capsaicin cough responsiveness. In conclusion, respiratory symptoms elicited by perfume may reflect local hyperreactivity related to defensive reflexes in the airways, and measurements of the capsaicin cough reflex are relevant when patients with lower respiratory symptoms related to environmental perfume exposures are investigated.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16524439

(2006) Crystal structures of acetylcholinesterase in complex with HI-6, Ortho-7 and obidoxime: Structural basis for differences in the ability to reanimate tabun conjugates.

Inhibition of acetylcholinesterase (AChE) by organophosphorus compounds (OPs) such as pesticides and nerve agents causes acute toxicity or death of the intoxicated individual. The inhibited AChE may be reactivated by certain oximes as antidotes for clinical treatment of OP-intoxications. Crystal structures of the oximes HI-6, Ortho-7 and obidoxime in complex with Mus musculus acetylcholinesterase (mAChE) reveal different roles of the peripheral anionic site (PAS) in the binding of the oximes. A limited structural change of the side chains of Trp286 and Asp74 facilitates the intercalation of the 4-carboxylamide pyridinium ring of HI-6 between the side chains of Tyr124 and Trp286. The 2-carboxyimino pyridinium ring of HI-6 is accommodated at the entrance of the catalytic site with the oximate forming a hydrogen bond to the main-chain nitrogen atom of Phe295. In contrast to HI-6, the coordination of Ortho-7 and obidoxime within the PAS is facilitated by an extended structural change of Trp286 that allows one of the carboxyimino pyridinium rings to form a cation-pi interaction with the aromatic groups of Tyr72 and Trp286. The central chain of Ortho-7 and obidoxime
is loosely coordinated in the active-site gorge, whereas the second 2-carboxyimino pyridinium ring is accommodated in the vicinity of the phenol ring of Tyr337. The structural data clearly show analogous coordination of Ortho-7 and obidoxime within the active-site gorge of AChE. Different ability to reactivate AChE inhibited by tabun is shown in end-point reactivation experiments where HI-6, Ortho-7 and obidoxime showed an efficiency of 1, 45 and 38%, respectively. The low efficiency of HI-6 and the significantly higher efficiency of Ortho-7 and obidoxime may be explained by the differential binding of the oximes in the PAS and active-site gorge of AChE.


BACKGROUND: Mind/body practices that elicit the relaxation response (RR) are currently practiced by over 30% of American adults. RR elicitation reduces volumetric oxygen consumption (VO(2)) from rest and counteracts the effects of stress, although the mechanisms mediating the RR remain unknown. This study was designed to investigate whether RR elicitation is mediated by nitric oxide (NO). We developed a method to quantify depth of RR using change in VO(2) (slope) during RR elicitation. We evaluated whether depth of RR elicitation was correlated with changes in NO, as measured by percentage changes in fractional exhaled nitric oxide (F(E)NO).

MATERIAL/METHODS: We conducted a randomized, controlled trial, in which 46 subjects were randomized to either 8-weeks of RR training using audiotapes (n=34) or 8-weeks of exposure to a control condition--receiving health-education by audiotapes (n=12). Prior to randomization, VO(2) and F(E)NO were measured while subjects listened to a control audiotape. Eight weeks later, VO(2) and F(E)NO were measured while the RR group listened to a RR-eliciting audiotape and the control group listened to a control audiotape. RESULTS: Prior to receiving any training, there was no association between VO(2) slope and F(E)NO. After training, there was an inverse correlation between VO(2) slope and F(E)NO in the RR group (r = -0.41, P=0.037, n=26), but not in the control group (r=0.12, P=0.78, n=8). CONCLUSIONS: Depth of RR elicitation was associated with increased concentrations of F(E)NO after RR training. The RR may be mediated by NO helping to explain its clinical effects in stress-related disorders.


(2006) Illnesses you have to fight to get: facts as forces in uncertain, emergent illnesses.

Chronic fatigue syndrome and multiple chemical sensitivity are two clusters of illnesses that are pervaded by medical, social and political uncertainty. This article examines how facts are talked about and experienced in struggles over these emergent, contested illnesses in the US. Based principally on a large archive of internet newsgroup postings, and also on fieldwork and on published debates, it finds that (1) sufferers describe their experiences of being denied healthcare and legitimacy through bureaucratic categories of exclusion as dependent upon their lack of biological facts; (2) institutions manage these exclusions rhetorically through exploiting the open-endedness of science to deny efficacy to new facts; (3) collective patient action responds by archiving the systematic nature of these exclusions and developing counter-tactics. The result is the maintenance of these very expensive struggles for all involved.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16085344

(2006) [Psychiatric disorders of environmental outpatients--results of the standardized psychiatric interview (CIDI) from the German multi-center study on Multiple Chemical Sensitivity (MCS)].

BACKGROUND: A nationwide, environmental outpatient-based multi-center two-phase study on Multiple Chemical Sensitivity (MCS) was conducted from 1999 until 2004. The aim of the study was to characterize more precisely the health-complaints relevant for the MCS-phenomenon. A standardized psychiatric interview (CIDI), used to identify frequency, character and duration of psychiatric disorders and their chronological relation to the environment-related health complaints of the patients, formed part of the extensive diagnostic procedure. METHOD: 251 (86.3%) of the 291 attendees of the environmental outpatient departments in Aachen, Berlin, Bredstedt, Freiburg, Giessen and Munich, were examined using the German version (M-CIDI/DIA-X) of the Composite International Diagnostic Interview. RESULTS: 83.7% (lifetime prevalence rate) fulfilled the diagnostic criteria of at least one psychiatric disorder, with the 12-month and 4-week prevalence rates being 76.5% and 64.5%, respectively. Environmental outpatients, in all prevalence periods, had significantly higher rates of psychiatric disorders than the comparable general population. Somatoform disorders were most frequently diagnosed, followed by depressive and phobic disorders. For 81.2% of the patients the psychiatric disorder started long before the environment-related health complaints (average 17 years). CONCLUSIONS: This study confirms the results of earlier studies, i.e. that patients with environment-related health complaints suffer from psychiatric disorders more frequently than the general
population. The high environmental outpatients really suffer from psychosomatic complaints, but attribute the causes to the environment. Application of specific therapeutic regimen is recommended for those patients, whose psychiatric disorders are safeguarded diagnostically and for whom a relevant exposure is unlikely.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16802422


A systematic review of provocation studies of persons reporting multiple chemical sensitivities (MCS) was conducted from databases searched from inception to May 2006. Thirty-seven studies were identified, testing 784 persons reporting MCS, 547 control subjects, and 180 individuals of whom a subset were chemically sensitive. Blinding was inadequate in most studies. In 21 studies odors of chemicals were probably apparent; 19 of these reported positive responses to provocations among chemically sensitive individuals, and 1 study demonstrated that negative expectations were significantly associated with increased symptom reporting after provocations. Seven studies used chemicals at or below odor thresholds, and 6 failed to show consistent responses among sensitive individuals after active provocation. Six studies used forced-choice discrimination and demonstrated that chemically sensitive individuals were not better at detecting odor thresholds than nonsensitive participants. Three studies tested individuals by using nose clips/face masks and confirmed response, possibly mediated through eye exposure. Three studies used olfactory masking agents to conceal stimuli, and none of these found associations between provocations and response. We conclude that persons with MCS do react to chemical challenges; however, these responses occur when they can discern differences between active and sham substances, suggesting that the mechanism of action is not specific to the chemical itself and might be related to expectations and prior beliefs.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17137865

(2006) Gene expression profiles of the rat brain both immediately and 3 months following acute sarin exposure.
We have studied sarin-induced global gene expression patterns at an early time point (15 min; 0.5xLD50) and a later time point (3 months; 1xLD50) using Affymetrix: Rat Neurobiology U34 chips in male, Sprague-Dawley rats and have identified a total of 65 (early) and 38 (late) genes showing statistically significant alterations from control levels at 15 min and 3 months, respectively. At the early time point, those that are classified as ion channel, cytoskeletal and cell adhesion molecules, in addition to neuropeptides and their receptors predominated over all other groups. The other groups included: cholinergic signaling, calcium channel and binding proteins, transporters, chemokines, GABAergic, glutamatergic, aspartate, catecholaminergic, nitric oxide synthase, purinergic, and serotoninergic signaling molecules. At the late time point, genes that are classified as calcium channel and binding proteins, cytoskeletal and cell adhesion molecules and GABAergic signaling molecules were most prominent. Seven molecules (Ania-9, Arrb-1, CX-3C, Gabab-1d, Nos-2a, Nrxn-1b, PDE2) were identified that showed altered persistent expression in both time points. Selected genes from each of these time points were further validated using semi quantitative RT-PCR approaches. Some of the genes that were identified in the present study have been shown to be involved in organophosphate-induced neurotoxicity by both other groups as well as ours. Principal component analysis (PCA) of the expression data from both time points was used for comparative analysis of the gene expression, which indicated that the changes in gene expression were a function of dose and time of euthanasia after the treatment. Our model also predicts that besides dose and duration of post-treatment period, age and possibly other factors may be playing important roles in the regulation of pathways, leading to the neurotoxicity.

(2006) Toxicogenomic studies of the rat brain at an early time point following acute sarin exposure.
Damodaran, TV, Greenfield, ST, Patel, AG, Dressman, HK, S, KL and Abou-Donia, MB

We have studied sarin-induced global gene expression patterns at an early time point (2 h: 0.5xLD50) using Affymetrix Rat Neurobiology U34 chips and male Sprague-Dawley rats. A total of 46 genes showed statistically significant alterations from control levels. Three gene categories contained more of the altered genes than any other groups: ion channel (8 genes) and calcium channel and binding proteins (6 genes). Alterations were also found in the following gene groups: ATPases and ATP-based transporters (4), growth factors (4), G-protein-coupled receptor pathway-related molecules (3), neurotransmission and neurotransmitter transporters (3), cytoskeletal and cell adhesion molecules (2), hormones (2), mitochondria-associated proteins (2), myelin proteins (2), stress-activated molecules (2), cytokine (1), caspase (1), GABAergic (1), glutamergic (1), immediate early gene (1), prostaglandin (1), transcription factor (1), and tyrosine phosphorylation molecule (1). Persistent alteration of the following genes also were noted: Arrb1, CaMKIIa,
CaMKII’d, Clcn5, IL-10, c-Kit, and Plp1, suggesting altered GPCR, kinase, channel, and cytokine pathways. Selected genes from the microarray data were further validated using relative RT-PCR. Some of those genes (GFAP, NF-H, CaMKIIa, Calm, and MBP) have been shown by other laboratories and ours, to be involved in the pathogenesis of sarin-induced pathology and organophosphate-induced delayed neurotoxicity (OPIDN). Induction of both proapoptotic (Bcl2l11, Casp6) and antiapoptotic (Bcl-X) genes, besides suppression of p21, suggest complex cell death/protection-related mechanisms operating early on. Principal component analysis (PCA) of the expression data confirmed that the changes in gene expression are a function of sarin exposure, since the control and treatment groups separated clearly. Our model (based on current and previous studies) indicates that both degenerative and regenerative pathways are activated early and contribute to the level of neurodegeneration at a later time, leading to neuro-pathological alterations.


The quality and quantity of the data about the risk posed to humans by individual pesticides vary considerably. Unlike obvious birth defects, most developmental effects cannot be seen at birth or even later in life. Instead, brain and nervous system disturbances are expressed in terms of how an individual behaves and functions, which can vary considerably from birth through adulthood. In this article I challenge the protective value of current pesticide risk assessment strategies in light of the vast numbers of pesticides on the market and the vast number of possible target tissues and end points that often differ depending upon timing of exposure. Using the insecticide chlorpyrifos as a model, I reinforce the need for a new approach to determine the safety of all pesticide classes. Because of the uncertainty that will continue to exist about the safety of pesticides, it is apparent that a new regulatory approach to protect human health is needed.


Currently, the major determinants of children's exposure to pesticides are not fully understood, and approaches for measuring and assessing dermal exposure in a residential setting have not been sufficiently evaluated. In one approach, dermal exposure is estimated using empirically derived transfer coefficients. To assess the
feasibility of using this approach for assessing children's exposure to pesticides, we conducted a study was conducted in a child care center that had a preexisting contract with a pest control service for regular monthly pesticide applications. Children in the selected child care center were monitored using full-body cotton garments to measure dermal loading. Pesticide residues on classroom surfaces were measured in the areas where the children spent time. Measured surface-wipe loadings ranged from 0.47 to 120 ng/cm$^{2}$, and total garment loadings ranged from 0.5 to 660 pg/cm$^{2}$. The garment and surface loading measurements were used to calculate dermal-transfer coefficients for use in assessing children's residential exposure to pesticides. Dermal-transfer coefficients calculated using these data range from approximately 10 to 6,000 cm$^{2}$/hr. The wide range in these values demonstrates the importance of developing standard surface-measurement protocols if this approach is to be used to assess dermal exposure in a residential environment. The upper-range values resulting from this study were found to be similar to the default value used by the U.S. Environmental Protection Agency to assess children's dermal exposures resulting from contact with indoor surfaces. Key words: children, dermal exposure assessment, dermal-transfer coefficients, FQPA, pesticide exposure.sch
produce long-lasting changes in anxiety-related neural circuitry. This suggests that odor-triggered symptoms associated with an aversive event may persist in MCS patients because of the ability of some chemicals to alter fear or anxiety circuitry in the brain.


OBJECTIVES: Increased vulnerability to stress has been suggested as a possible mechanism behind medically unexplained conditions such as sensitivity to electricity and common smells. This study examined whether subjective environmental annoyance among the general population is associated with increased physiological reactivity or subjective stress scores. METHODS: Four groups were studied (N=141): an electrically annoyed (N=17), a smell-annoyed (N=29), and a generally annoyed group (N=39) and a reference group matched for age, gender, and socioeconomic status (N=56). Over 5 days, the participants collected saliva for cortisol determination at awakening, 30 minutes after awakening, 8 hours after awakening, and at 9 o’clock in the evening. On the evening preceding the fifth day, the participants ingested a 0.5-mg dexamethasone tablet so that possible differential suppression of the hypothalamic-pituitary-adrenal (HPA) axis could be assessed. Each day, the participants also rated their subjective stress and health complaints. RESULTS: No significant differences were found between the groups regarding cortisol secretion over 5 days. The dexamethasone suppression test showed inhibited cortisol secretion in all four groups. No associations were found between the cortisol concentrations and the self-reported stress scores or subjective health complaints. CONCLUSIONS: Although the environmentally annoyed groups showed no signs of increased HPA-axis activation, being annoyed by both electrical devices and smells seems to be related to increased psychological activation in terms of self-reported stress. Because the participants were otherwise healthy and recruited from the general population, the results imply that subtle psychological stress processes may be important in the early development of environmental annoyance.


OBJECTIVE: Patients with environmental illness experience a large number of psychological symptoms. The nature of these symptoms and their pathogenesis (toxicogenic versus psychogenic) is controversial. The objective was to (1) characterize the nature of the psychological symptoms according to well-established diagnostic criteria, and (2) to investigate the association between toxicological factors and psychological symptoms. METHODS: Toxic burden, somatic morbidity, and psychiatric morbidity were assessed in 309 outpatients with environmental illness and 59 semiconductor industry workers matched for age and gender. Psychiatric disorders were assessed by a structured psychiatric interview (SCID), and distress was assessed by the Symptom-Checklist-90-Revised (SCL-90-R). Routine and specific laboratory tests in blood and urine samples were used to assess chemical exposures. RESULTS: Overall psychiatric morbidity was significantly higher in patients than in controls according to SCID (75% versus 24%). Somatoform, mood, and anxiety disorders were significantly more frequent in patients with environmental illness. They also revealed marked stress on the SCL-90-R somatization subscale and scored significantly higher than controls on most of the other subscales. Industry workers from the control group tended to have higher urine metal concentrations than environmental illness patients and similar concentrations of solvents in blood. CONCLUSION: Our data extend previous findings of high psychiatric morbidity in patients with environmental illness. They do not support the notion of a direct causal link between chemical exposure and the psychological symptoms.


We compared the MMPI-2 profiles of adults with multiple chemical sensitivity (MCS), epileptic seizures (ES), and nonepileptic seizures (NES). Both NES and MCS are medically unexplained conditions. In previous studies profiles associated with NES were elevated on scales Hs and Hy, compared with profiles associated with ES. We predicted that profiles associated with MCS would be elevated on Hs and Hy compared with the ES group. Patients with ES and NES were diagnosed after intensive EEG monitoring using published criteria. MCS was diagnosed if there was a complaint of illness in response to multiple common odors at levels that are not noxious to most people. All the MCS cases had legal claims for injury related to chemical exposures. The results showed that on MMPI-2 scales Hs, D, and Hy the MCS group had means significantly higher than both the ES and NES groups. Fake Bad Scale scores were elevated in 11 MCS cases, and regression-based estimates of Fake Bad Scale scores showed elevation in the MCS group compared with both seizure groups. We conclude that MMPI-2 data, obtained from people seeking financial compensation, indicate that there is a strong psychological component to MCS symptoms.
Background Multiple chemical sensitivity (MCS) has an estimated American prevalence of 15%, and no consistently abnormal laboratory tests are available to assist in its diagnosis. Some physicians treating MCS patients have observed changes in intra-erythrocytic minerals (IEMs). As co-factors, minerals could influence detoxication of xenobiotics. Aim To test whether IEM differed comparing MCS cases with controls.
Methods A total of 408 women meeting validated inclusion and exclusion criteria for MCS participated in this case-control study. Results No statistically significant differences were observed. However, for copper, chromium, magnesium, molybdenum, sulphur and zinc, mean detectable levels were all lower in cases. No dose-response relationships were found. Conclusion IEM measurements do not appear to provide useful diagnostic markers for MCS.

OBJECTIVE: The objective of this study was to examine the psychometric qualities of a brief screening measure for idiopathic environmental intolerance (IEI), the Chemical Odor Sensitivity Scale (COSS). METHODOLOGY: The COSS was administered together with other measures of environmental sensitivity, IEI, and symptom scales in large samples (students, individuals with IEI, and individuals without IEI). RESULTS: The COSS achieved high internal consistency (.88 < or = Cronbach's alpha < or = .96) and good factorial, convergent, and discriminant validity across diverse samples. In a longitudinal sample, the COSS and other IEI features were stable across time. According to receiver operating characteristic analyses, the COSS performs adequately in screening individuals likely to meet case criteria for IEI. CONCLUSIONS: The favorable psychometric qualities of the COSS recommend the scale as a useful tool both for assessing self-reported chemical odor sensitivity as a vulnerability marker and for screening for IEI.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16813848

Background. Previous studies suggest that idiopathic environmental intolerance (IEI) is a variant of somatoform disorders (SFDs) or the so-called functional somatic syndromes. Little is known, however, about the stability and the psychological predictors of IEI.

Method. This prospective study examined the 1-year stability of somatic symptoms and IEI features in three diagnostic groups: 49 subjects with IEI, 43 subjects with SFD but without IEI, and 54 subjects (control group, CG) with neither IEI nor SFD. The predictive value of typical psychological predictors for somatization was tested using zero-order correlations and multiple linear regression analyses.

Results. Somatic symptoms and IEI features proved to be temporally stable over the 1-year follow-up period. The SFD and IEI groups scored significantly higher than CG on all measures of somatic symptoms and on questionnaires assessing psychological predictors for somatization. Measures of trait negative affectivity (NA), somatic symptom attribution and somatosensory amplification predicted somatic symptom severity within the IEI and SFD groups, both at baseline and 1 year later. The strongest predictors of IEI complaints in the IEI group were somatic attributions, followed by prominent cognitions of environmental threat and a tendency to focus on unpleasant bodily sensations and to consider them as pathological.

Conclusions. IEI and SFD are highly stable conditions. In both SFD and IEI, NA and the processes of symptom perception, interpretation and attribution contribute substantially to the persistence of typically somatoform symptoms and IEI complaints. Treatment of IEI and SFD should address these psychological factors and mechanisms.

----------------------------------------

(2006) [Multiple chemical sensitivity in sick-building syndrome].

The sick building syndrome includes irritation of the eyes and the respiratory tract neurotoxicity affection and skin problems, which can occur in individuals under improperly ventilated buildings. Poor air quality, as shown in CO2 atmospheric levels of more than 1,000 ppm, results in a pathological exposure to biological and chemical products. We present a work-related case of multiple chemical hypersensitivity from a dialysis unit that had no air renewal. This person, who was submitted to continuous exposure despite having taken corrective measures in the ventilation, developed chronic fatigue syndrome. An acoustic voice observation alerted of the case which led to the analysis of the environmental conditions which confirmed the relationship between multiple chemical hypersensitivity and chronic fatigue syndrome. This case stresses the neglected fact that all health service centres pose a high risk of chemical
exposure and that there exists a lack of rigoroursness in putting in practice scientific medical knowledge.


---------------------------------------------------------------


Neurodevelopmental disabilities affect 3-8% of the 4 million babies born each year in the U.S. alone, with known etiology for less than 25% of those disabilities. Numerous investigations have sought to determine the role of environmental exposures in the etiology of a variety of human neurodevelopmental disorders (e.g., learning disabilities, attention deficit-hyperactivity disorder, intellectual disabilities) that are manifested in childhood, adolescence, and young adulthood. A comprehensive critical examination and discussion of the various methodologies commonly used in investigations is needed. The Hershey Medical Center Technical Workshop: Optimizing the design and interpretation of epidemiologic studies for assessing neurodevelopmental effects from in utero chemical exposure provided such a forum for examining these methodologies. The objective of the Workshop was to develop scientific consensus on the key principles and considerations for optimizing the design and interpretation of epidemiologic studies of in utero exposure to environmental chemicals and subsequent neurodevelopmental effects. (The Panel recognized that the nervous system develops post-natally and that critical periods of exposure can span several developmental life stages.) Discussions from the Workshop Panel generated 17 summary points representing key tenets of work in this field. These points stressed the importance of: a well-defined, biologically plausible hypothesis as the foundation of in utero studies for assessing neurodevelopmental outcomes; understanding of the exposure to the environmental chemical(s) of interest, underlying mechanisms of toxicity, and anticipated outcomes; the use of a prospective, longitudinal cohort design that, when possible, runs for periods of 2-5 years, and possibly even longer, in an effort to assess functions at key developmental epochs; measuring potentially confounding variables at regular, fixed time intervals; including measures of specific cognitive and social-emotional domains along with non-cognitive competence in young children, as well as comprehensive measures of health; consistency of research design protocols across studies (i.e., tests, covariates, and analysis styles) in an effort to improve interstudy comparisons; emphasis on design features that minimize introduction of systematic error at all stages of investigation: participant selection, data collection and analysis, and interpretation of results; these would include (but not be limited to)
reducing selection bias, using double-blind designs, and avoiding post hoc formulation of hypotheses; a priori data analysis strategies tied to hypotheses and the overall research design, particularly for methods used to characterize and address confounders in any neurodevelopmental study; actual quantitative measurements of exposure, even if indirect, rather than methods based on subject recall; careful examination of standard test batteries to ensure that the battery is tailored to the age group as well as what is known about the specific neurotoxic effects on the developing nervous system; establishment of a system for neurodevelopmental surveillance for tracking the outcomes from in utero exposure across early developmental time periods to determine whether central nervous system injuries may be lying silent until developmentally challenged; ongoing exploration of computerized measures that are culturally and linguistically sensitive, and span the age range from birth into the adolescent years; routine incorporation of narrative in manuscripts concerning the possibility of spurious (i.e., false positive and false negative) test results in all research reportage (this can be facilitated by detailed, transparent reporting of design, covariates, and analyses so that others can attempt to replicate the study); forthright, disciplined, and intellectually honest treatment of the extent to which results of any study are conclusive— that is, how generalizable the results of the study are in terms of the implications for the individual study participants, the community studied, and human health overall; confinement of reporting to the actual research questions, how they were tested, and what the study found, and avoiding, or at least keeping to a minimum, any opinions or speculation concerning public health implications; education of clinicians and policymakers to critically read scientific reports, and to interpret study findings and conclusions appropriately; and recognition by investigators of their ethical duty to report negative as well as positive findings, and the importance of neither minimizing nor exaggerating these findings.

(2006) In utero exposure to nicotine and chlorpyrifos alone, and in combination produces persistent sensorimotor deficits and Purkinje neuron loss in the cerebellum of adult offspring rats.
Abou-Donia, MB, Khan, WA, Dechkovskaia, AM, Goldstein, LB, Bullman, SL and Abdel-Rahman, A Journal/Arch Toxicol.
This study was carried out to investigate the effect of in utero exposure to the cholinotoxicants, nicotine and chlorpyrifos, alone or in combination on neurobehavioral alterations and neuronal morphology latter in adult age. In the present study, 90 days old (corresponding to a human adult age) male and female offspring rats were evaluated for neurobehavioral, and neuropathological alterations following maternal, gestational exposure to nicotine and chlorpyrifos (O,O-diethyl-O-3,5,6-trichloro-2-pyridinyl phosphorothioate), alone and in combination. Female Sprague-Dawley rats (300-350 g) with timed-pregnancy were treated with nicotine (3.3 mg/kg/day, in bacteriostatic water via s.c. implantation of mini osmotic pump), chlorpyrifos (1.0 mg/kg, daily, dermal, in 75% ethanol, 1.0 ml/kg) or a combination of both chemicals, on gestational days (GD) 4-20. Control animals
received bacteriostatic water via s.c. implantation of mini osmotic pump and dermal application of 70% ethanol. The offspring at postnatal day (PND) 90 were evaluated for neurobehavioral performance, changes in the activity of plasma butyrylcholinesterase (BChE) and acetylcholinesterase (AChE), and neuropathological alterations in the brain. Neurobehavioral evaluations included beam-walk score, beam-walk time, incline plane performance and forepaw grip time. Male and female offspring from mothers treated with nicotine and CPF, alone or in combination showed impairments in the performance of neurobehavioral tests, indicating sensorimotor deficits. Female offspring from mothers treated with a combination of nicotine and chlorpyrifos showed significant increase in plasma BChE activity. Brain regional AChE activity showed differential increases in male and female offspring. Brainstem and cerebellum of female offspring from mothers treated with nicotine or chlorpyrifos, alone or in combination showed increased AChE activity, whereas brainstem of male offspring from mothers treated with nicotine alone or a combination of nicotine and chlorpyrifos showed increase in AChE activity. Also, male offspring exposed in utero to nicotine exhibited increased AChE activity. Histopathological evaluations using cresyl violet staining showed a decrease in surviving Purkinje neurons in the cerebellum in offspring of all treatments groups. An increase in glial fibrillary acidic protein (GFAP) immuno-staining was observed in cerebellum white matter as well as granular cell layer (GCL) of cerebellum following all exposures. These results indicate that in utero exposure to nicotine and chlorpyrifos, alone and in combination produced significant sensorimotor deficits in male and female offspring, differential increase in brain AChE activity, a decrease in the surviving neurons and an increased expression of GFAP in cerebellum in adult offspring rats at a corresponding human adult age. Collectively, this study demonstrates that maternal exposure to environmental neurotoxic chemicals, i.e., nicotine and chlorpyrifos leads to developmental abnormalities in the offspring that persist latter into adulthood.

(2006) [Consensus document on multiple chemical sensitivity (MCS)].
Journal/Med Lav. 97: 621-5.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17017389

(2006) [Significance of the determination of lymphocyte subpopulations in the environmental medicine].
Journal/Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 49: 468-84.
Chlorpyrifos is an irreversible inhibitor of cholinesterase (ChE), and inhibition of ChE is believed to be the most sensitive effect in all animal species evaluated and in humans. Recent epidemiology studies reported associations between umbilical cord plasma chlorpyrifos levels and fetal birth weight decreases among minority women living in New York City during pregnancy. These associations raise questions whether impaired fetal development is the critical effect rather than the inhibition of ChE as is currently believed so. We analyze the available information from epidemiology studies and animal studies in order to identify the relative sensitivity of decreased birth weight and inhibition of ChE from exposure to chlorpyrifos. We find that the positive associations from some epidemiology studies are different from other epidemiology investigations. Moreover, a direct comparison of experimental animal neonatal information shows that cholinesterase inhibition is a more sensitive indicator of adverse effect than reduced body weight, and that neonates are equally, or perhaps less sensitive to cholinesterase inhibition than their maternal parent. Based on a review of human studies and comparison of human cord blood chlorpyrifos concentrations with blood chlorpyrifos concentrations that in animals caused effects with good dose-response, it appears unlikely that the exposure level encountered by the population reported in [Whyatt, R.M., Rauh, V., Barr, D.B., Camann, D.E., Andrews, H.F., Garfinkel, R., Hoepner, L.A., Diaz, D., Dietrich, J., Reyes, A., Tang, D., Kinney, P.L., Perera, F.P., 2004. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. Environ. Health Perspect. 112, 1125-1132.] study would cause any fetal developmental effect. Moreover, the critical effect for chlorpyrifos still appears to be cholinesterase inhibition.
Zaitseva, NV, Ulanova, TS, Karnazhitskaia, TD and Teploukhova, NV Journal/Gig Sanit. 58-61.

-------------------------------------------------------------------

(2005)  [Indoor air pollution in newly built or renovated elementary schools and its effects on health in children].

PURPOSE: To elucidate the actual status of indoor air pollution at newly built or renovated elementary schools, and to evaluate its effects on health symptoms in the affected children. METHODS: In the classrooms of four newly built or renovated elementary schools in Osaka Prefecture, indoor air levels of formaldehyde and volatile organic compounds (VOC) were measured immediately, 1 month, 3 months, 10 months and 22 months after the completion of the construction work. Also, questionnaire surveys regarding subjective symptoms of sick building syndrome were conducted before and after the renovation on the children who attended classes in the renovated rooms. RESULTS: In the newly built computer classroom, more formaldehyde was detected one month after the completion of the construction work, when computers and furniture were carried in, than immediately after the completion of the work. Then, during the summer season, even 10 months and 22 months after completion of the new building, formaldehyde above the guideline values was detected. In the renovated common classrooms, the formaldehyde level was the same as that in the classrooms which did not undergo renovation, but VOC levels were higher immediately after the completion of the construction work, and the toluene level was above the guideline value. In 4-story reinforced concrete school buildings, indoor air pollution tended to be higher on the third and the fourth floors than on the first and the second floors. In 3-story school buildings, indoor air pollution tended to be higher on the third floor than on the second floor. The survey of subjective symptoms of the children revealed a tendency toward an increase in the prevalence of sick building syndrome after a renovation. However, the actual number of the children complaining of the symptoms hardly changed. Instead, the number of symptoms for each subject increased, and this increase was significant in 5th and 6th grade boys. CONCLUSION: In the some classrooms of newly built or renovated elementary schools, chemical substances above the guideline values may be detected. In such classrooms, more ventilation is required.

-------------------------------------------------------------------

(2005)  [Clinical evaluation of 30 patients with interstitial cystitis complicated by fibromyalgia].
PURPOSE: Although interstitial cystitis (IC) complicated by fibromyalgia (FM) is yet unreported in Japan, we encountered patients with the complications almost as frequently as in the USA. We report the present status of such patients and the significance of this complication. PATIENTS AND METHODS: We evaluated the clinical findings of 30 patients with IC complicated by FM in the last four years. RESULTS: Average IC symptom index and problem index was 14.9 and 14.6, respectively. Average numbers of tender points for the criteria for FM was 16 locations. Both diseases have some similarities in the decrease in pain threshold, extensive pain, factors exacerbating symptoms and treatment methods. CONCLUSION: Approximately 11% of patients with IC have a complication of FM. They feel isolated due to the lack of understanding of the disease and endure generalized intolerable pain.


The growth of indoor molds and their resulting products (e.g., spores and mycotoxins) can present health hazards for human beings. The efficacy of chlorine dioxide gas as a fumigation treatment for inactivating sick building syndrome-related fungi and their mycotoxins was evaluated. Filter papers (15 per organism) featuring growth of Stachybotrys chartarum, Chaetomium globosum, Penicillium chrysogenum, and Cladosporium cladosporioides were placed in gas chambers containing chlorine dioxide gas at either 500 or 1,000 ppm for 24 h. C. globosum was exposed to the gas both as colonies and as ascospores without asci and perithecia. After treatment, all organisms were tested for colony growth using an agar plating technique. Colonies of S. chartarum were also tested for toxicity using a yeast toxicity assay with a high specificity for trichothecene mycotoxins. Results showed that chlorine dioxide gas at both concentrations completely inactivated all organisms except for C. globosum colonies which were inactivated an average of 89%. More than 99% of ascospores of C. globosum were nonculturable. For all ascospore counts, mean test readings were lower than the controls (P < 0.001), indicating that some ascospores may also have been destroyed. Colonies of S. chartarum were still toxic after treatment. These data show that chlorine dioxide gas can be effective to a degree as a fumigant for the inactivation of certain fungal colonies, that the perithecia of C. globosum can play a slightly protective role for the ascospores and that S. chartarum, while affected by the fumigation treatment, still remains toxic.
(2005) Comparison of conventional and integrated pest management programs in public schools.

This study compared an integrated pest management (IPM) program with conventional, calendar-based pest control in nine North Carolina elementary schools. Both programs primarily targeted the German cockroach, Blattella germanica (L.). The IPM program relied heavily on monitoring and baiting, whereas the conventional approach used baseboard and crack-and-crevice sprays of insecticides. Within the constraints of an existing pest management contract, we quantified service duration, materials used, cost, levels of cockroach infestation, and the pesticide residues generated by the two service types. IPM services were significantly more time-consuming than conventional services, resulting in a significantly higher cost associated with labor. Nevertheless, the two types of treatments incurred similar total costs, and the efficacy of both treatments was also similar. Most importantly, pest monitoring, a central element of the IPM program, revealed few cockroaches and indicated that most of the conventional treatments were unnecessary. Environmental residues of the organophosphate pesticides acephate, chlorpyrifos, and propetamphos were significantly higher in swab samples taken in the conventionally treated schools. This study demonstrates that an IPM program is an appropriate and preferable alternative to conventional methods of pest control in the school environment.

----------------------------------------

(2005) [Multiple chemical sensitivity (MCS) -- a case series].

BACKGROUND AND OBJECTIVE: The phenomenon of Multiple Chemical Sensitivity which generally cannot be explained organically is frequently associated with psychic impairment. This case series deals with the question if in addition to a standardized interview a routine psychiatric-psychosomatic examination alters the classification if a patient suffers from symptoms compatible with MCS or not. METHODS: Nine consecutive outpatients (m = 3, f = 6, mean age 44 yrs) of the environmental medicine centre were investigated. Somatic diseases were evaluated by standard medical procedures and emotional disturbances were assessed by the Munich Composite International Diagnostic Interview (M-CIDI) and a psychiatric-psychosomatic examination. RESULTS: In all but one patients emotional disturbances (F-codes of the ICD-10) were diagnosed by the M-CIDI and the psychiatric-psychosomatic examination. The diagnoses of the M-CIDI and the psychiatric-psychosomatic examination often did not match. MCS was ruled out in seven patients. CONCLUSIONS: According to the criteria defined by Cullen (5), emotional disturbances must be ruled out before MCS is diagnosed. Therefore, an examination by a specialist in psychiatry or psychosomatics is mandatory because evaluation solely
based on the M-CIDI is insufficient. Performing a routine psychiatric-psychosomatic examination, MCS could be ruled out much more often than previously.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15712020


Grasshopper sound production, in the context of mate finding, courtship, and rivalry, is controlled by the central body complex in the protocerebrum. Stimulation of muscarinic acetylcholine receptors in the central complex has been demonstrated to stimulate specific singing in various grasshoppers including the species Chorthippus biguttulus. Sound production elicited by stimulation of muscarinic acetylcholine receptors in the central complex is inhibited by co-applications of various drugs activating the nitric oxide/cyclic guanosine monophosphate (cGMP) signaling pathway. The nitric oxide-donor sodium nitroprusside caused a reversible suppression of muscarine-stimulated sound production that could be blocked by 1H-[1,2,4]oxadiazolo-[4,3-a]quinoxaline-1-one (ODQ), which prevents the formation of cGMP by specifically inhibiting soluble guanylyl cyclase. Furthermore, injections of both the membrane-permeable cGMP analog 8-Br-cGMP and the specific inhibitor of the cGMP-degrading phosphodiesterase Zaprinast reversibly inhibited singing. To identify putative sources of nitric oxide, brains of Ch. biguttulus were subjected to both nitric oxide synthase immunocytochemistry and NADPH-diaphorase staining. Among other areas known to express nitric oxide synthase, both procedures consistently labeled peripheral layers in the upper division of the central body complex, suggesting that neurons supplying this neuropil contain nitric oxide synthase and may generate nitric oxide upon activation. Exposure of dissected brains to nitric oxide and 3-(5'hydroxymethyl-2'-furyl)-1-benzyl indazole (YC-1) induced cGMP-associated immunoreactivity in both the upper and lower division. Therefore, both the morphological and pharmacological data presented in this study strongly suggest a contribution of the nitric oxide/cGMP signaling pathway to the central control of grasshopper sound production.

(2005) Health in the Arctic Circle.  
Webster, P  
(2005) **Air pollution and cancer: biomarker studies in human populations.**

Large cohort studies in the U.S. and in Europe suggest that air pollution may increase lung cancer risk. Biomarkers can be useful to understand the mechanisms and to characterize high-risk groups. Here we describe biomarkers of exposure, in particular DNA adducts as well as markers of early damage, including mutagenicity, other endpoints of genotoxicity and molecular biomarkers of cancer. Several studies found an association between external measures of exposure to air pollution and increased levels of DNA adducts, with an apparent levelling-off of the dose-response relationship. Also, numerous experimental studies in vitro and in vivo have provided unambiguous evidence for genotoxicity of air pollution. In addition, due to the organic extracts of particulate matter [especially various polycyclic aromatic hydrocarbon (PAH) compounds], particulate air pollution induces oxidative damage to DNA. The experimental work, combined with the data on frequent oxidative DNA damage in lymphocytes in people exposed to urban air pollution, suggests 8-oxo-dG as one of the important promutagenic lesions. Lung cancer develops through a series of progressive pathological changes occurring in the respiratory epithelium. Molecular alterations such as loss of heterozygosity, gene mutations and aberrant gene promoter methylation have emerged as potentially promising molecular biomarkers of lung carcinogenesis. Data from such studies relevant for emissions rich in PAHs are also summarized, although the exposure circumstances are not directly relevant to outdoor air pollution, in order to shed light on potential mechanisms of air pollution-related carcinogenesis.

(2005) **Structural basis for transcription inhibition by tagetitoxin.**

Tagetitoxin (Tgt) inhibits transcription by an unknown mechanism. A structure at a resolution of 2.4 A of the Thermus thermophilus RNA polymerase (RNAP)-Tgt complex revealed that the Tgt-binding site within the RNAP secondary channel overlaps that of the stringent control effector ppGpp, which partially protects RNAP from Tgt inhibition. Tgt binding is mediated exclusively through polar interactions with the beta and beta' residues whose substitutions confer resistance to Tgt in vitro. Importantly, a Tgt phosphate, together with two active site acidic residues, coordinates the third Mg(2+) ion, which is distinct from the two catalytic metal ions. We show that Tgt inhibits all RNAP catalytic reactions and propose a mechanism in which the Tgt-bound Mg(2+) ion has a key role in stabilization of an inactive transcription intermediate. Remodeling of the active site by metal ions could be a common theme in the regulation of catalysis by nucleic acid enzymes.
(2005) Concentrations of airborne culturable bacteria in 100 large US office buildings from the BASE study.
Tsai, FC and Macher, JM Journal/Indoor Air. 15 Suppl 9: 71-81.

This paper presents summary statistics of airborne culturable bacteria from the US Environmental Protection Agency Building Assessment Survey and Evaluation (BASE) study. Air samples were collected with single-stage, multiple-hole, agar impactors in 100 large office buildings in 1994-1998 to obtain normative data on indoor environmental quality. Bacterial concentrations were compared by incubation temperature, location, season, and climate zone. Forty-one percent of the samples were below the 2- or 5-min detection limits (18 or 7 CFU/m³, respectively) but less than 1% were overgrown. Mesophilic bacteria (30 degrees C) accounted for >95% of culturable bacteria, both indoors and outdoors. Average concentrations were higher outdoors, except for Gram-positive cocci, which were the only group that were significantly higher indoors (39 vs. 24 CFU/m³), and Gram-negative cocci, for which both concentrations were low and the difference was not significant. Outdoor concentrations of culturable bacteria were somewhat higher in winter (194 vs.165 CFU m³), and the two dominant outdoor groups were unknown bacteria and Gram-positive rods. Conversely, indoor concentrations were significantly higher in summer (116 vs. 87 CFU/m³), consisting primarily of unknown bacteria and Gram-positive cocci. Bacterial concentrations were within the ranges reported in previous studies of non-problem buildings, and the extreme aggregated indoor concentrations (e.g. the 90th percentile, 175 CFU/m³) of these 100 representative buildings may serve as upper bounds to develop interpretation guidelines for office environments and similar non-manufacturing workplaces in various climate zones. PRACTICAL IMPLICATIONS: The Building Assessment Survey and Evaluation (BASE) study was one of the most comprehensive investigations of indoor environmental quality in which a standardized protocol was used to measure bioaerosols in 100 typical US office buildings. The information on the indoor and outdoor concentrations of airborne bacteria in different climate zones during the heating and cooling seasons has expanded the baseline data available for interpretation of measurements from building investigations. With suggested refinements, the BASE protocol may serve as a guide for future studies of bioaerosol concentrations, building characteristics, and occupant perceptions of the indoor environment.

According to the chemical genetic approach, small molecules that bind directly to proteins are used to analyze protein function, thereby enabling the elucidation of complex mechanisms in mammal cells. Thus, it is very important to identify the molecular targets of compounds that induce a unique phenotype in a target cell. Phoslactomycin A (PLMA) is known to be a potent inhibitor of protein Ser/Thr phosphatase 2A (PP2A); however, the inhibitory mechanism of PP2A by PLMA has not yet been elucidated. Here, we demonstrated that PLMA directly binds to the PP2A catalytic subunit (PP2Ac) in cells by using biotinylated PLMA, and the PLMA-binding site was identified as the Cys-269 residue of PP2Ac. Moreover, we revealed that the Cys-269 contributes to the potent inhibition of PP2Ac activity by PLMA. These results suggest that PLMA is a PP2A-selective inhibitor and is therefore expected to be useful for future investigation of PP2A function in cells.


(2005) A smelly situation!

(2005) mGlu and NMDA receptor contributions to capsaicin-induced thermal and mechanical hypersensitivity.

Metabotropic glutamate (mGlu) receptors are G protein-coupled receptors, some of which are localized in the spinal cord dorsal horn, and are involved with pain perception. The anti-nociceptive effects of intrathecal (i.t.) pretreatment with various mGlu receptor agonists and antagonists were assessed in Long Evans rats with mechanical and thermal hypersensitivity after sub-dermal injection of capsaicin in the hindpaw. Selective group II (aminopyrrolidine-2R,4R-dicarboxylate, APDC) and group III (l-2-amino-4-phosphonobutyrate, L-AP4) agonists, as well as selective mGlu(1) (1-aminoindan-1,5(R,S)-dicarboxylic acid, AIDA) and mGlu(5) (2-methyl-6-(phenylethynyl)-pyridine, MPEP) receptor subtype antagonists were compared with that of an NMDA receptor antagonist (dizocilpine maleate, MK-801). The rats were observed for signs of capsaicin-induced mechanical and thermal hypersensitivity 15 min after capsaicin injection, and 20 min following i.t. drug
administration. Results indicate there was a dose-dependent reduction in capsaicin-induced mechanical hypersensitivity for all mGlu receptor agents; with maximal increases in mechanical thresholds that were 7-fold for AIDA and APDC, 7.5-fold for L-AP4 and 5.6-fold for MPEP. However, only a weak reduction (often non-significant) in thermal hypersensitivity was observed with each of the mGlu receptor drugs; thermal latencies were maximally increased by 125% (AIDA), 0% (MPEP), 8% APDC and 205% (L-AP4). By contrast, the highest dose of MK-801 was able to significantly reduce both mechanical (maximal 6.67-fold increase in threshold) and thermal (maximal 3-fold increase in latencies) hyperalgesia. We conclude that mGlu receptors contribute to the development of mechanical allodynia, but not thermal hyperalgesia, following capsaicin injury; while iGluRs may contribute to both thermal and mechanical hypersensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15721164


The human health risk for chronic illnesses involving multiple body systems following inhalation exposure to the indoor environments of water-damaged buildings (WDBs) has remained poorly characterized and the subject of intense controversy. The current study assessed the hypothesis that exposure to the indoor environments of WDBs with visible microbial colonization was associated with illness. The study used a cross-sectional design with assessments at five time points, and the interventions of cholestyramine (CSM) therapy, exposure avoidance following therapy, and reexposure to the buildings after illness resolution. The methodological approach included oral administration of questionnaires, medical examinations, laboratory analyses, pulmonary function testing, and measurements of visual function. Of the 21 study volunteers, 19 completed assessment at each of the five time points. Data at Time Point 1 indicated multiple symptoms involving at least four organ systems in all study participants, a restrictive respiratory condition in four participants, and abnormally low visual contrast sensitivity (VCS) in 18 participants. Serum leptin levels were abnormally high and alpha melanocyte stimulating hormone (MSH) levels were abnormally low. Assessments at Time Point 2, following 2 weeks of CSM therapy, indicated a highly significant improvement in health status. Improvement was maintained at Time Point 3, which followed exposure avoidance without therapy. Reexposure to the WDBs resulted in illness reacquisition in all participants within 1 to 7 days. Following another round of CSM therapy, assessments at Time Point 5 indicated a highly significant improvement in health status. The group-mean number of symptoms decreased from 14.9+/−0.8 S.E.M. at Time Point 1 to 1.2+/−0.3 S.E.M., and the VCS deficit of approximately 50% at Time Point 1 was fully resolved. Leptin and MSH levels showed statistically significant improvement. The results indicated that CSM was an effective therapeutic
agent, that VCS was a sensitive and specific indicator of neurologic function, and that illness involved systemic and hypothalamic processes. Although the results supported the general hypothesis that illness was associated with exposure to the WDBs, this conclusion was tempered by several study limitations. Exposure to specific agents was not demonstrated, study participants were not randomly selected, and double-blinding procedures were not used. Additional human and animal studies are needed to confirm this conclusion, investigate the role of complex mixtures of bacteria, fungi, mycotoxins, endotoxins, and antigens in illness causation, and characterize modes of action. Such data will improve the assessment of human health risk from chronic exposure to WDBs.

(2005) An antisense oligonucleotide to the N-methyl-D-aspartate (NMDA) subunit NMDAR1 attenuates NMDA-induced nociception, hyperalgesia, and morphine tolerance.

We determined whether the i.t. administration of an 18-mer phosphodiester antisense oligodeoxynucleotide (ODN) that reduces the expression of the rat NMDAR1 subunit of the N-methyl-d-aspartate (NMDA) receptor would affect nociceptive behaviors and prevent the development of morphine tolerance. Rats received 5 microl of i.t. saline, 30 nM antisense, or mismatch ODN twice a day for 5 days (NMDA-induced nociception, NMDA-induced thermal hyperalgesia, NR1 mRNA, and ligand binding studies) or for 3 days (formalin study). For the tolerance study, 5 days of ODNs or saline were followed by 3 days of concurrent administration of ODNs or saline (twice a day) and i.t. morphine (three times a day). Antisense, but not mismatch, results in the reduction of formalin phase 2 flinching by 50%, the spinal cord dorsal horn levels of NMDAR1 mRNA by 30%, and ligand binding by 50%. The i.t. ED(50) for NMDA-induced nociceptive behaviors is doubled, and thermal hyperalgesia is blocked by antisense treatment. The effects of antisense on NMDA-induced nociception and thermal hyperalgesia are completely reversed by discontinuing antisense. The coadministration of antisense with increasing doses of i.t. morphine for 3 days attenuates the development of morphine tolerance. These results demonstrate that an in vivo antisense targeting of the NMDAR1 subunit results in antihyperalgesic effects and a partial blockade of spinal morphine tolerance. They provide additional support for the critical role of the NMDA receptor in these forms of spinal nociception and in the development of morphine tolerance and suggest the potential therapeutic utility of this approach.

Children’s exposure to volatile organic compounds as determined by longitudinal measurements in blood.

Blood concentrations of 11 volatile organic compounds (VOCs) were measured up to four times over 2 years in a probability sample of more than 150 children from two poor, minority neighborhoods in Minneapolis, Minnesota. Blood levels of benzene, carbon tetrachloride, trichloroethylene, and m-/p-xylene were comparable with those measured in selected adults from the Third National Health and Nutrition Examination Survey (NHANES III), whereas concentrations of ethylbenzene, tetrachloroethylene, toluene, 1,1,1-trichloroethane, and o-xylene were two or more times lower in the children. Blood levels of styrene were more than twice as high, and for about 10% of the children 1,4-dichlorobenzene levels were greater than or equal to 10 times higher compared with NHANES III subjects. We observed strong statistical associations between numerous pairwise combinations of individual VOCs in blood (e.g., benzene and m-/p-xylene, m-/p-xylene and o-xylene, 1,1,1-trichloroethane and m-/p-xylene, and 1,1,1-trichloroethane and trichloroethylene). Between-child variability was higher than within-child variability for 1,4-dichlorobenzene and tetrachloroethylene. Between- and within-child variability were approximately the same for ethylbenzene and 1,1,1-trichloroethane, and between-child was lower than within-child variability for the other seven compounds. Two-day, integrated personal air measurements explained almost 79% of the variance in blood levels for 1,4-dichlorobenzene and approximately 20% for tetrachloroethylene, toluene, m-/p-xylene, and o-xylene. Personal air measurements explained much less of the variance (between 0.5 and 8%) for trichloroethylene, styrene, benzene, and ethylbenzene. We observed no significant statistical associations between total urinary cotinine (a biomarker for exposure to environmental tobacco smoke) and blood VOC concentrations. For siblings living in the same household, we found strong statistical associations between measured blood VOC concentrations.

Chlamydophila pneumoniae antibodies in office workers with and without inflammatory rheumatic diseases in a moisture-damaged building.

Environmental illness in athletes.
This article examines environmental illness in athletes. Causes, symptoms, and treatment of heat-related illness, cold-related illness, and altitude-related illness are discussed.

---


http://www.sciencedirect.com/science/article/B6T4S-4FMRB8W-4/2 2c976359def9737a0a848267f7b9f6f6

---


The increasing use of organophosphorus insecticides in agriculture and inside homes and schools, as well as its widespread existence in the environment, poses a potential health hazard. As the use of these agents increases, acute and chronic exposure has become more common. As with other organophosphates, chlorpyrifos kills insects and other animals, including human beings, because of its toxicity to the nervous system. Exposure of pregnant women to organophosphates is an important clinical entity because of its effects on two organisms--mother and fetus. There are few reports about fetal toxicity of organophosphates in the literature because of the relatively few cases reported. In this paper we report a case of intoxication from chlorpyrifos, an organophosphorus compound, during pregnancy, causing fetal death.

---


We studied the change in the hypothalamo-pituitary-adrenal gland (HPA) axis upon adding prior toluene inhalation to our previous formaldehyde inhalation experiments to determine whether short term exposure to relatively high levels of toluene triggers multiple chemical sensitivity (MCS). Data come from immunocytochemical, morphometrical and RT-PCR measurements. Four groups of adult female mice were
exposed to differing concentrations (0, 80, 400, and 2,000 ppb) of formaldehyde for 16 hr/day, 5 days/week for twelve weeks, after the mice were exposed intranasally to 500 ppm toluene per mouse for 6 hr/day, for 3 days. We found that the number of corticotropin releasing hormone (CRH)-immunoreactive (ir) neurons was up-regulated according to the amount of formaldehyde as well as inhalation of formaldehyde alone in our previous experiment. The proportion of adrenocorticotropic hormone (ACTH)-ir cells increased according to the formaldehyde concentration, though there was no significant difference between the 400 and 2,000 groups. The number of ACTH-ir cells was higher in the 400 group than in the other groups (0, 80, and 2,000). Expression of ACTH-mRNA was also up-regulated according to the quantity of formaldehyde. The sinusoid in the anterior pituitary showed more dilatation in the 400 and 2,000 groups than in the control group, especially in the 2,000 group. We propose that exposure to toluene prior to inhalation of formaldehyde has no effect on the HPA axis and as a trigger of MCS, although greater sinusoid dilatation was found in the anterior pituitary gland at higher concentrations of formaldehyde.


OBJECTIVE: This study was conducted to confirm the definition of multiple chemical sensitivity (MCS) in actual life: that multiple symptoms are provoked in multiple organs by exposure to, and ameliorated by avoidance of, multiple chemicals at low levels. We used the Ecological Momentary Assessment to monitor everyday symptoms and the active sampling and passive sampling methods to measure environmental chemical exposure. METHODS: Eighteen patients with MCS, diagnosed according to the 1999 consensus criteria, and 12 healthy controls participated in this study. Fourteen patients and 12 controls underwent 1-week measurement of physical and psychologic symptoms and of the levels of exposure to various chemicals. Linear mixed models were used to test the hypotheses regarding the symptom profile of MCS patients. RESULTS: Some causative chemicals were detected in 11 of 14 MCS patients. Two other patients did not report any hypersensitivity episodes, whereas passive sampling showed far less exposure to chemicals than control subjects. Another subject reported episodic symptoms but was excluded from the following analyses because no possible chemical was detected. Eleven of the 17 physical symptoms and all four mood subscales examined were significantly aggravated in the interview based on "patient-initiated symptom prompts." On the other hand, there were no differences in physical symptoms or mood subscales between MCS patients and control subjects in the interview based on "random prompts." CONCLUSIONS: MCS patients do not have
either somatic or psychologic symptoms under chemical-free conditions, and symptoms may be provoked only when exposed to chemicals.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15784800

(2005) Associations among sick building syndrome, psychosocial factors, and personality traits.

A mailed questionnaire assessed personality traits of a cohort of 194 subjects followed from 1988 to 1998 measured by the Karolinska Scales of Personality and Sense of Coherence Scale, medical symptoms, and 3 VAS scales on Perceived Psychosocial Work Satisfaction. Subjects initially worked in 19 Swedish buildings with indoor environmental problems. There was a relatively high correlation between SOC scores and KSP scale scores (R^2=.54 in men and .55 in women), and there was a sex-KSP interaction on the association between the two sets of scores. An increase of symptom score (SC difference) during the follow-up period was associated with higher psychic anxiety (p<.01 for both men and women), higher socialization (p<.01 for men) and lower inhibition of aggression (p<.05 for men), in stepwise multiple linear regression models. Moreover, the perceived satisfaction scores were associated with personality scale scores, and subjects with a higher sense of coherence reported higher work satisfaction (p<.01). In conclusion, personality aspects seem to play an important role for reporting medical symptoms, work satisfaction, work stress, and climate of cooperation at work, but different personality aspects could be important in men and women.

(2005) Structural and enzymatic parameters that determine alkyl dehydrogenation/hydroxylation of capsaicinoids by cytochrome p450 enzymes.
Reilly, CA and Yost, GS Journal/Drug Metab Dispos. 33: 530-6.

Previous studies on the metabolism of capsaicinoids, natural products isolated from chili peppers, demonstrated the production of unique macrocyclic, alkyl dehydrogenated, omega-, and omega-1-hydroxylated products. This study investigated the structural and enzymatic parameters that direct selective alkyl dehydrogenation and hydroxylation of capsaicinoids, using a variety of structurally related capsaicinoid analogs and cytochrome P450 (P450) enzymes. CYP2C9 preferentially catalyzed alkyl dehydrogenation, whereas CYP2E1 and 3A4 catalyzed omega- and omega-1-hydroxylation, respectively. Analysis of incubations containing various P450s and structural variants of capsaicin by liquid chromatography-tandem mass spectrometry demonstrated similarities in the rate of capsaicinoid metabolism, but
marked differences in the metabolite profiles. Production of macrocyclic and omega-1-hydroxylated metabolites from the various capsaicinoids was dependent on the structure of the alkyl terminus and P450 enzyme. A tertiary carbon at the omega-1 position, coupled to an adjacent unsaturated bond at the omega-2,3 position, enhanced the formation of the macrocyclic and dehydrogenated metabolites and were requisite structural features for omega-1-hydroxylated product formation. Conversely, substrates lacking these structural features were efficiently oxidized to the omega-hydroxylated metabolite. These data were consistent with our hypothesis that metabolism of the alkyl portion of capsaicinoids was governed, in part, by the stability and propensity to form an intermediate radical and a carbocation, and a direct interaction between the alkyl terminus and the heme of many P450 enzymes. These results provided valuable insights into potential mechanisms by which P450s metabolize capsaicinoids and highlight critical chemical features that may also govern the metabolism of structurally related compounds including fatty acids, monoterpenes, and isoprenoids.


Increasingly greater evidence exists as to the influence which diet and exposure to low doses of toxic substances during the prenatal stage and early childhood has on health and well-being throughout later stages of life. Following the WHO and European Union recommendations in 2003, the Cooperative Environment and Childhood Research Network was set up to study the effects of the environment and diet on fetal and early childhood development in different geographical areas of Spain. This Network integrates different multidisciplinary research groups and is comprised of six cohorts--three pre-existing and three de novo--which will follow up prospectively 3,600 pregnant women, from the start of pregnancy up to age 4-6 years of the child. This network's general objectives are: (1) To describe individual exposure to toxic substances in the environment during gestation and early childhood. (2) To evaluate the effects of exposure to toxic substances and diet on fetal and early childhood development. (3) To evaluate the interaction among toxic, nutritional and genetic factors in fetal and early childhood development. The follow-up is done every three months during gestation, at birth, at age one and up to age four or six. The information is gathered by means of questionnaires, clinical data, physical examinations, echographs, biomarkers and environmental measurements. The general characteristics of the network and a description of the current situation of each one of the cohorts are provided in this study.
BACKGROUND: Auditory processing disorders (APD) result from dysfunctions in processes dedicated to audition. They effect the processing of information in the auditory modality. Besides several audiometric procedures, the suggestion has been made to use a newly developed questionnaire to assess APD; however, data on the reliability and validity of this psychometric tool are still lacking. METHODS: In a retrospective analysis, questionnaire data from 483 children referred to us because of suspected APD were examined and a factorial analysis was performed. RESULTS: Only one factor could be extracted. However, this did not explain much of the variance. DISCUSSION: According to our results, APD can be assumed to be a one dimensional construct. In addition, noise hypersensitivity may be separable from other APD complaints.

OBJECTIVE: To review the nontoxic harmful effects that poor indoor air quality caused by fungi can have on health. DATA SOURCES: We searched PubMed for publications related to the various topics discussed in this review, and we relied on our knowledge of the field. STUDY SELECTION: Where more than one publication was relevant, we attempted to identify a consensus of the reports and cited the most relevant articles. Priority was given to randomized controlled trials and expert reports when available, although much of the information herein relates to laboratory research. RESULTS: Actively growing fungal colonies can release volatile substances that have an unpleasant smell, leading to psychological responses in the occupants such as fatigue and nausea. Symptoms that are likely caused by indoor fungi include respiratory complaints that involve the nose and lungs, eye symptoms, and mucous membrane irritation. These adverse effects can occur by a variety of mechanisms, including IgE-mediated hypersensitivity, fungal infection, irritant reaction to spores or fungal metabolites, and possibly toxic reaction to mycotoxins. CONCLUSIONS: Reduced fungal exposure can reasonably be expected to improve health. Removal of moisture from the indoors and proper maintenance of air filters can aid in prevention and elimination of fungi from the home environment. Small areas of present contamination can be cleaned with a dilute bleach solution, which kills viable colonies and removes their mycelia. If fungal contamination is not addressed early, substantial damage can occur, requiring professional remediation. Above all, the individual should not panic at the first sight of fungi growing in the home. Regular inspection and cleaning can prevent many fungus-related problems.

INTRODUCTION: In response to the 11 September 2001 terrorist attacks on the World Trade Center (WTC), the United States Public Health Service (USPHS) deployed Disaster Medical Assistance Teams (DMATs) and the Commissioned Corps to provide on-site, primary medical care to anyone who presented. Patients included rescue and recovery workers, other responders, and some members of the general public.

OBJECTIVE: A descriptive analysis of WTC-USPHS patient records was conducted in order to better understand the short-term impact of the WTC site on the safety and health of individuals who were at or near the site from 14 September-20 November 2001.

METHODS: The Patient Treatment Record forms that were completed for each patient visit to these USPHS stations over the 10-week deployment period were reviewed. Results: Patient visits numbered 9,349, with visits peaking during Week 2 (21-27 September). More than one-quarter of the visits were due to traumatic injuries not including eye injuries (n = 2,716; 29%). Respiratory problems comprised more than one-fifth of the complaints (n = 2,011; 22%). Eye problems were the third most frequent complaint (n = 1,120; 12%). With respect to the triage class, the majority of visits fell into the lowest category of severity (n = 6,237; 67%).

CONCLUSION: USPHS visits probably were skewed to milder complaints when compared to analyses of employer medical department reports or hospital cases; however, given the close proximity of the USPHS stations to the damage, analysis of the USPHS forms provides a more complete picture of the safety and health impact on those who were at or near the WTC site.

(2005) A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures.

Inner-city minority populations are high-risk groups for adverse birth outcomes and also more likely to be exposed to environmental contaminants, including environmental tobacco smoke (ETS), benzo[a]pyrene B[a]P, other ambient polycyclic aromatic hydrocarbons (global PAHs), and residential pesticides. The Columbia Center for Children's Environmental Health (CCCEH) is conducting a prospective cohort study of 700 northern Manhattan pregnant women and newborns to examine the effects of prenatal exposure to these common toxicants on fetal growth, early neurodevelopment,
and respiratory health. This paper summarizes results of three published studies demonstrating the effects of prenatal ETS, PAH, and pesticides on birth outcomes and or neurocognitive development [Perera FP, Rauh V, Whyatt RM, Tsai WY, Bernert JT, Tu YH, et al. Molecular evidence of an interaction between prenatal environment exposures on birth outcomes in a multiethnic population. Environ Health Perspect 2004;12:630-62; Rauh VA, Whyatt RM, Garfinkel R, Andrews H, Hoepner L, Reyes A, et al. Developmental effects of exposure to environmental tobacco smoke and material hardship among inner-city children. Neurotoxicol Teratol 2004;26:373-85; Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, et al. Prenatal insecticide exposures, birth weight and length among an urban minority cohort. Environ Health Perspect, in press]. To evaluate the effects of prenatal exposure to ETS, PAHs, and pesticides, researchers analyzed questionnaire data, cord blood plasma (including biomarkers of ETS and pesticide exposure), and B[a]P-DNA adducts (a molecular dosimeter of PAHs). Self-reported ETS was associated with decreased head circumference (P = 0.04), and there was a significant interaction between ETS and adducts such that combined exposure had a significant multiplicative effect on birth weight (P = 0.04) and head circumference (P = 0.01) after adjusting for confounders. A second analysis examined the neurotoxic effects of prenatal ETS exposure and postpartum material hardship (unmet basic needs in the areas of food, housing, and clothing) on 2-year cognitive development. Both exposures depressed cognitive development (P < 0.05), and there was a significant interaction such that children with exposure to both ETS and material hardship exhibited the greatest cognitive deficit (7.1 points). A third analysis found that cord chlorpyrifos, and a combined measure of cord chlorpyrifos, diazinon, and propoxur-metabolite, were inversely associated with birth weight and/or length (P < 0.05). These results underscore the importance of policies that reduce exposure to ETS, air pollution, and pesticides with potentially adverse effects on fetal growth and child neurodevelopment.


http://www.sciencedirect.com/science/article/B6T4S-4FDMYM5-6/2a002066085ab0776f6c1f015d306e25f

(2005) [Multiple chemical sensitivity, a disease commonly missed].
query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16137487


1. The aim of this paper was to determine the different signalling cascades involved in contraction of the rat urinary bladder detrusor muscle mediated via muscarinic acetylcholine receptors (muscarinic AChR). Contractile responses, phosphoinositides (IPs) accumulation, nitric oxide synthase (NOS) activity and cyclic GMP (cGMP) production were measured to determine the reactions associated with the effect of cholinergic agonist carbachol. The specific muscarinic AChR subtype antagonists and different inhibitors of the enzymatic pathways involved in muscarinic receptor-dependent activation of NOS and cGMP were tested. 2. Carbachol stimulation of M(3) and M(4) muscarinic AChR increased contractility, IPs accumulation, NOS activity and cGMP production. All of these effects were selectively blunted by 4-DAMP and tropicamide, M(3) and M(4) antagonists respectively. 3. The inhibitors of phospholipase C (PLC), calcium/calmodulin (CaM), neuronal NOS (nNOS) and soluble guanylate cyclase, but not of protein kinase C and endothelial NOS (eNOS), inhibited the carbachol action on detrusor contractility. These inhibitors also attenuated the muscarinic receptor-dependent increase in cGMP and activation of NOS. 4. In addition, sodium nitroprusside and 8-bromo-cGMP, induced negative relaxant effect. 5. The results obtained suggest that carbachol activation of M(3) and M(4) muscarinic AChRs, exerts a contractile effect on rat detrusor that is accompanied by an increased production of cGMP and nNOS activity. The mechanism appears to occur secondarily to stimulation of IPs turnover via PLC activation. This in turn, triggers cascade reactions involving CaM, leading to activation of nNOS and soluble guanylate cyclase. They, in turn, exert a modulator inhibitory cGMP-mediated mechanism limiting the effect of muscarinic AChR stimulation of the bladder.

(2005) [Topical problems of methodology for assessing a risk and its role in the improvement of a sociohygienic monitoring system].
Onishchenko, GG Journal/Gig Sanit. 3-6.
(2005) The rapid monitoring of ivermectin treatment: will school-based surveys provide the answer?

The data on ivermectin-treatment coverage recorded in household surveys sometimes conflict with those recorded in school-based surveys or in the relevant treatment registers maintained by community-directed distributors (CDD). An attempt has now been made, in two sites in Nigeria (Enugu and Kaduna states) and one in Sudan (Abu Hamad province), to determine how well these three sets of data are correlated (and to explore the effectiveness of several alternative channels for the delivery of treatment-monitoring forms to schools). Using a cross-sectional approach, data were collected from primary schools, households and treatment registers. Calculation of Pearson’s correlation coefficients (r) indicated that, overall, the data from the household surveys were very similar to those collected using the school-based strategy (r=0.66; P<0.0001) or from the treatment registers of the CDD (r=0.86; P<0.0001). The information recorded in the CDD registers also closely matched that recorded in the school-based surveys (r=0.67; P<0.0001). These encouraging results for the pooled data masked some inter-site differences. The correlation between the household-survey and treatment-register data was, for example, only good in Enugu (r=0.89; P<0.001), and was too weak to be statistically significant in Abu Hamad or Kaduna. Although the results of the school-based survey in Kaduna also did not closely correlate with those of the corresponding household survey (r=0.10; P=0.71), the household survey at this site was probably not conducted as well as those at the two other sites. In general, it appears that school-based surveys are an effective means of monitoring community coverage with ivermectin, rapidly, accurately and at relatively low cost. It is therefore recommended that school-based methods of monitoring of coverage are adopted by programme managers.


Anormal chemosensory perception has been identified as a possible mechanism underlying odor intolerance, but research in this domain has yet been rather limited. The main objective of the present study was to investigate total perceived intensity, unpleasantness, sensory irritation, and cortical activity assessed with chemosensory event-related potentials (ERPs) for three concentrations of pyridine ranging from predominantly olfactory to trigeminal in activation. Results from 19 individuals with self-reported chemical hypersensitivity and 19 controls with self-reported normal chemical sensitivity show that the hypersensitive group, compared to controls, rated the pyridine stimuli to be more intense and unpleasant, and that these group differences increased with pyridine concentration. Sensory irritation was also the perceptual dimension found to correlate strongest with score on the chemical sensitivity scale. However, no group differences were found in ERP amplitudes or latencies. These findings suggest that self-reported chemical hypersensitivity (1) can be associated with anormal chemosensory perception, (2) may be more closely related to trigeminal function than to olfaction, and (3) has a neural basis at a higher cortical level than that captured by chemosensory ERPs.

Nordin, S, Broman, DA and Wulff, M Journal/Physiol Behav. 84: 175-9.

Previous findings indicating that pregnant women experience a shift in odor sensitivity and hedonics raise the question of whether these changes evoke adverse reactions to odorous and pungent environmental substances in daily activities, to a larger extent in pregnant than in nonpregnant women. Forty-four women in pregnancy weeks 21-23 and 44 nonpregnant women were therefore compared with respect to affective reactions to and behavioral disruptions by odorous/pungent daily environments by means of the questionnaire-based, 21-item Chemical Sensitivity Scale (CSS). This scale refers to neurasthenic and sensory/somatic symptoms and includes the 11 items of the Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SHR). This latter scale refers predominantly to sensory/somatic symptoms. To investigate whether there is a general environmental hypersensitivity during pregnancy, the Noise Sensitivity Scale (NSS) was used that is analogous to the CSS (including 11 NSS items corresponding to those of the CSS-SHR; "NSS-SHR"). Results show that the two groups were similar with respect to scores on both the CSS and NSS, whereas the pregnant women had higher scores than the nonpregnant women on the CSS-SHR, but not on the "NSS-SHR". These results suggest that pregnant women to a larger extent than nonpregnant women manifest an odor intolerance that affects their daily activities, with predominantly sensory/somatic symptoms, which appears not to be due to a general environmental hypersensitivity. This behavior may have embryo- and maternal-protective functions.
The adverse health effects caused by indoor air pollution are termed "sick building syndrome". We report such a patient whose symptoms appeared in the workplace. A 36-year-old female office worker developed nausea and headache during working hours in a refurbished office. After eight months of seeking help at other clinics or hospitals without improvement, she was referred to our hospital. At that time she reacted to the smells of various chemicals outside of the office building. Biochemical findings were all within normal ranges. Specific IgE antibody to cedar pollen was positive and the ratio of TH1/TH2 was 4.5. In the Eye Tracking Test (ETT), vertical eye movement was saccadic. Her anxiety level was very high according to the State-Trait Anxiety Inventory (STAI) questionnaire. Subjective symptoms, ETT findings and anxiety levels on STAI gradually improved during two years of follow-up. One year after the onset of her illness, the formaldehyde concentrations in the building air ranged from 0.017-0.053 ppm. Even though relatively low, chemical exposure from building materials such as formaldehyde induced a range of symptoms. Also, lack of recognition by superiors and doctors that sick building syndrome might have been the source of her illness coupled with her high state of anxiety may have exacerbated her symptoms and led to the onset of multiple chemical sensitivity. Thus psychosocial factors may contribute to sick building syndrome in the workplace.
(2005) Proinflammatory activation of macrophages by basic calcium phosphate crystals via protein kinase C and MAP kinase pathways: a vicious cycle of inflammation and arterial calcification?

Basic calcium phosphate (BCP) crystal deposition underlies the development of arterial calcification. Inflammatory macrophages colocalize with BCP deposits in developing atherosclerotic lesions and in vitro can promote calcification through the release of TNF alpha. Here we have investigated whether BCP crystals can elicit a proinflammatory response from monocyte-macrophages. BCP microcrystals were internalized into vacuoles of human monocyte-derived macrophages in vitro. This was associated with secretion of proinflammatory cytokines (TNFalpha, IL-1beta and IL-8) capable of activating cultured endothelial cells and promoting capture of flowing leukocytes under shear flow. Critical roles for PKC, ERK1/2, JNK, but not p38 intracellular signaling pathways were identified in the secretion of TNF alpha, with activation of ERK1/2 but not JNK being dependent on upstream activation of PKC. Using confocal microscopy and adenoviral transfection approaches, we determined a specific role for the PKC-alpha isozyme. The response of macrophages to BCP crystals suggests that pathological calcification is not merely a passive consequence of chronic inflammatory disease but may lead to a positive feed-back loop of calcification and inflammation driving disease progression.

(2005) Re: "do we need genomic research for the prevention of common diseases with environmental causes?"

Moen, BE Journal/Psychoneuroendocrinology. 30: 1039-42.

Large numbers of studies of multiple chemical sensitivity (MCS) have been performed, particularly in clinical settings. Epidemiological studies in the area are scarce, and this is also the case for cacosmia. Very few have studied the work place conditions for the MCS patient at the onset of symptoms, neither the chemical exposure nor psychosocial conditions. This type of research is of interest to understand the development of the syndrome and to suggest preventive actions in the work places.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15964144
Patients complaining of upper and lower airway symptoms caused by scents and chemicals have previously been shown to have increased cough sensitivity to inhaled capsaicin, but the precise mechanisms behind this reaction are unknown. Hypothesizing that a neurochemical alteration related to sensory hyperreactivity (SHR) of the airway mucosa occurs, we measured levels of nerve growth factor (NGF) in nasal lavage fluid (NAL) before and after capsaicin inhalation provocations and related the capsaicin cough sensitivity to the NGF levels. Thirteen patients with SHR and 14 control subjects were provoked with capsaicin inhalation at three different doses. We measured NGF in NAL before and after provocation and recorded cough and capsaicin-induced symptoms. All subjects demonstrated a dose-dependent cough response to capsaicin inhalation, with a more pronounced effect in patients than in controls. Basal levels of NGF were significantly lower in the patient group than in the control subjects (p < 0.01). After capsaicin provocation, the patients showed a significant increase in NGF (p < 0.01), which was related to capsaicin cough sensitivity. The findings demonstrate that, in patients with airway symptoms induced by scents and chemicals, SHR is real and measurable, demonstrating a pathophysiology in the airways of these patients compared to healthy subjects.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16002371

(2005) [Children's health status under ambient air pollution].
Mikhailova, EV Journal/Gig Sanit. 49-51.

The present study was undertaken to comparatively assess the health status of organized preschool children living under varying man-made pollution. Pilot and control districts differing in the level of man-made ambient air pollution were identified. The morbidity and physical development of children in these areas were studied. Fewer healthy children and more ailing children, more children with dysfunctions of organs and systems, and more sick children, as well as more physically retarded children were detected in the higher man-made loaded district of an industrial town.
(2005) Molds in floor dust and building-related symptoms among adolescent school children: a problem for boys only?
Meyer, HW, Wurtz, H, Suadicani, P, Valbjorn, O, Sigsgaard, T and Gyntelberg, F

In this stratified cross-sectional study in eight 'wet' and seven 'dry' schools, 1024 adolescent school children reported potentially building-related symptoms (BRS) in self-administered questionnaires. From their classrooms dust samples were collected from floors, ventilation ducts, and air; settled dust was collected in cardboard boxes over a period of 5 months. Measurements of temperature, relative humidity and CO2 were performed. BRS were strongly associated with personal factors like recent airway infections, hay fever, asthma and psycho-social work load, but also to molds in floor dust and presence of mechanical ventilation. The association between molds in floor dust and BRS has in stratified analyses shown a strong association among adolescent school boys, and no association among adolescent school girls using multivariable analyses controlling for relevant confounders. In contrast to the menstruating school girls, the symptoms among the small group of not yet menstruating girls were associated with the levels of molds in floor dust. Their symptom prevalences were very similar to those of the boys. This finding makes us suggest a new hypothesis: The higher endogenous estrogen levels of sexually matured adolescent females seems to protect them from the effects of molds in dust, despite their overall higher symptom prevalence. PRACTICAL IMPLICATIONS: In this cross-sectional epidemiological study of adolescent school children we found independent significant positive associations between building-related symptoms and viable molds in floor dust in boys and non-menstruating girls. In contrast, no such associations were seen among menstruating girls. The identification of these two susceptible groups adds further support the relevance of minimizing sources of dust and mold exposure.


The objective was to develop an experimental setup for human exposure to mold spores, and to study the clinical effect of this exposure in sensitive subjects who had previously experienced potentially building-related symptoms (BRS) at work. From three water-damaged schools eight employees with a positive histamine release test to Penicillium chrysogenum were exposed double- blinded to either placebo, approximately 600,000 spores/m3 air of P. chrysogenum or approximately 350,000 spores/m3 of Trichoderma harzianum for 6 min on three separate days. A statistically significant rise in symptoms from mucous membranes appeared from the 9-graded symptom scale after exposure to T. harzianum or placebo. Dichotomizing the data, whether the participants experienced at least a two-step rise on the symptom scale or
not, gave borderline increase in mucous membrane symptoms after exposure to P. chrysogenum. In conclusion this is, to our knowledge, the first study to successfully conduct a human exposure to a highly controlled dose of fungal material aerosolized directly from wet building materials. This short-term exposure to high concentrations of two different molds induced no more reactions than exposure to placebo in eight sensitive school employees. However, a statistical type II error cannot be excluded because of the small sample size. PRACTICAL IMPLICATIONS: In this double blind, placebo controlled study of mold exposure changes in symptoms, objective measurements and blood samples were small and mostly non-significant, and at the same level as after placebo exposure. The developed exposure system based on the Particle-Field and Laboratory Emission Cell (P-FLEC) makes it possible to deliver a precise and highly controlled dose of mold spores from water-damaged building materials, imitating realistic field exposure conditions. The present experiment is too small to rule out an effect of mold exposure; long-term experimental exposure studies on larger number of subjects are needed.

Meklin, T, Potus, T, Pekkanen, J, Hyvarinen, A, Hirvonen, MR and Nevalainen, A

Effects of renovation on symptom prevalence and microbial status were studied in two moisture-damaged schools and in two non-damaged schools with longitudinal cross-sectional surveys before and after repairs. Over 1300 schoolchildren aged 6-17 returned questionnaires before and after repairs. After full renovation in one of the damaged schools, elevated concentrations and increased frequencies of indoor air fungi normalized and a significant decrease in the prevalence of 10 symptoms of 12 studied was observed among schoolchildren. No change in microbial conditions was seen after partial repairs in the other damaged school, and only slight improvement was observed in symptom prevalence. The change in the prevalence of symptoms in the reference schools was minor. The results suggest that increased symptom prevalence among schoolchildren in moisture-damaged schools can be managed with proper repair of the moisture damage. PRACTICAL IMPLICATIONS: This longitudinal intervention study showed the positive effects of the moisture and mold damage repairs of a school building on children’s health. The success necessitates however, a thorough renovation including appropriate ventilation. Monitoring of airborne viable microbes revealed the damage status of the building and thus could be used as a tool in evaluating the quality of repairs.

Recognition of temperature is a critical element of sensory perception and allows us to evaluate both our external and internal environments. In vertebrates, the somatosensory system can discriminate discrete changes in ambient temperature, which activate nerve endings of primary afferent fibers. These thermosensitive nerves can be further segregated into those that detect either innocuous or noxious (painful) temperatures; the latter neurons being nociceptors. We now know that thermosensitive afferents express ion channels of the transient receptor potential (TRP) family that respond at distinct temperature thresholds, thus establishing the molecular basis for thermosensation. Much is known of those channels mediating the perception of noxious heat; however, those proposed to be involved in cool to noxious cold sensation, TRPM8 and TRPA1, have only recently been described. The former channel is a receptor for menthol, and links the sensations provided by this and other cooling compounds to temperature perception. While TRPM8 almost certainly performs a critical role in cold signaling, its part in nociception is still at issue. The latter channel, TRPA1, is activated by the pungent ingredients in mustard and cinnamon, but has also been postulated to mediate our perception of noxious cold temperatures. However, a number of conflicting reports have suggested that the role of this channel in cold sensation needs to be confirmed. Thus, the molecular logic for the perception of cold-evoked pain remains enigmatic. This review is intended to summarize our current understanding of these cold thermoreceptors, as well as address the current controversy regarding TRPA1 and cold signaling.


Male Wistar rats were trained in an eight-arm radial maze task (two sessions per day, delayed-non-matching-to-sample) that included an intramaze static magnetic field "cue" (185 microT) specific to the entrance point of one of the arms. Rats were exposed daily for 60 min to a complex magnetic field waveform (theta-burst pattern, 200-500 nT), presented with several different interstimulus intervals (ISIs), either
immediately following training sessions or immediately preceding testing sessions. Application of the theta-burst stimulus with a 4000 ms ISI significantly improved the rats' memory for the arm of the radial maze whose position was indicated by the presence of a static magnetic field cue. Reference memory errors were homogeneously distributed among all eight arms of the maze for sham-exposed rats, and among the other seven arms of the maze for complex magnetic field-treated rats. These results suggest that static magnetic field cues may be salient orienting cues even in a microenvironment such as a radial maze, but their use as a cue during maze learning in rats is dependent on whole-body application of a specific time-varying complex magnetic field.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15823929


PURPOSE OF REVIEW: This article will focus on the role of risk factors including genetic factors in the development of sensitization and occupational asthma. RECENT FINDINGS: We will review the recent literature published on the genetics of occupational asthma, especially on genes coding for class II human leukocyte antigen and on respiratory antioxidant mechanisms. We will also discuss published work on non-occupational asthma and on allergic rhinitis because this information may contribute to a better understanding of the mechanisms involved in occupational asthma and serve to confirm data obtained on the disease. To date, although some progress has been made in the field of occupational asthma genetics, most studies were based on small sample sizes, findings were not replicated, and gene-environment interactions have not yet been established. SUMMARY: Occupational asthma is a widespread and frequent condition and has relevant long-term adverse health and economic consequences. The search for risk factors including genetic factors in the development of the disease and an understanding of the mechanisms of interaction between genes and environment are important because the identification of individuals who are susceptible to occupational asthma together with an effective control of exposure to respiratory sensitizers in the workplace may be helpful in preventing the disease.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15764899

(2005) Facial Expressions of Emotion Reveal Neuroendocrine and Cardiovascular Stress Responses.

6193e04d00557ea32468df52554d8a3a


More and more self-declared electromagnetic hypersensitive patients are entering physicians' practices seeking help. To assess the prevalence of cases and the opinion of Austrian physicians regarding the potential health-relevance of environmental electromagnetic fields ("electromagnetic pollution"), a statistical investigation among general practitioners was undertaken, with surprising results. Only one-third report on never having been asked about the health impact of electromagnetic pollution by patients. An overwhelming percentage of general practitioners (up to 96%) to some degree, or totally, believe in a health-relevant role of environmental electromagnetic fields, and only 39% have never associated health symptoms with "electromagnetic pollution". Two-thirds are consulted occasionally or even frequently by self-declared electromagnetic hypersensitive patients. However, sound information seems to be lacking. Knowledge on existing electromagnetic exposure limits and on environmental field levels in relation to them is poor. It is remarkable that authorities play a marginal role in informing physicians. Only 4% mention having received information on "electromagnetic pollution" from such a source. It is rather remarkable that there is such a widespread contradiction between physicians' opinions and established national and international health risk assessment. With respect to the frequency with which doctors are confronted with this issue, the results demonstrate an urgent need for action.


PURPOSE OF REVIEW: Sick building syndrome is a poorly understood condition that can be vexing to clinicians and public health investigators alike. Concerns about possible causes have recently shifted to bioaerosols, especially indoor mold contamination. Recently, controversy over the health effects of indoor bioaerosols has intensified in the media and in medical forums. Allergists and other clinicians are increasingly being asked to evaluate cases of sick building syndrome attributed to
bioaerosol exposure. Although allergy may play a role, it is unlikely to fully explain the nonspecific symptoms of the condition. This review of recent literature will attempt to put into context the roles of allergy and nonallergic mechanisms in sick building syndrome. RECENT FINDINGS: Epidemiological and toxicological studies have provided further evidence of a possible link between bioaerosol exposure and sick building syndrome, but continue to have methodological limitations. Cross-sectional studies of building occupants have found associations between bioaerosols and symptoms of the condition, but case definitions and exposure assessment remain problematic. Attempts to develop better exposure assessment and biomonitoring methods have made limited progress. Toxicological studies of inhalation of bioaerosols continue to indicate potential toxicity, but at doses that are not comparable to human exposures indoors. SUMMARY: Epidemiological studies suggest an association between bioaerosols and sick building syndrome, and toxicological studies have provided some evidence supporting biological plausibility. However, the extent to which bioaerosol exposure may explain the nonspecific symptoms of the condition is unclear. Nonspecific inflammatory responses to bioaerosols, modified by psychosocial factors such as stress, may be a promising area for continued research.


PURPOSE: To validate and extend the US case definition for the Multiple Chemical Sensitivity Syndrome (MCS) from 1999 by a systematic literature-review. DATA SOURCE: MEDLINE-research from 1997 to August 2003, research in the Cochrane-Library in August 2003, earlier reviews since 1997. STUDY SELECTION: Headings and abstracts were screened by one reviewer. All references dealing with multiple chemical sensitivities (MCS) which covered topics of interest such as symptom-profiles, differential diagnostic procedures, etc. were included in the analysis. DATA EXTRACTION AND SYNTHESIS: Topic-specific data extraction and synthesis was done by one reviewer. Data interpretation was discussed by all other authors. RESULTS: Out of 1429 references 36 publications proved to be suitable for the review. The results can be summarized as follows: exposure-related symptoms associated with self-reported multiple chemical sensitivities can be divided into non-specific complaints of the central nervous system--CNS (main characteristics) and functional disturbances in other organ systems (optional complaints). There is a significant overlap of MCS, CFS and fibromyalgie. At present no standards for a diagnostic procedure based on the criteria outlined above are existing CONCLUSIONS: MCS should only be diagnosed in patients who are mainly suffering from exposure-related non-specific complaints of the Central nervous system. The suggested diagnostic procedure follows the guidelines for CFS which are extended by diagnostic clarification of functional disturbances in other organ systems.
query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15971853

(2005) **Cholestyramine feeding lowers number of colonic apoptotic cells in rat.**

Secondary bile acids that are formed in the colon by bacterial action have the potential property of eliciting pathological conditions. Apoptosis of mucosal epithelial cells is recognized as an adaptation that may counteract such pathologies. Cholestyramine, an anion exchange resin that sequesters bile salts in the gut, could decrease levels of secondary bile salt stress and thus conserve the potency of the protective action. Two groups of rats were studied: those fed 4% cholestyramine and those fed regular rat food. Rats were fed cholestyramine for 7, 14, 21, or 28 d. All animals were evaluated for cell death (apoptosis) using in situ TUNEL staining, and confirmed with single-stranded DNA (ssDNA). The effect of cholestyramine on the proliferating cell nuclear antigen (PCNA) in colonic crypt cells was also examined. Our data shows that animals fed cholestyramine for 28 d show evidence of a significant decrease in the levels of apoptotic cells in their large intestines, particularly goblet cells, when compared with the control animals and no change in cell proliferation. Thus, cholestyramine may serve as an alternative in attenuating apoptosis associated with inflammatory disorders that can result in significant enterocyte and goblet-cell death.

(2005) **Health determinants in Europe for indoor and outdoor pollutants from a public health and social medicine view.**

(2005) **Indoor air and human exposure assessment--needs and approaches.**

The Commission launched on June 9, 2004 the Environment and Health Action Plan to reduce diseases caused by a polluted environment. The plan would develop an EU system integrating information on the state of the environment, the ecosystem and human health. The action plan identifies 13 actions (including an action on indoor air quality), which refer to initiatives on how to better understand the environment-health link and establish how environmental exposure leads to epidemiological effects. The
ultimate goal of the proposed "Environment and Health Strategy" is to develop an environment and health "cause-effect framework" that will provide the necessary information for the development of Community policy dealing with sources and the impact pathway of health stressors. The need for policy-science interface in the EU guided in the last few years the research on indoor air pollution. In particular, the lack of information regarding human exposure to air pollutants makes it necessary, in line with the Environment and Health Action Plan, to develop targeted strategies to evaluate the impact of indoor air pollution on human health. This includes apart from specific measurements in selected confined spaces (homes, schools, public buildings, etc.), large-scale monitoring campaigns at European level, specifically designed to assess indoor and outdoor air quality and personal exposure to pollutants in combination with micro-environmental activity patterns. Information from these studies will be considered as crucial for a first evaluation of the overall situation in indoor environments and the possible sources and source strengths of pollutants to which humans are exposed during working, commuting and rest time. As a first approach to systematically evaluate the relationship between indoor air pollution and human (chronic) exposure to pollutants, we started at the end of 2003 with the AIRMEX project (Indoor Air Monitoring and Exposure Assessment Study). In the frame of AIRMEX, measuring campaigns in various cities in Southern and Central Europe were carried out to estimate indoor/outdoor relationships and personal exposure concentrations for selected volatile organic compounds (aromatics, carbonyls, terpenoids). In agreement with the overall scope of the project, the measuring objects included public buildings (town halls, guild halls), schools and kindergartens. Personal exposure measurements were conducted with employers and/or teachers working in the selected occupational environments. Preliminary results indicate that personal exposure concentrations are higher than the indoor/outdoor concentrations. In most cases they are twice as high (or even higher) as indoor concentrations and significantly higher than outdoor concentrations.


Air pollution continues to be a major public health concern in industrialized cities throughout the world. Recent population and epidemiological studies that have associated ozone and particulate exposures with morbidity and mortality outcomes underscore the important detrimental effects of these pollutants on the lung. Inter-individual variation in human responses to air pollutants suggests that some subpopulations are at increased risk to the detrimental effects of pollutant exposure, and it has become clear that genetic background is an important susceptibility factor. Environmental exposures to inhaled pollutants and genetic factors associated with disease risk likely interact in a complex fashion that varies from one population to another. The relationships between the genetic background and disease risk and severity is often evaluated through traditional family-based linkage studies and
positional cloning techniques. Case-control studies based on association of disease or disease subphenotypes with candidate genes may have certain advantages over family pedigree studies, and have become useful for understanding complex disease phenotypes. This is based in part on continued development of quantitative analysis and development of mapping technologies. Linkage analyses with genetically standardized animal models are useful to identify genetic determinants of host responses to environmental stimuli. For example, linkage analyses using inbred mice have identified chromosomal segments (quantitative trait loci, QTL) that contain genes that control susceptibility to the lung inflammatory and immune dysfunction responses to ozone, nitrogen dioxide, zinc oxide, and sulfate-associated particles. Candidate genes within the pollutant susceptibility QTLs have been tested for proof-of-concept using gene-targeting and overexpression models. Importantly, significant homology exists between the human and mouse genomes. Therefore, comparative mapping between the human and mouse genomes should yield candidate susceptibility genes that may be tested by association studies in humans. The combined human studies and mouse modeling will provide important insight to understanding genetic factors that contribute to differential susceptibility to pollutants in human populations.

---

Kirrane, BM and Hoffman, RS Journal/Jama. 294: 2431; author reply 2431.

---

(2005) Do we need genomic research for the prevention of common diseases with environmental causes?

Concerns have been raised about the value of genomic research for prevention and public health, especially for complex diseases with risk factors that are amenable to environmental modification. Given that gene-environment interactions underlie almost all human diseases, the public health significance of genomic research on common diseases with modifiable environmental risks is based not necessarily on finding new genetic "causes" but on improving existing approaches to identifying and modifying environmental risk factors to better prevent and treat disease. Such applied genomic research for environmentally caused diseases is important, because 1) it could help stratify disease risks and differentiate interventions for achieving population health benefits; 2) it could help identify new environmental risk factors for disease or help confirm suspected environmental risk factors; and 3) it could aid our understanding of disease occurrence in terms of transmission, natural history, severity, etiologic heterogeneity, and targets for intervention at the population level. While genomics is
still in its infancy, opportunities exist for developing, testing, and applying the tools of genomics to clinical and public health research, especially for conditions with known or suspected environmental causes. This research is likely to lead to population-wide health promotion and disease prevention efforts, not only to interventions targeted according to genetic susceptibility.

(2005) Structure-reactivity studies of serum paraoxonase PON1 suggest that its native activity is lactonase.
Khersonsky, O and Tawfik, DS Journal/Biochemistry. 44: 6371-82.

PON1 is the best-studied member of a family of enzymes called serum paraoxonases, or PONs, identified in mammals (including humans) and other vertebrates as well as in invertebrates. PONs exhibit a range of important activities, including drug metabolism and detoxification of organophosphates such as nerve agents. PON1 resides on HDL (the "good cholesterol") and is also involved in the prevention of atherosclerosis. Despite this wealth of activities, the identity of PON1's native substrate, namely, the substrate for which this enzyme and other enzymes from the PON family evolved, remains unknown. To elucidate the substrate preference and other details of PON1 mechanism of catalysis, structure-activity studies were performed with three groups of substrates that are known to be hydrolyzed by PON1: phosphotriesters, esters, and lactones. We found that the hydrolysis of aryl esters is governed primarily by steric factors and not the pK(a) of the leaving group. The rates of hydrolysis of aliphatic esters are much slower and show a similar dependence on the pK(a) of the leaving group to that of the nonenzymatic reactions in solution, while the aryl phosphotriesters show much higher dependence than the respective nonenzymatic reaction. PON1-catalyzed lactone hydrolysis shows almost no dependence on the pK(a) of the leaving group, and unlike all other substrates, lactones seem to differ in their K(M) rather than k(cat) values. These, and the relatively high rates measured with several lactone substrates (k(cat)/K(M) approximately 10(6) M(-)(1) s(-)(1)) imply that PON1 is in fact a lactonase.


BACKGROUND: Three well-accepted mechanisms of mold-induced disease exist: allergy, infection, and oral toxicosis. Epidemiologic studies suggest a fourth category described as a transient aeroirritation effect. Toxic mold syndrome or inhalational toxicity continues to cause public concern despite a lack of scientific evidence that supports its existence. OBJECTIVES: To conduct a retrospective review of 50 cases of
purported mold-induced toxic effects and identify unrecognized conditions that could explain presenting symptoms; to characterize a subgroup with a symptom complex suggestive of an aeroirritation-mediated mechanism and compare this group to other diagnostic categories, such as sick building syndrome and idiopathic chemical intolerance; and to discuss the evolution of toxic mold syndrome from a clinical perspective. METHODS: Eighty-two consecutive medical evaluations were analyzed of which 50 met inclusion criteria. These cases were critically reviewed and underwent data extraction of 23 variables, including demographic data, patient symptoms, laboratory, imaging, and pulmonary function test results, and an evaluation of medical diagnoses supported by medical record review, examination, and/or test results. RESULTS: Upper respiratory tract, lower respiratory tract, systemic, and neurocognitive symptoms were reported in 80%, 94%, 74%, and 84% of patients, respectively. Thirty patients had evidence of non-mold-related conditions that explained their presenting complaints. Two patients had evidence of allergy to mold allergens, whereas 1 patient exhibited mold-induced psychosis best described as toxic agoraphobia. Seventeen patients displayed a symptom complex that could be postulated to be caused by a transient mold-induced aeroirritation. CONCLUSION: The clinical presentation of patients with perceived mold-induced toxic effects is characterized by a disparate constellation of symptoms. Close scrutiny revealed a number of preexisting diagnoses that could plausibly explain presenting symptoms. The pathogenesis of aeroirritation implies completely transient symptoms linked to exposures at the incriminated site. Toxic mold syndrome represents the furtive evolution of aeroirritation from a transient to permanent symptom complex in patients with a psychogenic predisposition. In this respect, the core symptoms of toxic mold syndrome and their gradual transition to chronic symptoms related to nonspecific environmental fragrances and irritants appear to mimic what has been observed with other pseudodiagnostic categories, such as sick building syndrome and idiopathic chemical intolerance.

(2005) Angiotensin II blocks memory consolidation through an AT2 receptor-dependent mechanism.

RATIONALE AND OBJECTIVES: Several studies suggest that the brain renin-angiotensin system is involved in memory consolidation. However, the participation of angiotensin II (AII) in this process is controversial. This is probably due to the fact that many of the studies carried out to elucidate this matter employed multitrial learning paradigms together with pretraining intracerebroventricular infusions, and therefore were unable to distinguish between consolidation and retrieval related events and lacked anatomical specificity. To circumvent this problem, we analyzed the role played in memory consolidation by AII using the hippocampal-dependent, one-trial, step-down inhibitory avoidance task (IA) in combination with stereotaxically localized
intrahippocampal infusion of drugs. METHODS AND RESULTS: Rats bilaterally implanted with infusion cannulae into the CA1 region of the dorsal hippocampus (CA1) were trained in IA and tested for memory retention 24 h later. We found that when infused into CA1 immediately or 30 min after training but not later, AII produced a dose-dependent amnesic effect without altering locomotor activity, exploratory behavior or anxiety state. The amnesic effect of AII was not mimicked by angiotensin IV (AIV) and was totally blocked by the AII-type 2 receptor (AT2) antagonist, PD123319, but not by the AII-type 1 receptor (AT1) antagonist, losartan. Importantly, when infused alone, neither PD123319 nor losartan produced any effect on memory retention.

CONCLUSIONS: Our data indicate that, when given into CA1, AII blocks memory formation through a mechanism involving activation of AT2 receptors; however, endogenous AII does not seem to participate in the consolidation of IA long-term memory.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15551065


Mast cells participate in allergies, and also in immunity and inflammation by secreting proinflammatory cytokines. Flavonoids are naturally occurring polyphenolic plant compounds, one group of which -- the flavonols, inhibits histamine and some cytokine release from rodent basophils and mast cells. However, the effect of flavonols on proinflammatory mediator release and their possible mechanism of action in human mast cells is not well defined. Human umbilical cord blood-derived cultured mast cells (hCBMCs) grown in the presence of stem cell factor (SCF) and interleukin (IL)-6 were preincubated for 15 min with the flavonols quercetin, kaempferol, myricetin and morin (0.01, 0.1, 1, 10 or 100 microM), followed by activation with anti-IgE. Secretion was quantitated for IL-6, IL-8, tumor necrosis factor-alpha (TNF-alpha), histamine and tryptase levels. Release of IL-6, IL-8 and TNF-alpha was inhibited by 82-93% at 100 microM quercetin and kaempferol, and 31-70% by myricetin and morin. Tryptase release was inhibited by 79-96% at 100 microM quercetin, kampferol and myricetin, but only 39% by morin; histamine release was inhibited 52-77% by the first three flavonols, but only 28% by morin. These flavonols suppressed intracellular calcium ion elevations in a dose-response manner, with morin being the weakest; they also inhibited phosphorylation of the calcium-insensitive protein kinase C theta (PKC theta). Flavonol inhibition of IgE-mediated proinflammatory mediator release from hCBMCs may be due to inhibition of intracellular calcium influx and PKC theta signaling. Flavonols may therefore be suitable for the treatment of allergic and inflammatory diseases.
Antimuscarinic agents are the predominant pharmacological treatment for patients with overactive bladder (OAB). These drugs are thought to act primarily through antagonism at muscarinic M3 receptors located at neuromuscular junctions in the human bladder detrusor muscle. Several of these drugs have been shown to be efficacious in ameliorating the symptoms of OAB in older patients, but most currently available agents lack selectivity for the M3 receptor subtype, and interaction with other muscarinic receptor subtypes throughout the body may adversely affect a variety of physiological functions and result in unwanted side effects, including cognitive dysfunction. With the recent availability of antimuscarinic agents that show increased selectivity for M3 receptors relative to other muscarinic subtypes, an invitational expert panel meeting was convened to review not only the mechanisms by which antimuscarinic agents could affect cognitive function, but also the published literature on cognitive adverse events. A review of the literature shows that the cholinergic system in the central nervous system (CNS) exerts a major influence on cognitive processes, in particular memory via M1 cholinergic receptors. In addition, recent evidence suggests a role for M2 receptors in mediating cognitive function. Thus, cognitive dysfunction (including memory loss) during treatment with nonselective antimuscarinic agents for OAB is of growing concern, particularly in older patients and those with mild cognitive impairment or dementia. Increased blood-brain barrier permeability, which can occur with advanced age and certain comorbidities, may also facilitate CNS access of antimuscarinic agents (regardless of their physiochemical properties) and add to antimuscarinic burden. On the basis of available evidence, antimuscarinic agents with selectivity for M3 over M1 and M2 receptors, limited CNS penetration, or both may therefore offer a favorable balance of efficacy in treating OAB together with a reduced risk of adverse cognitive events in the older population.
(2005) [Use of complementary and alternative medicine in patients with fibromyalgia].


OBJECTIVE: This article views, collectively, the problems associated with darkroom disease, multiple chemical sensitivity and latex allergy. Each is discussed individually to establish a case definition. METHOD: Common threads and similarities are identified among the 3 conditions along with potential sources. RESULTS: A model is proposed to change attitudes among radiographers in individual departments to improve workplace safety. CONCLUSION: We propose the use of an established health education/disease prevention model to change the attitudes of radiographers toward chemical threats.


Johansson, A, Bramerson, A, Millqvist, E, Nordin, S and Bende, M Journal/Int Arch Occup Environ Health. 78: 559-64.

Objectives: The present study was performed to determine the prevalence of odour intolerance in adults with respect to both self-reported general intolerance and affective and behavioural consequences. Furthermore, we aimed to relate odour intolerance to explanatory variables and risk factors. Method: This is a cross-sectional, population-based epidemiological study. A random sample of 1900 inhabitants from the age of 20, stratified for age and gender, were recruited. Subjects were invited for clinical examinations that included questions about general odour intolerance, respiratory symptoms and smoking habits, as well as a smell identification test. The chemical sensitivity scale for sensory hyperreactivity (CSS-SHR) was used to quantify affective and behavioural consequences. Results: In total 1387 volunteers (73% of the sample) were investigated. The overall prevalence of self-reported general odour intolerance was 33% (95% confidence interval (CI): 30-36%), with problems mainly from the upper respiratory tract. The prevalence of affective and behavioural consequences of odour intolerance (CSS-SHR score >/=43) was 19% (95% CI: 15-22%). The risk for the latter condition was increased in women compared with men.
(odds ratio = 2.3: 95% CI: 1.5-3.6), but no increased risk was found related to current smoking or impaired sense of smell. Conclusion: This study demonstrates that intolerance to odours is a widespread problem in society, and that it is about twice as common in women than in men.

(2005) Physiologic and symptomatic responses to low-level substances in individuals with and without chemical sensitivities: a randomized controlled blinded pilot booth study.

We conducted a pilot study using a randomized, single-blind, placebo-controlled exposure among 10 individuals with and 7 without reported chemical sensitivities in a dedicated testing chamber. Objectives of the study were to explore the length of the adaptation period to obtain stable readings, evaluate responses to different substances, and measure the level and type of symptomatic and physiologic reactions to low-level exposures. Reported and observed symptoms, electrodermal response, heart rate, skin temperature, surface electromyogram, respiratory rate, contrast sensitivity, and the Brown-Peterson cognitive test were used and compared between cases and controls and between test substances (glue, body wash solution, dryer sheet) and control substances (unscented shampoo and clean air). Subjects with chemical sensitivities (cases) took longer to adapt to baseline protocols than did controls. After adaptation, despite small study numbers, cases displayed statistically significant responses (all measures, p < 0.02) in tonic electrodermal response to test substances compared with controls and compared with the control substance. Symptoms were also higher in cases than in controls for the body wash solution (p = 0.05) and dryer sheets (p = 0.02). Test-retest showed good agreement for both symptoms and tonic electrodermal responses (McNemar’s test, p = 0.32 and p = 0.33, respectively). Outside of skin conductance, other measures had no consistent patterns between test and control substances and between cases and controls. This study shows the importance of using an adaptation period in testing individuals with reported chemical sensitivities and, despite small numbers, raises questions about underlying mechanisms and level of reactivity to low-level chemical exposures in sensitive individuals.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16140624

(2005) [The treatment of patients with toxic encephalopathy caused by using surrogate psychoactive manganese-containing compounds].
Toxic encephalopathy caused by using surrogate psychoactive manganese-containing compounds was characterized clinically by a combination of parkinsonian, dystonic and pseudobulbar syndromes, eye-movement disturbances, autonomic insufficiency, affective disorders and moderate intellectual and memory impairment. Pharmacotherapeutic efficacy of mexidol has been studied. The results of the study showed that mexidol therapeutic course has a moderate effect on the expression of movement disorders and intellectual and memory impairment. Mexidol treatment significantly reduced severity of affective disorders and improved quality of life and daily activity of patients.

(2005) [Chemical sensitivity (CS)].


(2005) [An enzyme immunoassay laboratory for detection of viral water contamination markers].
Il'in, SN, Malyshev, VV, Duvanova, EM and Rogozhneva, IV Journal/Gig Sanit. 62-5.

(2005) [Estimation of exposure to fluoride in "Los Altos de Jalisco", Mexico].

OBJECTIVE: To estimate the level of fluoride exposure and human health risks in Los Altos de Jalisco (Jalisco State Heights) region. MATERIAL AND METHODS: This study was conducted between May and July 2002. The fluoride concentrations of 105 water wells and six tap water samples were electrochemically measured. Exposure doses to fluoride and total intake of fluoride were estimated for babies (10 kg), children (20 kg), and adults (70 kg). RESULTS: The fluoride concentration of the water samples ranged from 0.1 to 17.7 mg/l. More than 45% of the water samples exceeded the national guideline value for fluoride of 1.5 mg/l. The estimated values of the exposure doses to fluoride and total intake of fluoride were in the range of 0.04-1.8 mg/kg/d and 0.5-18.4 mg/d, respectively. CONCLUSIONS: Dental fluorosis, skeletal fluorosis, and bone fractures are some of the potential health risks due to the intake of high doses of fluoride for the population of Los Altos de Jalisco. In order to reduce health risks,
fluoridated salt, fluoridated toothpastes, and drinking water containing more than 0.7 mg/l of fluoride should be avoided.


It has been suggested that chemicals and, more specifically, chemical interactions, are involved as causative agents in deployment-related illnesses. Unfortunately, this hypothesis has proven difficult to test, because toxicological investigations of deployment-related chemicals are usually carried out on surrogate animals and are difficult to extrapolate to humans. Other parts of the problem, such as the definition of variation within human populations and the development of methods for designating groups or individuals at significantly greater risk, cannot be carried out on surrogate animals, and the data must be derived from humans. The relatively recent availability of human cell fractions, such as microsomes, cytosol, etc., human cells such as primary hepatocytes, recombinant human enzymes, and their isoforms and polymorphic variants has enabled a significant start to be made in developing the human data needed. These initial studies have examined the human metabolism by cytochrome P450, other phase I enzymes, and their isoforms and, in some cases, their polymorphic variants of compounds such as chlorpyrifos, carbaryl, DEET, permethrin, and pyridostigmine bromide, and, to a lesser extent, other chemicals from the same chemical and use classes, including solvents, jet fuel components, and sulfur mustard metabolites. A number of interactions at the metabolic level have been described both with respect to other xenobiotics and to endogenous metabolites. Probably the most dramatic have been seen in the ability of chlorpyrifos to inhibit not only the metabolism of other xenobiotics such as carbaryl and DEET but also to inhibit the metabolism of steroid hormones.

The cloned genes encoding carboxylesterase E3 in the blowfly Lucilia cuprina and its orthologue in Drosophila melanogaster were expressed in Sf9 cells transfected with recombinant baculovirus. Resistance of L. cuprina to organophosphorus insecticides is due to mutations in the E3 gene that enhance the enzyme’s ability to hydrolyse insecticides. Previous in vitro mutagenesis and expression of these modifications (G137D, in the oxyanion hole and W251L, in the acyl pocket) have confirmed their functional significance. We have systematically substituted these and nearby amino acids by others expected to affect the hydrolysis of pyrethroid insecticides. Most mutations of G137 markedly decreased pyrethroid hydrolysis. W251L was the most effective of five substitutions at this position. It increased activity with trans permethrin 10-fold, and the more insecticidal cis permethrin >130-fold, thereby decreasing the trans:cis hydrolysis ratio to only 2, compared with >25 in the wild-type enzyme. Other mutations near the bottom of the catalytic cleft generally enhanced pyrethroid hydrolysis, the most effective being F309L, also in the presumptive acyl binding pocket, which enhanced trans permethrin hydrolysis even more than W251L. In these assays with racemic 1RS cis and 1RS trans permethrin, two phases were apparent, one being much faster suggesting preferential hydrolysis of one enantiomer in each pair as found previously with other esterases. Complementary assays with individual enantiomers of deltamethrin and the dibromo analogue of cis permethrin showed that the wild type and most mutants showed a marked preference for the least insecticidal 1S configuration, but this was reversed by the F309L substitution. The W251L/F309L double mutant was best overall in hydrolysing the most insecticidal 1R cis isomers. The results are discussed in relation to likely steric effects on enzyme-substrate interactions, cross-resistance between pyrethroids and malathion, and the potential for bioremediation of pyrethroid residues.


This review summarizes recent work on two basic processes of central nervous system (CNS) control of cholinergic outflow to the airways: 1) transmission of bronchoconstrictive signals from the airways to the airway-related vagal preganglionic neurons (AVPNs) and 2) regulation of AVPN responses to excitatory inputs by central GABAergic inhibitory pathways. In addition, the autocrine-paracrine modulation of AVPNs is briefly discussed. CNS influences on the tracheobronchopulmonary system are transmitted via AVPNs, whose discharge depends on the balance between excitatory and inhibitory impulses that they receive. Alterations in this equilibrium may lead to dramatic functional changes. Recent findings indicate that excitatory signals arising from bronchopulmonary afferents and/or the peripheral chemosensory system activate second-order neurons within the nucleus of the solitary tract (NTS), via a
glutamate-AMPA signaling pathway. These neurons, using the same neurotransmitter-receptor unit, transmit information to the AVPNs, which in turn convey the central command to airway effector organs: smooth muscle, submucosal secretory glands, and the vasculature, through intramural ganglionic neurons. The strength and duration of reflex-induced bronchoconstriction is modulated by GABAergic-inhibitory inputs and autocrine-paracrine controlling mechanisms. Downregulation of GABAergic inhibitory influences may result in a shift from inhibitory to excitatory drive that may lead to increased excitability of AVPNs, heightened airway responsiveness, and sustained narrowing of the airways. Hence a better understanding of these normal and altered central neural circuits and mechanisms could potentially improve the design of therapeutic interventions and the treatment of airway obstructive diseases.


OBJECTIVES: Environmental clinics are frequented by patients with fears and complaints related to environmental triggers. A dose-independent overreaction to small doses of widely used and generally non-toxic chemicals is referred to as multiple chemical sensitivity (MCS), but no clearly defined clinical syndrome with objective physical findings has been delineated so far. We aimed to obtain information about symptoms, supposed environmental triggers, the frequency of self-reported chemical sensitivity, and of the diagnosis MCS in Germany. METHODS: We conducted a representative survey among 2032 adult Germans. RESULTS: We found self-reported chemical sensitivity in 9% and physician-diagnosed MCS in 0.5% of our representative sample. Physical complaints were common in the whole study population and in chemically sensitive individuals, but there was no clear-cut symptom constellation among the latter. The most common complaints were headache, fatigue, sleep disturbances, joint pain, mood changes and nervousness. A subjective connection between complaints and environmental triggers was denied by 67% of the whole group and by 35% of the self-reported chemically sensitive. Factor analysis of environmental triggers suggested that a specific exposure situation rather than chemical similarity is the basis for individual trigger combinations. CONCLUSIONS: The prevalence of subjective sensitivity towards chemicals is similar to such rates reported from other countries. There is a relatively low awareness of the MCS-concept, and it appears to be diagnosed less frequently than, e.g., in the USA. Since symptoms and triggers in chemically sensitive individuals did not differ from the general population, our data do not suggest the existence of a widespread new syndrome related to chemical sensitivities in Germany. We outline the limitations of self-reported chemical sensitivity as the major criterion for such a contentious diagnosis as MCS.
(2005) [Clinical aspects of patients with MCS - from the standpoint of allergy].
Hasegawa, M, Ohtomo, M, Mita, H and Akiyama, K Journal/Arerugi. 54: 478-84.

BACKGROUND: "Sick House Syndrome" is thought to be an illness caused by indoor environments such as allergens, bacteria and chemical compounds. But it is not yet an established clinical entity. "Sick House Syndrome" overlaps in part with Multiple Chemical Sensitivity (MCS) whose symptoms are induced by very small amount of volatile chemical compounds. METHODS: We selected possible cases of MCS from patients who visited our specially built facility for "Sick House Syndrome" by tentative criteria as follow: (1) histories of chemical compounds exposure, (2) multi-organ symptoms, (3) exclusion of other disease(s) which may be responsible for symptoms, (4) chronic symptoms. Clinical aspects of the possible cases were examined.
RESULTS: Fifty out of about 130 patients were the possible cases of MCS, 38 females and 12 males, aged 15 to 71 years old. Forty two out of 50 patients (84%) had a history and/or a complication of allergic diseases. This rate is much higher than the rate of prevalence of allergic diseases in Japanese population. Allergic rhinitis was the most popular allergic disease in the possible cases. Total IgE values were relatively low, 32 patients (64%) showed the IgE value below 200 IU/ml. No patients showed anti-formaldehyde IgE antibody. Decreased reactivity and decreased sensitivity of histamine release from peripheral blood were observed after challenge tests with chemical compounds. CONCLUSION: Allergic reactions can not be the causative mechanism(s) of the MCS, which is induced by multiple and different chemical compounds. Our results, however, suggest that patients having allergic diseases may be easily suffered from MCS or MCS may strengthen symptoms of allergic diseases.


OBJECTIVE: To test the hypotheses that both violence and traumatic stress symptoms are associated with negative health status among poor preschool children. STUDY DESIGN: This cross-sectional analysis of a Head Start preschool age cohort (n = 160) studied health outcomes parallel to those assessed in the 2001 National Health Interview Survey of child health (asthma, allergy, attention deficit hyperactivity disorder, global appraisal) as well as two stress-related somatic complaints, gastrointestinal problems and headache. Risk factors include sociodemographics, mothers' health
factors, extent of exposure to violence and maltreatment, and mother- and teacher-reported traumatic stress symptoms. RESULTS: Compared with poor children in the National Health Interview Survey and their Head Start peers, children exposed to violence and those with high levels of traumatic stress had significantly worse outcomes, in a dose-response relation. Being abused, exposed to domestic violence, and having a mother using substances were associated with a higher number of health problems. The hierarchical model established the mother's own poor physical health and the child's level of traumatic stress as the strongest predictors of poor child health. CONCLUSIONS: These two risk factors are amenable to intervention by health care providers who treat children.


(2005) [Significant increase of functional status and decrease of fatigue in patients with chronic fatigue syndrome after completing cognitive behavioural group therapy].

Multiple-chemical sensitivity (MCS) is a condition in which individuals have an acute hypersensitivity to low levels of chemicals found in everyday substances, such as household cleaning agents, pesticides, fresh paint, new carpeting, synthetic building materials, newsprint, perfume, and numerous other petrochemical products. This condition continues to remain somewhat of a mystery to the medical community, and its true prevalence rate is unknown because many cases are not identified and reported as MCS. This article will inform the reader about the condition of MCS.


PURPOSE: Food avoidance is central to the treatment of environmental sensitivity (ES), a chronic, often debilitating, multisystem disorder characterized by adverse reactions to non-noxious levels of environmental substances. Because prolonged food avoidance could impact nutritional health, the purpose of this research was to assess adequacy and quality of diets consumed by women diagnosed with ES. 

METHODS: Twelve women aged 37 to 50 recruited from the Nova Scotia Environmental Health Clinic completed a four-day food record during the spring and summer of 1998.

RESULTS: When adequacy of nutrient intake was assessed by comparison to the Estimated Average Requirement, the most limited nutrients in the diet were folate, vitamin B6, vitamin B12, and magnesium. Only one woman exceeded the Adequate Intake for calcium. When diet quality was assessed using the Healthy Eating Index, the majority of women (75%) scored in the "needs improvement" category; intake of milk and dietary variety scored the lowest. Women consumed very few servings from "other foods", defined in the food guide as foods containing mostly sugar and mostly fat.

CONCLUSIONS: The results of this study suggest that women diagnosed with ES would benefit from counselling on ways to increase dietary variety, which would lead to improved nutrient intake, and ways to increase calcium intake.


In this qualitative study, the authors asked respondents with multiple chemical sensitivity (MCS) in an open-ended question how having the condition affected their identities. Authors then examined responses for themes, which they discuss within the framework of critical theory. Emergent themes included loss of a stable, familiar personality, loss of self-positioning, emotional suppression to meet others' expectations, redesigning the planned life, forced growth, struggling with support, discovering the spiritual self, and identity reconsolidation. The authors compare findings with published works on adjustment to chronic illness and other delegitimized illnesses, find them to be fairly congruent, and then discuss problems regarding cultural acceptance of MCS as a condition caused by chemical exposure.


Historically, the concept of a mind-body duality in medicine, which supports a biomedical approach to pain management, has impeded the development of adequate treatments for persistent pain conditions and diseases. Although usually there is an initiating pathophysiologic nociceptive cause of pain, over time, the conditioning of neurophysiologic and affective systems by environmental and internal events can promote chronicity and frustrate the efforts of physicians to attenuate nociceptive processes. A full elucidation of the environmental and psychological factors contributing to pain and suffering may prove difficult using a traditional biomedical approach. Prevention of chronicity, by early identification and treatment of pain generators and the pain response to tissue injury and by recognition of those general factors that contribute to risk for chronicity (e.g., depressive illness, poor pain control), is crucial for any healthcare system that wishes to reduce the morbidity and costs of persistent pain. Goal-directed, outcomes-focused biopsychosocial treatment plans that efficiently integrate physical, behavioral, and medical approaches more frequently achieve better pain control and improved function. The following article presents a general overview of evidence for effectiveness of these approaches and some central principles of integrated treatment planning.


Individual differences in detoxication capacities for specific organophosphorous (OP) compounds are due largely to differences in catalytic efficiency or abundance of the HDL-associated enzyme, paraoxonase (PON1). First, we provide evidence that children less than 2 years of age represent a particularly susceptible population for OP exposure due to low abundance of PON1 and variable onset of plasma PON1 activity. Second, we describe studies examining the neurotoxic effects of chronic, low-level OP pesticide exposure in mice. PON1 knockout (PON1(-/-)) and wild-type mice were exposed chronically (PN4 to PN21) to low levels of chlorpyrifos oxon (CPO). Endpoints included cholinesterase activity, histopathology, gene expression, and behavior. Even at PN4, when PON1 levels were low in wild-type mice, PON1(-/-) mice were more sensitive to inhibition of brain cholinesterase by CPO. At PN22, and persisting as long as 4 months, chronic developmental exposure to 0.18 mg/kg/d or 0.25 mg/kg/d CPO resulted in perinuclear vacuolization of cells in a discrete area of the neocortex and irregular distribution of neurons in the cortical plate, with an increase in the number of affected cells at 0.25mg/kg/d. Third, we describe a transgenic mouse model in which human transgenes encoding either hPON1Q192 or hPON1R192 were expressed at equal levels in place of mouse PON1. The developmental onset of expression followed the mouse time course and was identical for the two transgenes, allowing these mice to be used to assess the importance of the Q192R polymorphism during development. Adult mice expressing hPON1R192 were significantly more resistant than hPON1Q192
mice to CPO toxicity. Our studies indicate that children less than 2 years old, especially those homozygous for PON1Q192, would be predicted to be particularly susceptible to CPO toxicity.


PURPOSE: The manifestation of Parkinson's disease (PD) is characterized by bradykinesia, resting tremor, and rigidity. The etiology of PD remains unknown. Recently several studies suggest that some environmental and genetic factors may be related to the cause of PD. Genetic variation in xenobiotic metabolizing enzymes involved in the disposition of pesticides, such as paraoxonase I (PON 1), may increase the risk of PD. We investigated the association between PON1 polymorphism, pesticides exposure and risk of Parkinson's disease in Taiwanese population.

METHODS: We enrolled 162 controls and 125 patients with idiopathic PD. Histories of exposures to environmental factors and other information were collected with a questionnaire filled out during a face-to-face interview with the subject. The data included years of farming, drinking water sources, occupational exposures to pesticides, duration and the initial age of the pesticides exposure. Buccal mucosa cells are collected from each subject and PON1 polymorphism at codon 54 (L and M alleles) is studied with PCR-based restriction fragment length polymorphism (RFLP) analysis.

RESULTS: There is significant association between the risk of PD and exposure to pesticides (OR=1.72, 95% CI=1.07-2.75). On the other hand, no significant differences are found in PON1 genotype or allelic distribution between PD and control groups. We further investigated participants who had reported exposure to pesticides and found that the frequency distribution of PON1 genotypes did not differ significantly between patients and controls. CONCLUSION: The present survey reveals the close relationship between exposure to pesticides and Parkinson's disease. There are no significant differences in the distribution of PON1 genotypes between cases and controls.

(2005) [Chronic fatigue syndrome and multiple chemical hypersensitivity after insecticide exposure].

BACKGROUND AND OBJECTIVE: Chronic Fatigue Syndrome (CFS) and Multiple Chemical Sensitivity (MCS) are well-defined illnesses that may appear after some toxic exposures. PATIENTS AND METHOD: We report a consecutive series of 26 patients
who developed CFS after exposure to insecticide products. It was associated with MCS in a third of cases. RESULTS: Toxic exposure was of labour origin after returning to usual work place after a process of fumigation. In 42% of cases there was no fulfillment of fumigation safety rules. The majority of patients were mean-aged women who developed an acute upper airway inflammatory syndrome, without muscarinic or nicotinic manifestations, followed by digestive syndrome, neurocognitive, fibromyalgic and chronic fatigue manifestations. The course of disease was shorter than 1 year in 5 cases (19%), longer than 1 year in 15(58%), and disabling in 6 cases (23%). CONCLUSIONS: Due to the possible prevention of this toxic exposure, it is very important to carefully follow measures of environment isolation and ventilation after insecticide use in order to avoid the development of these diseases.


---------------------------------------------------------------

(2005) [Chronic fatigue syndrome and multiple chemical hypersensitivity after insecticide exposition.].

Background and objective: Chronic Fatigue Syndrome (CFS) and Multiple Chemical Sensitivity (MCS) are well-defined illnesses that may appear after some toxic exposures. Patients and method: We report a consecutive series of 26 patients who developed CFS after exposure to insecticide products. It was associated with MCS in a third of cases. RESULTS: Toxic exposure was of labour origin after returning to usual work place after a process of fumigation. In 42% of cases there was no fulfillment of fumigation safety rules. The majority of patients were mean-aged women who developed an acute upper airway inflammatory syndrome, without muscarinic or nicotinic manifestations, followed by digestive syndrome, neurocognitive, fibromyalgic and chronic fatigue manifestations. The course of disease was shorter than 1 year in 5 cases (19%), longer than 1 year in 15(58%), and disabling in 6 cases (23%). CONCLUSIONS: Due to the possible prevention of this toxic exposure, it is very important to carefully follow measures of environment isolation and ventilation after insecticide use in order to avoid the development of these diseases.

---------------------------------------------------------------

(2005) Sick building syndrome and perceived indoor environment in relation to energy saving by reduced ventilation flow during heating season: a 1 year intervention study in dwellings.
Ventilation in Scandinavian buildings is commonly performed by means of a constant flow ventilation fan. By using a regulated fan, it is possible to make a seasonal adjustment of outdoor ventilation flow. Energy saving can be achieved by reducing the mechanical ventilation flow during the heating season, when natural ventilation driven by temperature differences between outdoor and indoor is relatively high. This ventilation principle has been called 'seasonally adapted ventilation (SAV)'. The aim was to study if a 25-30% reduction of outdoor ventilation flow during heating season influenced sick building syndrome (SBS) and the perception of the indoor environment. This was done in a 1-year cross-over intervention study in 44 subjects in a multi-family building. During the first heating season (November to April), one part of the building (A) got a reduced flow during the heating season [0.4-0.5 air exchanges per hour (ACH)] while the other part (B) had constant flow (0.5-0.8 ACH). The next heating season, part A got constant flow, while part B got reduced ventilation flow. Reduced ventilation increased the relative air humidity by 1-3% in the living room (mean 30-37% RH), 1-5% in the bathroom (mean 48-58% RH) during heating season. The room temperature increased 0.1-0.3 degrees C (mean 20.7-21.6 degrees C), mean carbon dioxide (CO2) concentration in the bedroom increased from 920 to 980 p.p.m. at reduced flow. The indoor air quality was perceived as poorer at reduced outdoor airflow, both in the bedroom and in the apartment as a whole. There was a significant increase of stuffy odor (P = 0.05) at reduced outdoor airflow and the indoor air quality was perceived as poorer, both in the bedroom (P = 0.03) and in the apartment as a whole (P = 0.04). No significant influence on SBS symptoms or specific perceptions such as odors, draught, temperature, air dryness or stuffy air could be detected. In conclusion, reducing the ventilation flow in dwellings to a level below the current Swedish ventilation standard (0.5 ACH) may cause a perception of impaired air quality. Technical measurements could only demonstrate a minor increase of indoor temperature, relative air humidity, and bedroom CO2 concentration. This illustrates that it is important to combine technical measurements with a longitudinal evaluation of occupant reactions, when evaluating energy-saving measures. PRACTICAL IMPLICATIONS: It is important to combine technical measurements with a longitudinal evaluation of occupant reactions, when evaluating energy-saving measures. Reduction of outdoor airflow in dwellings below the current ventilation standard of 0.5 ACH may lead to a perception of impaired air quality, despite only a minor increase of bedroom CO2-concentration.


BACKGROUND: Exposure to perfume and fragrance products may, in some individuals, cause symptoms from the eyes and airways. The localization, character and risk factors of such symptoms in the general population are unknown.
OBJECTIVE: To investigate both the localization and character of symptoms from the eyes and airways elicited by fragrance products, and the associations between such symptoms and skin prick test reactivity (atopy), methacholine bronchial hyper-reactivity (BHR), allergic rhinitis and asthma. METHODS: A questionnaire on mucosal symptoms elicited by fragrance products was posted to 1189 persons who had participated in a Danish population-based study of allergic diseases in 1997/1998. The study included measurement of BHR, atopy, forced expiratory volume in 1 s (FEV1), and serum eosinophilic cationic protein (serum ECP). RESULTS: The response rate was 79.6%. Symptoms from the eyes or airways elicited by fragrance products were reported by 42%. BHR (adjusted odds ratio 2.3, 95% confidence interval 1.5-3.5) was independently associated with symptoms from the eyes and airways elicited by fragrance products. There were no significant associations between these symptoms and atopy, FEV1 or serum ECP. CONCLUSIONS: Mucosal symptoms from the eyes and airways were common in this population. BHR was a significant and independent predictor of these symptoms. The lack of association with atopy suggested that IgE-mediated allergic mechanisms do not play a major role in the development of these symptoms.


BACKGROUND: "Toxic mold syndrome" is a controversial diagnosis associated with exposure to mold-contaminated environments. Molds are known to induce asthma and allergic rhinitis through IgE-mediated mechanisms, to cause hypersensitivity pneumonitis through other immune mechanisms, and to cause life-threatening primary and secondary infections in immunocompromised patients. Mold metabolites may be irritants and may be involved in "sick building syndrome." Patients with environmental mold exposure have presented with atypical constitutional and systemic symptoms, associating those symptoms with the contaminated environment. OBJECTIVE: To characterize the clinical features and possible etiology of symptoms in patients with chief complaints related to mold exposure. METHODS: Review of patients presenting to an allergy and asthma center with the chief complaint of toxic mold exposure. Symptoms were recorded, and physical examinations, skin prick/puncture tests, and intracutaneous tests were performed. RESULTS: A total of 65 individuals aged 1 1/2 to 52 years were studied. Symptoms included rhinitis (62%), cough (52%), headache (34%), respiratory symptoms (34%), central nervous system symptoms (25%), and fatigue (23%). Physical examination revealed pale nasal mucosa, pharyngeal "cobblestoning," and rhinorrhea. Fifty-three percent (33/62) of the patients had skin reactions to molds. CONCLUSIONS: Mold-exposed patients can present with a variety of IgE- and non-IgE-mediated symptoms. Mycotoxins, irritation by spores, or
metabolites may be culprits in non-IgE presentations; environmental assays have not been perfected. Symptoms attributable to the toxic effects of molds and not attributable to IgE or other immune mechanisms need further evaluation as to pathogenesis. Allergic, rather than toxic, responses seemed to be the major cause of symptoms in the studied group.


Five hundred and twenty-two teachers from 15 public schools, eight 'water-damaged' schools, and seven 'non-damaged' schools with no visible water damage were included in a cross-sectional design. Mold growth was assessed by recording the amount of dust on the floor and in the air in classrooms and the content of a number of mold species in the dust (CFU/g dust). The evaluation of health symptoms included symptoms recorded by questionnaire and spirometry, bronchial challenge, and CO-diffusion capacity. Nasal lavage fluid was analyzed for IL-8 and ECP. Personal and psychosocial factors were included as confounders. In this study population mucus membrane irritation symptoms (MMI) and general symptoms were reported more frequently by women than by men with odds ratios ranging from 1.4 to 2.1. Women's reports of symptoms from mucous membranes and skin and general symptoms were positively associated with mold exposure. Odds ratio for 'difficult to concentrate' after adjustment for confounders was 11.2 (1.4-90.1, 95% CI) at high levels of mold exposure. None of the lung function tests performed in this study were associated with mold exposure, to the 'water damaged' vs. 'non-damaged' classification, or to the symptoms reported. IL-8 and ECP were not associated either. PRACTICAL IMPLICATIONS: Psychosocial and personal reasons dominate in MMI and general symptoms. Headache and difficulties to concentrate associated with indoor mold exposure, mainly for women. No lung function impairment associated with indoor mold exposure.

(2005)  Illnesses you have to fight to get: Facts as forces in uncertain, emergent illnesses.
Chronic fatigue syndrome and multiple chemical sensitivity are two clusters of illnesses that are pervaded by medical, social and political uncertainty. This article examines how facts are talked about and experienced in struggles over these emergent, contested illnesses in the US. Based principally on a large archive of internet newsgroup postings, and also on fieldwork and on published debates, it finds that (1)
sufferers describe their experiences of being denied healthcare and legitimacy through bureaucratic categories of exclusion as dependent upon their lack of biological facts; (2) institutions manage these exclusions rhetorically through exploiting the open-endedness of science to deny efficacy to new facts; (3) collective patient action responds by archiving the systematic nature of these exclusions and developing counter-tactics. The result is the maintenance of these very expensive struggles for all involved.

(2005) Crystal structure of methyl parathion hydrolase from Pseudomonas sp. WBC-3.

Methyl parathion hydrolase (MPH, E.C.3.1.8.1), isolated from the soil-dwelling bacterium Pseudomonas sp. WBC-3, is a Zn(II)-containing enzyme that catalyzes the degradation of the organophosphate pesticide methyl parathion. We have determined the structure of MPH from Pseudomonas sp. WBC-3 to 2.4 angstroms resolution. The enzyme is dimeric and each subunit contains a mixed hybrid binuclear zinc center, in which one of the zinc ions is replaced by cadmium. In both subunits, the more solvent-exposed beta-metal ion is substituted for Cd2+ due to high cadmium concentration in the crystallization condition. Both ions are surrounded by ligands in an octahedral arrangement. The ions are separated by 3.5 angstroms and are coordinated by the amino acid residues His147, His149, Asp151, His152, His234 and His302 and a water molecule. Asp255 and a water molecule serve to bridge the zinc ions together. MPH is homologous with other metallo-beta-lactamases but does not show any similarity to phosphotriesterase that can also catalyze the degradation of methyl parathion with lower rate, despite the lack of sequence homology. Trp179, Phe196 and Phe119 form an aromatic cluster at the entrance of the catalytic center. Replacement of these three amino acids by alanine resulted in a significant increase of K(m) and loss of catalytic activity, indicating that the aromatic cluster has an important role to facilitate affinity of enzyme to the methyl parathion substrates.

(2005) Targeting biologic markers in asthma--is exhaled nitric oxide the bull’s-eye?


Historically, identification of filamentous fungal (mold) species has been based on morphological characteristics, both macroscopic and microscopic. These methods may often be time-consuming and inaccurate, necessitating the development of identification protocols that are rapid, sensitive, and precise. The polymerase chain reaction (PCR) has shown great promise in its ability to identify and quantify individual organisms from a mixed culture environment; however, the cost effectiveness of single organism PCR reactions is quickly becoming an issue. Our laboratory has developed a simple method to identify multiple fungal species, Stachybotrys chartarum, Aspergillus versicolor, Penicillium purpurogenum, and Cladosporium spp. by performing multiplex PCR and distinguishing the different reaction products by their mobility during agarose gel electrophoresis. The amplified genes include the beta-Tubulin gene from A. versicolor, the Tri5 gene from S. chartarum, and ribosomal sequences from both P. purpurogenum and Cladosporium spp. This method was found to be both rapid and easy to perform, while maintaining high sensitivity and specificity for characterizing isolates, even from a mixed culture.


Because of the accumulating evidence that suggests that numerous unhealthy conditions in the indoor environment are the result of abnormal growth of the filamentous fungi (mold) in and on building surfaces, it is necessary to accurately reflect the organisms responsible for these maladies and to identify them in precise and timely manner. To this end, we have developed a method that is cost effective, easy to perform, and accurate. We performed a simple polymerase chain reaction restriction fragment length polymorphism (PCR/RFLP) analysis on multiple members of species known to negatively influence the indoor environment. The genera analyzed were Stachybotrys, Penicillium, Aspergillus, and Cladosporium. Each organism underwent PCR with universal primers that amplified ribosomal sequences generating products from 550 to 600 bp followed by enzymatic digestion with EcoRI, HaeIII, Mspl, and Hinfl. Our results show that using this combination of restriction enzymes enables the identification of these fungal organisms at the species level.
(2005) [Allergic diseases and immunological resistance in children from a petroleum area].
Dautov, FF, Iurk, SA and Khakimova, RF Journal/Gig Sanit. 51-3.

The incidence of allergic diseases was studied in the children living in an oil-extracting region of the Republic of Udmurtia. A hygienic assessment of the level of environmental pollution was made in the study areas. The increased atmospheric contamination was ascertained to cause an increase in the incidence of allergic diseases in children. There was a correlation between the concentration of noxious substances as part of the ambient air and the prevalence of allergic diseases in children. The studies suggest that the children living in the oil-extracting area have worse parameters of nonspecific resistance than do the control children. The findings serve as the basis for developing measure to lower environmental pollution and to reduce the incidence of allergic diseases in children.


The neuronal form of nitric oxide synthase (nNOS) was generally assumed to be constitutively expressed at a constant level. However, it is now becoming recognized that its expression can be modulated by a number of physiological and pathophysiological conditions. Previously, we reported that nNOS expression is up-regulated after prolonged muscarinic M(1) receptor stimulation. In this work, we report that muscarinic receptor activation signals the up-regulation of nNOS via multiple pathways in N1E-115 mouse neuroblastoma cells. These include protein kinase C (PKC) activation, cytosolic calcium mobilization and NO production. Further characterization showed that the half-life of nNOS is slightly, but significantly, increased in agonist-pretreated cells compared with vehicle-treated control cells. Based on these data, it appears that the level of nNOS expression is modulated in a complex manner by a number of mechanisms that include, but might not be limited to, those described here.

(2005) Studying toxicants as single chemicals: does this strategy adequately identify neurotoxic risk?
Cory-Slechta, DA Journal/Neurotoxicology. 26: 491-510.
Despite the fact that virtually all chemicals exposure of humans are to mixtures, and that these mixed exposures occur in the context of numerous other risk modifiers, our current understanding of human health risks is based almost entirely on the evaluation of chemicals studied in isolation. This paper describes findings from our collaborative studies that prompt questions about these approaches in the context of neurotoxicology. The first section describes studies investigating the interactions of maternal Pb exposure with maternal stress. Examined across a range of outcome measures, it shows that maternal Pb can modulate the effects of maternal stress, and, conversely, stress modifies the effects of Pb. Further, effects of Pb+stress could be detected in the absence of an effect of either risk factor alone, and, moreover, the profile of effects of Pb alone differs notably from that of Pb+stress. Collectively, interactions were not systematic, but differed by brain region, gender and outcome measure. A second section describes outcomes of studies examining combined exposures to the pesticides paraquat (PQ) and maneb (MB) during development which likewise reveal potentiated effects of combined exposures. They also demonstrate examples of both progressive and cumulative neurotoxicity, including a marked vulnerability following gestational exposure to MB, to the effects of PQ, a pesticide with no structural relationship to MB. The ability of current hazard identification and risk assessment approaches to adequately identify and encompass such effects remains an important unanswered question. One consideration proposed for further evaluating potential interactions that may be of significance for the nervous system is based on a multi-hit hypothesis. It hypothesizes that the brain may readily compensate for the effects of an individual chemical itself acting on a particular target system, but when multiple target or functional sites within that one system are attacked by different mechanisms (i.e., multiple chemical exposures or chemical exposures combined with other risk factors), homeostatic capabilities may be restricted, thereby leading to sustained or cumulative damage.


OBJECTIVES: Structural stigma and discrimination occur when an institution like a newspaper, rather than an individual, promulgates stigmatizing messages about mental illness. This study examined current trends in the news media on reporting topics of mental illness. METHODS: All relevant stories (N=3,353) in large U.S. newspapers were identified and coded during six weeklong periods in 2002. Stories were coded by themes that fit into four categories: dangerousness, blame, treatment and recovery, and advocacy action (that is, calls for public policy and action that increase the quality of care or opportunities for those with mental illness). RESULTS: Thirty-nine percent of all stories focused on dangerousness and violence; these stories most often ended up in the front section. Few stories promulgated the idea that either the person or the family was responsible for mental illness (2 percent). Instead, stories
about genetic or biological or environmental causation (for example, stress and trauma) were more common (15 percent). There were equal numbers of stories about biological and psychosocial treatments (13 and 14 percent, respectively). Four percent of all treatment-related stories addressed recovery. Twenty percent of stories contained themes that fell into the broad category of advocacy action. These stories addressed the shortage of resources in the public mental health arena, the need for better care, the absence of good-quality housing, and the goal of insurance parity.

CONCLUSIONS: Data on how mental illness is represented in newspapers yield a useful perspective on structural stigma and the policies and standards that are applied by the news media. These findings have implications for influencing the press.

Gamma-hexachlorocyclohexane (lindane) is a pesticide with the potential to produce long-term effects on fear or anxiety due to its targeting of the GABA(A) receptor in the brain. Multiple chemical sensitivity (MCS) is a human condition that has been attributed to repeated chemical exposures, with pesticides heavily implicated in the initiation of MCS. The symptoms in MCS patients are wide ranging but prominent among these in a subset of patients is increased evoked panic responses. Drawing a parallel between these responses in MCS patients and a panic model in rats, these studies explored a potential animal model for MCS. The effects of repeated lindane exposure on conditioned fear behavior was examined in adult male Sprague-Dawley rats. Animals were administered vehicle or lindane (intraperitoneally) for either 3days/week (1, 2 or 5mg) or 5days/week (2mg) over 2 weeks, and 18 days later were examined for anxiety levels on an elevated plus-maze. One day later, animals were trained for fear conditioning to an odor conditioned stimulus (CS). Freezing behavior was measured 1 day later in the context where pairing occurred, and then for a total of 6 days in a different environment in which either no CS or the CS was presented. After a second 18-day period of no treatment, rats were again tested for their freezing response to the CS for 2 days. Lindane pretreatment did not alter elevated plus-maze performance, nor did it alter contextual freezing behavior. However, pretreatment with lindane decreased the extinction of fear conditioning to the CS such that freezing behavior in controls was significantly lower than in lindane-pretreated rats, and this effect persisted during testing 18 days later. The results indicate that repeated low-level lindane exposure may produce long-lasting changes in anxiety-related neural circuitry. This suggests that odor-triggered symptoms associated with an aversive event may persist in MCS patients because of the ability of some chemicals to alter fear or anxiety circuitry in the brain.
(2005) **Evaluation of spermatogenesis and fertility in F1 male rats after in utero and neonatal exposure to extremely low frequency electromagnetic fields.**

Aim: To determine whether in utero and neonatal exposure to a 60 Hz extremely low frequency electromagnetic field (EMF) results in spermatotoxicity and reproductive dysfunction in the F1 offspring of rats. Methods: Age-matched, pregnant Sprague-Dawley rats were exposed continuously (21 h/day) to a 60 Hz EMF at field strengths of 0 (sham control), 5, 83.3 or 500 microT from day 6 of gestation through to day 21 of lactation. The experimentally generated magnetic field was monitored continuously (uninterrupted monitoring over the period of the study) throughout the study. Results: No exposure-related changes were found in exposed or sham-exposed animals with respect to the anogenital distance, preputial separation, testis weight, testicular histology, sperm count, daily sperm production, sperm motility, sperm morphology and reproductive capacity of F1 offspring. Conclusion: Exposure of Sprague-Dawley rats to a 60 Hz EMF at field strengths of up to 500 microT from day 6 of gestation to day 21 of lactation did not produce any detectable alterations in offspring spermatogenesis and fertility.


(2005) **Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma.**

BACKGROUND: In the United States, Puerto Ricans and Mexicans have the highest and lowest asthma prevalence, morbidity, and mortality, respectively. Ethnic-specific differences in the response to drug treatment may contribute to differences in disease outcomes. Genetic variants at the beta(2)-adrenergic receptor (beta(2)AR) may modify asthma severity and albuterol responsiveness. We tested the association of beta(2)AR genotypes with asthma severity and bronchodilator response to albuterol in Puerto Ricans and Mexicans with asthma. METHODS: We used both family-based and cross-sectional tests of association with 8 beta(2)AR single nucleotide polymorphisms in 684 Puerto Rican and Mexican families. Regression analyses were used to determine the interaction between genotype, asthma severity, and bronchodilator drug responsiveness. RESULTS: Among Puerto Ricans with asthma, the arginine (Arg) 16 allele was associated with greater bronchodilator response using both family-based
and cross-sectional tests (p = 0.00001-0.01). We found a strong interaction of baseline FEV(1) with the Arg16Glycine (Gly) polymorphism in predicting bronchodilator response. Among Puerto Ricans with asthma with baseline FEV(1) < 80% of predicted, but not in those with FEV(1) > 80%, there was a very strong association between the Arg16 genotype and greater bronchodilator responsiveness. No association was observed between Arg16Gly genotypes and drug responsiveness among Mexicans with asthma. CONCLUSIONS: Ethnic-specific pharmacogenetic differences exist between Arg16Gly genotypes, asthma severity, and bronchodilator response in Puerto Ricans and Mexicans with asthma. These findings underscore the need for additional research on racial/ethnic differences in asthma morbidity and drug responsiveness.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15557128


Given the suspected effects of estrogens on breast cancer, xenoestrogenic insecticides may be a risk factor. Studies of the weak xenoestrogen, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE), have failed to demonstrate a causal relationship, though another estrogenic organochlorine insecticide, dieldrin, belonging to the cyclodiene family, has recently been linked to breast cancer. Other cyclodiienes such as heptachlor epoxide (HE) and oxychlordane (OC) present in breast tissue have not been evaluated as rigorously, presumably due to their lower concentration and lower recovery using solvent extraction procedures. We used sparging extraction coupled with gas chromatography to determine the levels of HE, OC, and DDE in adipose tissue within breast biopsies in a series of 34 women evaluated for breast abnormality. Of the three insecticides tested, only HE (p=0.007) was positively associated with prevalence of breast cancer in the biopsies. In rapid, non-genomic studies using isolated human leukocytes, flow cytometric methods were used to measure HE-induced oxidants and DNA damage. These studies indicated that HE, at concentrations similar to those in breast biopsies, induced an inverted-U increase in intracellular oxidants and DNA strand breaks [both blocked by specific nitric oxide- (NO-) synthesis blockade with L-NmMA] in human polymorphonuclear leukocytes (PMNs). HE-treated PMNs also induced damage to surrounding lymphocytes in mixed-leukocyte incubations (also inhibited by NO blockade). The HE-induced changes in NO were inhibited by 17beta-estradiol-(17beta-E2) receptor antagonists and were mimicked by similar concentrations of 17beta-E2. The addition of tumor necrosis factor-alpha (TNF-alpha) increased intracellular oxidants and DNA damage and shifted the responses to lower HE concentrations. This study, along with others, suggests that HE-induced NO production may contribute to initiation, promotion, and progression of cancer.
MCS Scientific Studies Library.enl  Page 101


Acetylcholinesterase (AChE) is one of several hundred serine hydrolases in people potentially exposed to about 80 organophosphorus (OP) compounds important as insecticides or chemical warfare agents. The toxicology of OPs was interpreted until recently almost solely on the basis of AChE inhibition. It is assumed that each serine hydrolase has a specific function and proposed that every OP compound has a unique inhibitory profile. This review considers the progress in sifting the expanding list of potential serine hydrolase toxicological targets. About 50 serine hydrolase targets have been recognized but only a few studied thoroughly. The toxicological relevance of known secondary OP targets is established mainly from observations with humans (butyrylcholinesterase and neuropathy target esterase-lysophospholipase) and studies with mice (cannabinoid CB1 receptor, carboxylesterase, lysophospholipase and platelet activating factor acetylhydrolase) and hen eggs (arylformamidase or kynurenine formamidase). Pesticides most commonly shown to inhibit these targets in experimental vertebrates are chlorpyrifos and tribufos. Generally the levels of environmental and occupational OP pesticide exposure are well below those causing in vivo inhibition of secondary serine hydrolase targets. Although exposure to OP insecticides is decreasing from stricter regulations and the development of resistant pest strains, it will continue to some degree for decades in the future. Only two OPs are used as pharmaceuticals, i.e. echothiophate as an ophthalmic for treatment of glaucoma and metrifonate as an anthelmintic for Schistosoma (and formerly as a candidate drug for improved cognitive function in Alzheimer's disease). In safety evaluations, knowledge on known OP targets must be balanced against major gaps in current understanding since more than 75% of the serine hydrolases are essentially unknown as to OP targeting and relevance, i.e. it is not clear if they play a role in OP toxicology.


OBJECTIVE: The objective of this study was to investigate the linkage between asthma and chemical hypersensitivity. METHODS: The authors conducted a population study with a random sample of 1057 geographically weighted cases to determine the prevalence of both asthma and chemical hypersensitivity in the American population and to explore their co-occurrence. RESULTS: A total of 14.1% of the respondents reported being diagnosed with asthma and 11.2% reported a
hypersensitivity to chemicals. Of those with asthma, 27.2% also reported being hypersensitive to chemicals and 7.4% reported also being diagnosed with multiple chemical sensitivities (MCS). Of those diagnosed with MCS, 42% reported also being diagnosed with asthma. Additionally, 29.7% of those with asthma said air fresheners caused breathing difficulties, and 37.2% found scented products irritating.

CONCLUSIONS: The results indicate that there is significant overlap between some forms of asthma and chemical hypersensitivity.


BACKGROUND: The documentation produced by public and private institutions in relation to the chemical risk constitutes an essential tool for prevention. The objective of this research is to locate and to revise the documents related to the management of the prevention of chemical risk focus to PYMES in Spain from 1995 to 2004.

METHODS: The methodology carried out for the selection of the bibliographical materials has been the consultation of automated databases and Web pages.

RESULTS: 812 documents have been identified. Most corresponds to grey literature. The thematic more frequent has been the security and the most frequent objective of the papers has been the prevention. Most of the documents go to the technical sector.

CONCLUSIONS: The results suggest that although that there is a great diversity of documents in Spain dedicated to the prevention of chemical risk it seems convenient: 1) to increase their diffusion, 2) to pay attention to the communication of the risks, 3) to investigate and to translate the research in good practice.


There is significant evidence that the pathogenesis of several neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, Friedreich's ataxia (FRDA), multiple sclerosis and amyotrophic lateral sclerosis, may involve the generation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) associated with mitochondrial dysfunction. The mitochondrial genome may play an essential role in the pathogenesis of these diseases, and evidence for mitochondria being a site of damage in neurodegenerative disorders is based in part on observed decreases in the respiratory chain complex activities in Parkinson's, Alzheimer's, and Huntington's disease. Such defects in respiratory complex activities, possibly
associated with oxidant/antioxidant imbalance, are thought to underlie defects in energy metabolism and induce cellular degeneration. The precise sequence of events in FRDA pathogenesis is uncertain. The impaired intramitochondrial metabolism with increased free iron levels and a defective mitochondrial respiratory chain, associated with increased free radical generation and oxidative damage, may be considered possible mechanisms that compromise cell viability. Recent evidence suggests that frataxin might detoxify ROS via activation of glutathione peroxidase and elevation of thiols, and in addition, that decreased expression of frataxin protein is associated with FRDA. Many approaches have been undertaken to understand FRDA, but the heterogeneity of the etiologic factors makes it difficult to define the clinically most important factor determining the onset and progression of the disease. However, increasing evidence indicates that factors such as oxidative stress and disturbed protein metabolism and their interaction in a vicious cycle are central to FRDA pathogenesis. Brains of FRDA patients undergo many changes, such as disruption of protein synthesis and degradation, classically associated with the heat shock response, which is one form of stress response. Heat shock proteins are proteins serving as molecular chaperones involved in the protection of cells from various forms of stress. In the central nervous system, heat shock protein (HSP) synthesis is induced not only after hyperthermia, but also following alterations in the intracellular redox environment. The major neurodegenerative diseases, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease (HD) and FRDA are all associated with the presence of abnormal proteins. Among the various HSPs, HSP32, also known as heme oxygenase I (HO-1), has received considerable attention, as it has been recently demonstrated that HO-1 induction, by generating the vasoactive molecule carbon monoxide and the potent antioxidant bilirubin, could represent a protective system potentially active against brain oxidative injury. Given the broad cytoprotective properties of the heat shock response there is now strong interest in discovering and developing pharmacological agents capable of inducing the heat shock response. This may open up new perspectives in medicine, as molecules inducing this defense mechanism appear to be possible candidates for novel cytoprotection strategies. In particular, manipulation of endogenous cellular defense mechanisms, such as the heat shock response, through nutritional antioxidants, pharmacological compounds or gene transduction, may represent an innovative approach to therapeutic intervention in diseases causing tissue damage, such as neurodegeneration.

(2005) [Microbiological quality of indoor air at the School of Building and Environmental Engineering at Bialystok University of Technology]. Butarewicz, A Journal/Rocz Panstw Zakl Hig. 56: 199-206.

The investigation of microbiological rate of indoor air pollution on Faculty of Building and Environmental Engineering at Bialystok University of Technology were made by sedimentation method in accordance with Polish standards (PN-89/Z-04111/01,02,03).
Six series of measurements were carried out from autumn 2002 to spring 2003. The results show bad microbiological quality of indoor air on Faculty of Building and Environmental Engineering at Bialystok University of Technology. It was found that the number of Staphylococcus, Actinomycetales as well as the total count of bacteria were too high and broke the Polish regulations of the clear air. Because of the students' and other workers' safety, monitoring of microbiological pollution of the indoor air must be done and existing emergency to improve the quality of the air must be lead.


INTRODUCTION: The specific causes and mechanism(s) for asthma occurring among occupants of non-residential buildings with poor indoor air quality are not known, but allergic and nonallergic processes are possible explanations.

METHODS: Repeated indoor air quality measurements were made while employees were working in a building where cigarette smoking was allowed. Seven of 19 employees who sought medical care from their private physicians because of respiratory complaints received a diagnosis of asthma. Subsequently, 19 symptomatic employees were examined at the University of South Florida (USF) 2 +/- 0.8 months (mean +/- SD) after removal from the building.

RESULTS: The first floor of the building, where employee complaints were prevalent, was characterized by markedly reduced outdoor fresh air supply, diminished air circulation to the occupant spaces, and elevated airborne concentrations of formaldehyde. Nineteen workers examined at the USF 2 +/- 0.8 months after leaving the building reported ear, nose, and throat irritation and asthma-like symptoms while working in the building. There was resolution of symptoms in most of the seven employees (37%) with asthma previously diagnosed by their private physician. In fact, 16 of 19 subjects (84%) reported resolution or significant improvement of symptoms. Among 11 persons with symptoms suggesting asthma while working in the building, 4 persons (21%) showed a negative provocative concentration of methacholine producing a 20% fall in FEV1, including two subjects with doctor-diagnosed asthma.

CONCLUSIONS: Confirmation of building-related asthma is influenced by time factors and the clinical criteria used for diagnosis. A nonallergic mechanism seems operative in our cases. While considered an example of occupational asthma, building-related asthma is a challenge for the practicing physician to confirm retrospectively.

Insulin-stimulated glucose disposal in skeletal muscle proceeds predominantly through a nonoxidative pathway with glycogen synthase as a rate-limiting enzyme, yet the mechanisms for insulin activation of glycogen synthase are not understood despite years of investigation. Isolation of putative insulin second messengers from beef liver yielded a pseudo-disaccharide consisting of pinitol (3-O-methyl-d-chiro-inositol) beta-1,4 linked to galactosamine chelated with Mn(2+) (called INS2). Here we show that chemically synthesized INS2 has biological activity that significantly enhances insulin reduction of hyperglycemia in streptozotocin diabetic rats. We used computer modeling to dock INS2 onto the known three-dimensional crystal structure of protein phosphatase 2C (PP2C). Modeling and FlexX/CScore energy minimization predicted a unique favorable site on PP2C in a surface cleft adjacent to the catalytic center. Binding of INS2 is predicted to involve formation of multiple H-bonds, including one with residue Asp163. Wild-type PP2C activity assayed with a phosphopeptide substrate was potently stimulated in a dose-dependent manner by INS2. In contrast, the D163A mutant of PP2C was not activated by INS2. The D163A mutant and wild-type PP2C in the absence of INS2 had the same Mn(2+)-dependent phosphatase activity with p-nitrophenyl phosphate as a substrate, showing that this mutation did not disrupt the catalytic site. We propose that INS2 allosterically activates PP2C, fulfilling the role of a putative mediator mimetic of insulin signaling to promote protein dephosphorylation and metabolic responses.

-------------------------------------------------------------------


Environmental illnesses raise diagnostic and therapeutic conflicts in scientific discussions and clinical practice. When a patient's health-belief model, based on environmental origins, does not match that of the expert, the therapeutic relationship can be endangered. Our study investigates this discrepancy, which has not been empirically evaluated so far. Patient (n=61) and expert disease concepts were systematically investigated. Our results indicate that in cases in which both concepts are favourable, the patient suffered minor psychiatric disorders with stable psychic structures and the symptoms were associated with medical or environmental causes. If both concepts were unfavourable, a higher proportion of psychiatric disorders with unstable psychic structures were present. In the case of incongruent concepts, the expert evaluations allow a more accurate assessment of the psychiatric diagnoses, psychic states and the psychic attribution of somatic and psychic burden.
(2005) [Psychiatric, medical and environmental factors in patients suffering from environment-related disorders].

BACKGROUND: A multidisciplinary approach and a multi-modal methodology are needed to assess idiopathic environmental illnesses. SAMPLE: 61 patients took part in all diagnostic steps. METHOD: In the Basel pilot research project on environmental illness, a threefold diagnostic approach was established: patients had a medical and allergological examination, a psychiatric and psychological exploration and an environmental analysis of their homes. RESULTS: There is a clear psychological impact on environmental illness: 46 % of the symptoms could be traced back to psychological factors, and 18 % seemed to be influenced by them. Nevertheless, in 28 % more than one of the three dimensions was seen as important. Values within the self reporting questionnaires show high correspondence. Whereas patients and experts agree in many instances that there are psychological factors, they disagree in attributing clinical relevance to them. This discrepancy is helpful for explaining the difficulties therapists may encounter as to the patients' compliance.
CONSEQUENCES: Environmental illness should be diagnosed and treated on an interdisciplinary basis including psychosomatic medicine.


This review examines the current literature regarding psychiatric comorbidities associated with fibromyalgia. The aim of this review is to enhance understanding of psychiatric disorders that, alone or in combination with other physiologic (eg, neuroendocrine dysfunction) and psychosocial factors (eg, poor coping skills), may contribute to abnormal pain sensitivity and other illness behaviors of individuals with fibromyalgia. The review first identifies the psychiatric comorbidities that are associated most often with fibromyalgia and tend to aggregate within families of individuals with this disorder. It then examines the literature regarding the extent to which psychiatric illness, environmental stressors, or other psychosocial factors may contribute to the development of fibromyalgia. The review also presents recent findings concerning the extent to which psychosocial factors may contribute to treatment-related outcomes in pain and other health status variables among patients with fibromyalgia.
(2005) [Building related illness].

Following the changes carried out in recent years in buildings, such as ventilation systems, computers, etc., a series of diseases, that are related to this, have been described. This paper concentrates on the syndrome of the sick building, which is formed by a group of symptoms normally suffered by workers in the same "sick" building. This syndrome is related to its interior ambience, since the clinical manifestations appear some hours after entering the building and improves a few minutes after leaving this ambience. The origin is probably multifactorial: volatile airborne pollutants, the ventilation system, factors related to work organisation, or even dependent on the host. Since there is no single cause, we enumerate the risk factors in developing this syndrome as well as the steps for reaching a diagnosis and useful measures for preventing the sick building.


PURPOSE OF REVIEW: The accurate diagnosis of food allergy is crucial not only for the right treatment but also for the avoidance of unnecessary diets. The diagnostic work-up of suspected food allergy includes the measurement of food-specific IgE antibodies using serologic assays, the skin prick test, elimination diets and oral provocation tests. In addition, some approaches are either under further rigorous investigation (the atopy patch test) or are already in widespread use, particularly by practitioners of alternative or complementary medicine, but are considered unproven. These diagnostic methods include specific IgG to foods, provocation/neutralization testing, kinesiology, cytotoxic tests and electrodermal testing. This review covers some of the most common scientifically validated and unproven approaches used in the diagnosis of food allergy. RECENT FINDINGS: For specific serum IgE and the SPT, decision points have been established for some foods, allowing prediction of clinical relevance. The APT may be helpful, especially when considered in combination with defined levels of specific IgE. In regard to other approaches, most scientific studies do refute the usefulness of these approaches. SUMMARY: In most patients, controlled oral food challenges remain the gold standard in the diagnostic work-up of suspected food allergy. The skin prick test and measurement of specific IgE antibodies to food extracts, individual allergens or allergenic peptides are helpful in the diagnostic approach. Food-specific IgG continues to be an unproven or experimental test. The other alternative and complementary techniques have no proven benefit and may endanger patients via misdiagnosis.
(2005) Psychobiological personality dimensions in two environmental-illness patient groups.

The aim of the present study was to investigate the psychobiological personality dimensions in two subgroups of patients with environmental illness (EI). Fifty-nine patients, 34 women and 25 men (aged 32-69 years), were referred for symptoms allegedly caused by abnormal sensitivity to either dental fillings (DF; n=26) or electromagnetic fields (EMF; n=33). For the evaluation of personality, the Swedish 238-item version of the Temperament and Character Inventory (TCI) was used. Compared with a control group, the EMF group scored higher on the temperament dimension Persistence. The DF group scored higher on the TCI subscales Harm Avoidance (fatigability and asthenia) and Self-Directedness (self-acceptance). Women scored higher than men did on the Novelty Seeking and Reward Dependence (RD) dimensions in the DF group and on RD in the control group, indicating an inherited gender difference. No differences were found between men and women in the EMF group. Our results indicate that the high level of persistence found in the EMF group and the high level of fatigability and asthenia in combination with high self-acceptance found in the DF group represent vulnerable personalities. No significant differences were found between the two patient groups, indicating that these groups are quite similar regarding personality. This vulnerability can be expressed as various mental and somatic symptoms, which can be interpreted as EI symptoms by the affected individual.


INTRODUCTION: Previous research indicates that a large cohort of veterans from the 1991 Gulf War report polysymptomatic conditions. These syndromes often involve neurocognitive complaints, fatigue, and musculoskeletal symptoms, thus overlapping with civilian illnesses from low levels of environmental chemicals, chronic fatigue syndrome, and fibromyalgia. METHODS: To test for time-dependent changes over repeated intermittent exposures, we evaluated objective performance on a computerized visual divided attention test in chronically unhealthy Gulf War veterans (n = 22 ill with low-level chemical intolerance (CI); n = 24 ill without CI), healthy Gulf War veterans (n = 23), and healthy Gulf War era veterans (n = 20). Testing was done before and after each of three weekly, double blind, low-level JP-8 jet fuel or clean air sham exposure laboratory sessions, including acoustic startle stimuli. RESULTS: Unhealthy veterans receiving jet fuel had faster mean peripheral reaction times over
sessions compared with unhealthy veterans receiving sham clean air exposures. Unhealthy Gulf veterans with CI exhibited faster post- vs. pre-session mean central reaction times compared with unhealthy Gulf veterans without CI. Findings were controlled for psychological distress variables. DISCUSSION: These data on unhealthy Gulf veterans show an acceleration of divided attention task performance over the course of repeated low-level JP-8 exposures. The present faster reaction times are consistent with rat neurobehavioral studies on environmental toxicant cross-sensitization and nonlinear dose-response patterns with stimulant drugs, as well as some previous civilian studies using other exposure agents. Together with previous research findings, the data suggest involvement of central nervous system dopaminergic pathways in affected Gulf veterans.

(2005) Depression research in homeopathy: hopeless or hopeful?
Bell, IR Journal/Homeopathy. 94: 141-4.

(2005) All evidence is equal, but some evidence is more equal than others: can logic prevail over emotion in the homeopathy debate?

Bell, IR Journal/Explore (NY). 1: 299-301.


Male Wistar rats were exposed to one-trial step-down inhibitory avoidance training using a 0.5 mA footshock. Through bilaterally implanted indwelling cannulae, they received bilateral 0.5 microl infusions of saline, mecamylamine (1.0 or 10.0 microg side), or nicotine (0.6 or 3.0 microg/side) into the basolateral complex of the amygdaloid nucleus (BLA). Infusions were either 10 min before training (Experiment 1)
or 4 min after training (Experiment 2). In Experiment 1, the animals were tested three times: first for working memory (WM) 5 s after training, then for short-term memory (STM) 90 min later, and finally for long-term memory (LTM) 24 h later. Mecamylamine depressed and nicotine enhanced WM, STM, and LTM. In Experiment 2, the treatments were given after WM was presumably over. Again, mecamylamine inhibited and nicotine enhanced STM and LTM. The results indicate that nAChRs in BLA participate in the regulation of WM formation and STM and LTM acquisition and consolidation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15721794

(2005) Biologic monitoring of exposure to environmental chemicals throughout the life stages: requirements and issues for consideration for the National Children's Study.

Biomonitoring of exposure is a useful tool for assessing environmental exposures. The matrices available for analyses include blood, urine, breast milk, adipose tissue, and saliva, among others. The sampling can be staged to represent the particular time period of concern: preconceptionally from both parents, from a pregnant woman during each of the three trimesters, during and immediately after childbirth, from the mother postnatally, and from the child as it develops to 21 years of age. The appropriate sample for biomonitoring will depend upon matrix availability, the time period of concern for a particular exposure or health effect, and the different classes of environmental chemicals to be monitored. This article describes the matrices available for biomonitoring during the life stages being evaluated in the National Children's Study; the best biologic matrices for exposure assessment for each individual chemical class, including consideration of alternative matrices; the analytical methods used for analysis, including quality control procedures and less costly alternatives; the costs of analysis; optimal storage conditions; and chemical and matrix stability during long-term storage.

Baldwin, CM, Bell, IR, Guerra, S and Quan, SF Journal/Sleep Breath. 9: 111-8.

This study describes associations between obstructive sleep apnea (OSA), intake of food rich in antioxidant nutrients, and ischemic heart disease (IHD) in military veterans. Subjects were male veterans (n=211), 54 to 85 years of age, and enrolled in primary
care clinics at the Southern Arizona Veterans Affairs Health Care System (SAVAHCS), Tucson, AZ. Measures included the SAVAHCS Minority Vascular Center Questionnaire, the Sleep Heart Health Study Sleep Habits Questionnaire, the Arizona Food Frequency Questionnaire, height, weight, and blood pressure. Veterans with OSA were significantly more likely to be obese, to have elevated systolic blood pressure and physician-diagnosed IHD, more likely to undergo coronary angiography, and less likely to consume foods rich in cardioprotective antioxidants compared to veterans without OSA. After adjusting for confounding variables, the association between OSA and IHD remains significant [adjusted OR=2.99, confidence interval (CI)=1.07-8.42]. These data reinforce the importance of recognizing OSA within the veterans affairs health care system and suggest that early detection of OSA may improve veterans' health and well-being and reduce associated medical costs.


OBJECTIVE: Idiopathic environmental intolerance (IEI), also known as multiple chemical sensitivity, is a chronic, polysymptomatic condition that cannot be explained by an organic disease. Physical and psychological complaints are believed to be sustained by low levels of chemically unrelated substances in the environment. At present, it is unclear whether IEI is an environmental illness or a variant of somatoform disorders (SFD). This study examined whether IEI can be distinguished from SFD with respect to self-reported symptoms, trait anxiety, body-related cognitions, and symptom attributions. METHODS: We compared 54 subjects with IEI, 54 subjects with SFD but without IEI, and 44 subjects with neither IEI nor SFD on symptom scales, psychological questionnaires, and structured interviews for IEI, depression, anxiety, and SFD. RESULTS: More than half of the IEI subjects met Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria of SFD. This group shared both symptoms and psychological features of somatization with the SFD group. IEI subjects who did not fulfill criteria for a specific SFD were less impaired by their chemical sensitivity but differed nevertheless from nonsomatoform controls by significantly higher symptom scores, higher trait anxiety, a focus on autonomic sensations, and more pronounced somatic symptom attributions. These psychological features were significantly associated with the burden of somatic symptoms in both SFD and IEI. Furthermore, self-reported allergy but not total immunoglobulin E correlated with symptom burden in the total sample. CONCLUSIONS: The similarity of IEI and SFD regarding symptoms and psychological features of somatization support the hypothesis that IEI is a variant of SFD.

(2005) Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age.

STUDY OBJECTIVES: We sought to identify early life factors (ie, first 4 years) associated with wheeze, asthma, and bronchial hyperresponsiveness (BHR) at age 10 years, comparing their relative influence for these conditions. METHODS: Children were seen at birth, and at 1, 2, 4, and 10 years of age in a whole-population birth cohort study (1,456 subjects). Information was collected prospectively on genetic and environmental risk factors. Skin-prick testing was performed at 4 years of age. Current wheeze (in the last 12 months) and currently diagnosed asthma (CDA) [ie, current wheeze and ever-diagnosed asthmatic subject] were recorded at 10 years of age when BHR was measured at bronchial challenge. Independent significant risk factors for these outcomes were identified by logistic regression. RESULTS: Independent significance for current wheeze occurred with maternal asthma (odds ratio [OR], 2.08; 95% confidence interval [CI], 1.27 to 3.41) and paternal asthma (OR, 2.12; 95% CI 1.29 to 3.51), recurrent chest infections at 2 years (OR, 3.98; 95% CI, 2.36 to 6.70), atopy at 4 years of age (OR, 3.69; 95% CI, 2.36 to 5.76), eczema at 4 years of age (OR, 2.15; 95% CI, 1.24 to 3.73), and parental smoking at 4 years of age (OR, 2.18; 95% CI, 1.25 to 3.81). For CDA, significant factors were maternal asthma (OR, 2.26; 95% CI, 1.24 to 3.73), paternal asthma (OR, 2.30; 95% CI, 1.17 to 4.52), and sibling asthma (OR, 2.00; 95% CI, 1.16 to 3.43), recurrent chest infections at 1 year of age (OR, 2.67; 95% CI, 1.12 to 6.40) and 2 years of age (OR, 4.11; 95% CI, 2.06 to 8.18), atopy at 4 years of age (OR, 7.22; 95% CI, 4.13 to 12.62), parental smoking at 1 year of age (OR, 1.99; 95% CI, 1.15 to 3.45), and male gender (OR, 1.72; 95% CI, 1.01 to 2.95). For BHR, atopy at 4 years of age (OR, 5.38; 95% CI, 3.06 to 9.47) and high social class at birth (OR, 2.03; 95% CI, 1.16 to 3.53) proved to be significant.

CONCLUSIONS: Asthmatic heredity, predisposition to early life atopy, plus early passive smoke exposure and recurrent chest infections are important influences for the occurrence of wheeze and asthma at 10 years of age. BHR at 10 years of age has a narrower risk profile, suggesting that factors influencing wheezing symptom expression may differ from those predisposing the patient to BHR.


(2005) Risk factors for asthma and atopy.
PURPOSE OF REVIEW: The aim of this article is to provide information on risk factors associated with the development of atopy and asthma in childhood. RECENT FINDINGS: Several gene polymorphisms have been associated with susceptibility to asthma and allergy; complex gene-environmental interactions, however, appear to play a key role in the development of the disease. Early life sensitization to aeroallergens, presence of atopic dermatitis or allergic rhinitis, maternal smoking during pregnancy and children's environmental exposure to tobacco smoke, lower respiratory tract infections with respiratory syncytial virus and potentially with other viruses including rhinovirus and metapneumovirus, exposure to air pollutants, several perinatal factors other than maternal smoking, are among factors associated with an increased risk for development of chronic asthma. SUMMARY: The prevalence of asthma and allergic diseases is increasing progressively. Those who are involved in the care of young children should be prepared to recognize risk factors for development of these diseases and to appreciate the role of gene-environment interactions. Preventive measures established at an early age may modify the natural history of asthma and other allergic diseases.


SUMMARY This report reviews the safety of Ascorbic Acid the L-form, Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate as used in cosmetic formulations. These ingredients function primarily as antioxidants in cosmetics. Related ingredients (Ascorbyl Palmitate, Ascorbyl Dipalmitate, Ascorbyl Stearate, Erythorbic Acid, and Sodium Erythorbate) have been previously reviewed by the CIR Expert Panel and found "to be safe for use as cosmetic ingredients in the present practices of good use. " Ascorbic Acid functions as an antioxidant and pH adjuster in cosmetic formulations. Of the 431 formulations reported by FDA, 310 were used in hair dyes and colors at concentrations between 0.3% and 0.6%. The reported concentrations for other product categories were either very low ( < 0.01 %) or in the 5% to 10% range. One supplier reported preservative, skin-protectant, and sunscreen agent/UV filter functions for Ascorbic Acid in cosmetics. Calcium Ascorbate and Magnesium Ascorbate function as antioxidants and as skin-conditioning agents-miscellaneous in cosmetics, but are not currently used. Sodium Ascorbyl Phosphate functions as an antioxidant in cosmetic products and is used at concentrations ranging from 0.01 to 3%. Magnesium Ascorbyl Phosphate functions as an antioxidant in cosmetics and was reported being used in 37 formulations over a wide concentration range (0.001% to 3%). Sodium Ascorbate also functions as an antioxidant in cosmetics and was reported being used in 6 formulations over a wide concentration range (0.0003% to 0.3%). Ascorbic Acid is a GRAS
substance for use as a chemical preservative in foods and as a nutrient and/or dietary supplement. Calcium Ascorbate and Sodium Ascorbate are listed as GRAS substances for use as chemical preservatives. Estimates of median dietary intakes of Vitamin C for adults are 102 mg/day in the United States. The Tolerable Upper Intake Level for adults is set at 2 g/day according to the National Academy of Sciences. The adverse effects upon which the Upper Intake Level is based are osmotic diarrhea and gastrointestinal disturbances. L-Ascorbic Acid is readily and reversibly oxidized to L-dehydroascorbic acid and both forms exist in equilibrium in the body. In alkaline solution, L-dehydroascorbic acid is hydrolyzed to L-diketogulonic acid and this reaction is not reversible within the body. The Ascorbic Acid body pool of rats average ca. 10.7 mg/100 g/bw and was synthesized at an average of 2.6 mg/100 g/bw. Approximately 15% of Ascorbic Acid synthesized each day in rats was excreted in the urine. The remaining Ascorbic Acid was in part degraded to CO2 or oxalic acid. In guinea pigs, which require a dietary source of Ascorbic Acid, ca. 48% to 63% of ingested Ascorbic Acid was eliminated in the urine, 0.2% to 0.43% in the feces, and 5.5% in expired air. The incorporation of Ascorbic Acid was markedly greater in the adrenals, lungs, and bones of guinea pigs. In rats and guinea pigs devoid of Ascorbic Acid in the diet, an increased catabolism of Ascorbic Acid was evident. The degradation of Ascorbic Acid followed first order kinetics and the KM for the guinea pig small intestine was ca. 0.3 mM. Ascorbic Acid has an important relationship with the oxidation of transition metals such iron or copper at enzyme active sites and in food. Ascorbic Acid and Sodium Ascorbate acted as a nitrosation inhibitor in several food and cosmetic product studies. The octanol/water and stratum corneum/viable skin partition coefficients of Ascorbic Acid are 0.02 - +0.002 and 0.25 - + 0.13, respectively. Permeation rates through whole and stripped mouse skin were 3.43 f 0.74 ug/cm2/h and 33.2 f 5.2 ug/cm2/h. The following acute oral LD50s of Ascorbic Acid were re-reported: mouse > 5000 mg/kg bw, rat > 5000 mg/kg bw, rabbit > 2000 mg/kg bw, cat > 1000 mg/kg bw, dog > 5000 mg/kg bw, and guinea pig > 5000 mg/kg bw. The following oral Sodium Ascorbate LD50 values were estimated; mice > 5000 mg/kg bw, rats > 5000 mg/kg bw, and guinea pigs > 5000 mg/kg bw. The following acute parenteral LD50s of Ascorbic Acid were reported: mouse, 1058 to 5000 mg/kg/day; rat, 1000 to 5000 mg/kg/day; guinea pig, 500 to 2000 mg/kg/day; rabbit, 1000 mg/kg/day; cat, 500 to 1000 mg/kg/day; and dog, 200 mg/kg/day. Ascorbic Acid stimulated collagen production in human skin fibroblasts, pig vascular smooth muscle cells, and Tenon’s fibroblasts and enhanced mRNA transcription levels of type I and III collagen genes. Mice (500 to 1000 mg/kg bw) and guinea pigs (400 to 2500 mg/kg bw) receiving Ascorbic Acid orally daily for 7 days had no difference in appetite, weight gain, and general behavior compared to controls receiving no Ascorbic Acid; histological examination of the kidney, pancreas, liver, heart, and lungs showed no change. The maximum toxic dose of Ascorbic Acid in rats over a period of 10 weeks was 10 g/kg bw. Male and female F344/N rats and B6C3F1 mice were fed diets containing 0, 6000, 12,500, 25,000, 50,000, or 100,000 ppm Ascorbic Acid for 14 days. No compound-related clinical signs or gross or microscopic pathological effects were observed in either species. The following short-term parenteral Ascorbic Acid LD50s were reported: mouse, 1058 mg/kg/day (10 days); rat, > 600 mg/kg/day (28 days); guinea pig, 100 mg/kg/day (7 days); rabbit, 500 mg/kg/day (7 days); rabbit, 100 mg/kg/day (16 days); cat, > 500 mg/kg/day (9 days); and dog, >
2000 mg/kg/day (3 days). Male guinea pigs fed a control basal diet and given 0.5 mg to 250 mg Ascorbic Acid orally for 20 weeks had similar hemoglobin, blood glucose, serum iron, liver iron, and liver glycogen levels compared to control values. These doses of Ascorbic Acid were neither beneficial nor toxic to the guinea pigs. Male and female F344/N rats and B6C3F1, mice were fed diets containing 0, 6000, 12,500, 25,000, 50,000, or 100,000 ppm Ascorbic Acid for 91 days. Mean body weights were somewhat depressed in male mice and female rats receiving the greater doses of Ascorbic Acid. Cystic endometrial glands were found in the uteri of 4/9 female rats receiving 100,000 ppm compared to none of the controls. Alterations of the femoral bone marrow (reticulum-cell hyperplasia) were observed in 7/30 female rats receiving 25,000 ppm Ascorbic Acid or more. These changes were not seen in the female controls or in any male rat groups. Femoral bone marrow lesions were characterized by multiple foci of cells that appeared to be proliferating fibroblasts replacing the normal myeloid elements and fat cells of the marrow. Myeloid depletion was observed in 6/20 rats receiving 50,000 ppm or more Ascorbic Acid. Femoral lesions in the female rats were not considered to be potentially life-threatening. Minimum toxic doses of Sodium Ascorbate and Sodium Nitrite given to male and female Wistar rats concurrently for 6 months were 2% and 0.15%, respectively. Chronic Ascorbic Acid feeding studies showed toxic effects at dosages above 25 mg/kg bw in rats and guinea pigs. Groups of male and female rats given daily doses of 0, 1000, 1500, or 2000 mg/kg bw Ascorbic Acid for two years had no macro- or microscopically detectable toxic lesions. Mice given Ascorbic Acid subcutaneous and intravenous daily doses of Ascorbic Acid (500 to 1000 mg/kg bw) for 7 days had no changes in appetite, weight gain, and general behavior; histological examination of various organs showed no changes. Ascorbic Acid administration elevated retinal ascorbate and reduced the loss of rhodopsin and photoreceptor nuclei resulting from intense light, and was a photoprotectant when applied to mice and pig skin before exposure to both UVA and UVB. The inhibition of UVR-induced suppression of contact hypersensitivity was also noted. Magnesium Ascorbyl Phosphate administration immediately after exposure in hairless mice significantly delayed skin tumor formation and hyperplasia induced by chronic exposure to 2 kJ/m2 of UVB. Rabbit eyes subjected to severe alkali burns and 10% topical Ascorbic Acid had significantly lower percentage of ulceration or perforation when compared to controls receiving no Ascorbic Acid; alkali-injured rabbit eyes receiving a 10% Sodium Ascorbate solution had significantly lower ulcerations than in nontreated eyes, consistent with antioxidant properties. Pregnant mice and rats were given daily oral doses of 150, 250, 500, and 1000 mg/kg bw from days 6 to 15 of pregnancy. There were no indications of adult-toxic, teratogenic, or fetotoxic effects. There was no apparent effect on the embryonic and postpartum development of the young or on breeding behavior, pregnancy, parturition, and lactation capacity of the mother animals. The administration of 520 mg/kg bw of Ascorbic Acid to pregnant mice for 10 consecutive days had no clear effect on nidation or on maternal or fetal survival. The number of abnormalities observed in either soft or skeletal tissues of the treated group did not differ from those observed in the negative-control group. No increase in abortion or mortality was observed in offspring of guinea pigs, rats, and hamsters exposed to large daily doses of Ascorbic Acid during pregnancy. Ascorbic Acid was a nonteratogen in the in vitro micromass assay (single cell suspensions of midbrain and
limb-buds from 13-day rat embryos). Ascorbic Acid and Sodium Ascorbate were not genotoxic in several bacterial and mammalian test systems, consistent with the antioxidant properties of these chemicals. In the presence of certain enzyme systems or metal ions, positive results were seen, consistent with these chemicals acting as pro-oxidants in these test conditions. In rats given daily doses of 1000, 1500, or 2000 mg/kg bw of L-Ascorbic Acid for 2 years, no adverse effects were observed in hematological examinations, urinalysis, liver, or renal function tests. Gross examination revealed no toxic lesions attributable to Ascorbic Acid. The National Toxicology Program conducted a 2-year carcinogenesis bioassay of Ascorbic Acid (25,000 and 50,000 ppm) in F344/N rats and B6C3F1 mice. Ascorbic Acid was not carcinogenic in either sex of both rats and mice. Inhibition of carcinogenesis and tumor growth related to Ascorbic Acid’s antioxidant properties has also been reported. Sodium Ascorbate has been shown to promote the development of urinary carcinomas in two-stage carcinogenesis studies. This effect appears related to sodium ion concentration and pH in urine and can be produced by many chemicals. Ascorbic Acid was found to effectively inhibit nitrosamine yield in several test systems. Healthy adult males had increased oxalate excretion with the daily ingestion of 9 g of Ascorbic Acid. Excretion of Ascorbic Acid takes place by glomerular filtration and active tubular resorption. Ascorbic Acid was found in the following human tissues; adrenal glands, pituitary gland, liver, spleen, lungs, kidneys, testes, thyroid, heart muscle, skeletal muscle, brain, pancreas, eye lens, plasma, and saliva. The calculated KM and Vmax for Ascorbic Acid uptake in the human small intestine were 5.44 mM and 0.28 mM/cm/h, respectively. Absorption of Ascorbic Acid does decline at high doses. The typical body pool size is 1500 mg, of which 3% to 4% is utilized daily. The greatest human tissue concentrations are found in the adrenal and pituitary glands, with a lesser amount in the brain, pancreas, spleen, and liver. The renal threshold for Ascorbic Acid is reached at approximately 1.5 mg/dl of plasma. Average 24-h excretion in normal adults is 8 to 27 mg. Doses of Ascorbic Acid up to 6000 mg given to adults and children for more than 1400 days had toxic effects in five adults and four infants and included nausea, vomiting, diarrhea, flushing of the face, headache, fatigue, and disturbed sleep. No harmful effects were observed in one woman and three men given 1000 mg/day Ascorbic Acid administration for 3 months. Oxaluria, renal stones, acidosis, glycosuria, renal tubular disease, gastrointestinal disturbances, and fatigue were reported toxic effects in humans taking 250 mg to 15 g Ascorbic Acid per day. Dermal application of Ascorbic Acid to patients with radiation dermatitis and burn victims produced no adverse effects. Ascorbic Acid was a photoprotectant in clinical human UV studies at doses well above the MED. An opaque cream containing 5% Ascorbic Acid did not induce dermal sensitization in 103 human subjects. A product containing 10% Ascorbic Acid was a nonirritant in a 4-day minicumulative patch assay on human skin and a facial treatment containing 10% Ascorbic Acid was not a contact sensitizer in a maximization assay on 26 humans. Discussion The CIR Expert Panel determined the data provided in this report to be sufficient to assess the safety of L-Ascorbic Acid, Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate. Because of the structural and functional similarities of these ingredients, the Panel believes that the data on one ingredient can be extrapolated to all of them. These ingredients exhibited little acute or short-term
toxicity in animal studies and the toxicity seen in some clinical studies occurred only at extremely high ingestion levels which are not relevant to the use of these ingredients in cosmetics. Reproductive and developmental studies were negative. The Expert Panel was concerned that Ascorbic Acid was genotoxic in a few assay systems. In most of the other assay systems, Ascorbic Acid was not genotoxic. The Panel attributed the finding that Ascorbic Acid was genotoxic in these few as-say systems due to the presence of other chemicals, e.g., metals, or certain enzyme systems, which effectively convert Ascorbic Acid's antioxidant action to that of a pro-oxidant. When Ascorbic Acid acts as an antioxidant, the Panel concluded that Ascorbic Acid is not genotoxic. Supporting this view were the carcinogenicity studies conducted by the NTP, which demonstrated no evidence of carcinogenicity. The Panel did review studies in which Sodium Ascorbate acted as a tumor promoter in animals. These results were considered to be related to the concentration of sodium ions and the pH of urine in the test animals. Similar effects were seen with sodium bicarbonate. Because of the concern that certain metal ions may combine with these ingredients to produce pro-oxidant activity, the Panel cautioned formulators to be certain that these ingredients are acting as antioxidants in cosmetic formulations. The Panel considered that the clinical experience in which Ascorbic Acid was used on damaged skin with no adverse effects and the RIPT using 5% Ascorbic Acid with negative results supports the finding that this group of ingredients do not present a risk of skin sensitization. This data coupled with an absence of reports in the clinical literature of Ascorbic Acid sensitization, strongly supports the safety of these ingredients. Conclusion Based on the available data contained in this report, the CIR Expert Panel concludes that L-Ascorbic Acid, Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate are safe as used in cosmetic products.

(2005) [Medicoepidemilological assessment of the incidence of noncommunicable diseases in the population living in Yerevan].
Andzhelian, BO Journal/Gig Sanit. 18-20.

To examine the clinical and epidemiological features of non-communicable diseases at the population-based level is a highly promising line of the present-day studies in preventive medicine. The paper presents the data of the author's long-term hygienic studies of the health status of children in the organized collective bodies. Environmental pollution was found to affect the health status of not only children, but also that of adults. There is a geographical irregularity in the prevalence of non-communicable diseases by the microdistricts. At the same time, the pollution is caused by the fact that in Yerevan, there are numerous industrial enterprises and motor vehicles whose emission generates a high pollution, by increasing the incidence of respiratory and gastrointestinal diseases as compared with that in the dwellers living in a control non-industrial microdistrict.
(2005) Interaction between organophosphate compounds and cholinergic functions during development.

Organophosphate (OP) compounds exert inhibition on cholinesterase (ChE) activity by irreversibly binding to the catalytic site of the enzymes. For this reason, they are employed as insecticides for agricultural, gardening and indoor pest control. The biological function of the ChE enzymes is well known and has been studied since the beginning of the XXth century; in particular, acetylcholinesterase (AChE, E.C. 3.1.1.7) is an enzyme playing a key role in the modulation of neuromuscular impulse transmission. However, in the past decades, there has been increasing interest concerning its role in regulating non-neuromuscular cell-to-cell interactions mediated by electrical events, such as intracellular ion concentration changes, as the ones occurring during gamete interaction and embryonic development. An understanding of the mechanisms of the cholinergic regulation of these events can help us foresee the possible impact on environmental and human health, including gamete efficiency and possible teratogenic effects on different models, and help elucidate the extent to which OP exposure may affect human health. The chosen organophosphates were the ones mainly used in Europe: diazinon, chlorpyriphos, malathion, and phentoate, all of them belonging to the thionophosphate chemical class. This research has focused on the comparison between the effects of exposure on the developing embryos at different stages, identifying biomarkers and determining potential risk factors for sensitive subpopulations. The effects of OP oxonisation were not taken into account at this level, because embryonic responses were directly correlated to the changes of AChE activity, as determined by histochemical localisation and biochemical measurements. The identified biomarkers of effect for in vitro experiments were: cell proliferation, apoptosis as well as cell differentiation. For in vivo experiments, the endpoints were: developmental speed, size and shape of pre-gastrula embryos; developmental anomalies on neural tube, head, eye, heart. In all these events, we had evidence that the effects are mediated by ion channel activation, through the activation/inactivation of acetylcholine receptors (AChRs).

CONTEXT: Pesticides continue to be used on school property, and some schools are at risk of pesticide drift exposure from neighboring farms, which leads to pesticide exposure among students and school employees. However, information on the magnitude of illnesses and risk factors associated with these pesticide exposures is not available. OBJECTIVE: To estimate the magnitude of and associated risk factors for pesticide-related illnesses at schools. DESIGN, SETTING, AND PARTICIPANTS: Analysis of surveillance data from 1998 to 2002 of 2593 persons with acute pesticide-related illnesses associated with exposure at schools. Nationwide information on pesticide-related illnesses is routinely collected by 3 national pesticide surveillance systems: the National Institute for Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks pesticides program, the California Department of Pesticide Regulation, and the Toxic Exposure Surveillance System. MAIN OUTCOME MEASURES: Incidence rates and severity of acute pesticide-related illnesses. RESULTS: Incidence rates for 1998-2002 were 7.4 cases per million children and 27.3 cases per million school employee full-time equivalents. The incidence rates among children increased significantly from 1998 to 2002. Illness of high severity was found in 3 cases (0.1%), moderate severity in 275 cases (11%), and low severity in 2315 cases (89%). Most illnesses were associated with insecticides (n = 895, 35%), disinfectants (n = 830, 32%), repellents (n = 335, 13%), or herbicides (n = 279, 11%). Among 406 cases with detailed information on the source of pesticide exposure, 281 (69%) were associated with pesticides used at schools and 125 (31%) were associated with pesticide drift exposure from farmland. CONCLUSIONS: Pesticide exposure at schools produces acute illnesses among school employees and students. To prevent pesticide-related illnesses at schools, implementation of integrated pest management programs in schools, practices to reduce pesticide drift, and adoption of pesticide spray buffer zones around schools are recommended.


In this study an education, and a series of group sessions for patients with solvent-induced chronic toxic encephalopathy (TE) and their spouses are evaluated. Thirty-eight patients and 21 family members participated in a 1-day education scheduled with short lectures on the clinical examination of chronic toxic encephalopathy and the prognosis. A specialist in occupational medicine, a psychologist and a social worker gave the lectures. Small discussion groups were also arranged. Of the participants from the educational days, 16 TE patients and 14 wives attended a 10-week counselling and coping improvement program with separate group sessions once a week, for patients and spouses. Questionnaires were used to assess symptoms, social network, mastery and family climate, and the participants' satisfaction with the education and the group sessions. The majority of the participants experienced the 1-day information as useful and relevant. The 10-week group sessions
were rated as meaningful and the design, number, duration and frequency of the sessions equally good. Self-reported symptoms, social network and mastery were measured before the group sessions, and 3 and 9 months after breaking up the group sessions. In most measurements, there were no statistically significant differences between the three points in time. However, the wives improved more than did the patients but the effect was not lasting the whole follow-up period. Considering the patients’ dependence on their wives, it might be most important that the wives experienced some relief from their own symptoms.


BACKGROUND: Solvent-induced chronic toxic encephalopathy (TE) is a slowly developing brain disorder associated with both a direct effect on the nervous system and as indirect experienced psychological distress. It can presumably also imply negative influence on the subject's social surroundings. METHODS: Seventeen women married to men diagnosed with TE (WTE) and 51 referent women of the same age married to healthy husbands were examined. Symptoms, social network and coping style were measured by questionnaires. RESULTS: The WTE reported slightly more psychological distress and fewer social contacts than did the referents. The WTE did not report affected stress management. Retired women in the WTE group accounted for most of the deviances from the referents. CONCLUSIONS: The conclusion is that becoming a WTE does not necessarily imply more psychological distress, social isolation or poorer stress management capability if they continue with their work and social activities.

(2005) Variability in human sensitivity to 1,3-butadiene: influence of polymorphisms in the 5'-flanking region of the microsomal epoxide hydrolase gene (EPHX1).

The carcinogenic effects of 1,3-butadiene (BD), a mutagenic chemical widely used in the manufacture of synthetic rubber, are likely initiated through its epoxide metabolites. In humans, these epoxides are detoxified predominantly by hydrolysis, a reaction mediated by the microsomal epoxide hydrolase (mEH; EPHX1) enzyme. It appears reasonable to hypothesize that BD-exposed individuals possessing lower mEH detoxification capacity may have elevated risk of adverse health effects. The
interindividual levels of mEH enzymatic activity vary considerably, and polymorphisms in the mEH gene may contribute to this variability. In addition to the well-studied coding region polymorphisms encoding Tyr113His and His139Arg substitutions, seven other polymorphic sites in the 5'-flanking region of the mEH gene have been reported. These polymorphisms appear to differentially affect mEH gene transcriptional activities. The 5'-flanking region polymorphisms exist in two linkages, the -200 linkage (-200C/T, -259C/T, -290T/G) and the -600 linkage (-362A/G, -613T/C, -699T/C), whereas the -399T/C polymorphism exists as an independent site. Because these polymorphisms may affect total mEH enzymatic activity, we hypothesized that they influence the mutagenic response associated with occupational exposure to BD. We genotyped the 5'-region of the mEH gene in 49 non-smoking workers from two styrene-butadiene rubber facilities in southeast Texas and evaluated the linkage patterns against results obtained from an autoradiographic HPRT mutant lymphocyte assay, used as a biomarker of genotoxic effect. In the study population, 67% were exposed to low BD levels, <150 parts per billion, and 33% were exposed to >150 ppb. We used the observed HPRT mutant (variant) frequency (VF) in the studied population and a 4-way first-order interaction statistical model to estimate parameters that describe the influence of exposure, genotypes and the interaction between the two on the HPRT VF in the target population. The background (baseline) VF, defined as the VF (x 10(-6)) +/- S.E.M. at low levels of BD exposure (<150 ppb) where all the genotypes under study are homozygous wild-type, was estimated to be 4.02 +/- 1.32. Exposure to >150 ppb of BD alone resulted in an estimated increase in VF of 3.42 +/- 2.47 above the baseline level. Inheritance of the variant ATT allele in the -600 linkages resulted in an estimated increase in VF of 3.39 +/- 1.67 above the baseline level. When the interaction between BD exposure and the ATT allele in the -600 linkage group was considered, a statistically significant positive interaction was observed, with an estimated increase in the VF of 10.89 +/- 2.16 (95% CI = 6.56-15.20; p = 0.0027) above baseline. These new data confirm and extend our previous findings that sensitivity to the genotoxic effects of BD is inversely correlated with predicted mEH activity.


Maternal smoking during pregnancy is known to be a significant contributor to developmental neurological health problems in the offspring. In animal studies, nicotine treatment via injection during gestation has been shown to produce episodic hypoxia in the developing fetus. Nicotine delivery via mini osmotic pump, while avoiding effects due to hypoxia-ischemia, it also provides a steady level of nicotine in the plasma. In the present study timed-pregnant Sprague-Dawley rats (300-350 g) were treated with nicotine (3.3 mg/kg, in bacteriostatic water via s.c. implantation of mini osmotic pump)
from gestational days (GD) 4-20. Control animals were treated with bacteriostatic water via s.c. implantation of mini osmotic pump. Offspring on postnatal day (PND) 30 and 60, were evaluated for changes in the ligand binding for various types of nicotinic acetylcholine receptors and neuropathological alterations. Neurobehavioral evaluations for sensorimotor functions, beam-walk score, beam-walk time, incline plane and grip time response were carried out on PND 60 offspring. Beam-walk time and forepaw grip time showed significant impairments in both male and female offspring. Ligand binding densities for [3H]epibatidine, [3H]cytisine and [3H]alpha-bungarotoxin did not show any significant changes in nicotinic acetylcholine receptors subtypes in the cortex at PND 30 and 60. Histopathological evaluation using cresyl violet staining showed significant decrease in surviving Purkinje neurons in the cerebellum and a decrease in surviving neurons in the CA1 subfield of hippocampus on PND 30 and 60. An increase in glial fibrillary acidic protein (GFAP) immuno-staining was observed in cerebellum white matter as well as granular cell layer of cerebellum and the CA1 subfield of hippocampus on PND 30 and 60 of both male and female offspring. These results indicate that maternal exposure to nicotine produces significant neurobehavioral deficits, a decrease in surviving neurons and an increased expression of GFAP in cerebellum and CA1 subfield of hippocampus of the offspring on PND 30 and 60. The results show that although 60-day-old male and female rat offspring of mothers exposed to nicotine during gestation did not differ from control in body weight gain or nicotinic acetylcholine receptors ligand binding, they exhibited significant sensorimotor deficits that were consistent with the neuropathological alterations seen in the brain. These neurobehavioral and pathological deficits indicate that maternal nicotine exposure may produce long-term adverse health effects in the offspring.

(2004) Octanol modulation of neuronal nicotinic acetylcholine receptor single channels.
Zuo, Y, Yeh, JZ and Narahashi, T Journal/Alcohol Clin Exp Res. 28: 1648-56.

BACKGROUND: We have previously shown that alcohols exert a dual action on neuronal nicotinic acetylcholine receptors (AChRs), with short-chain alcohols potentiating and long-chain alcohols inhibiting acetylcholine (ACh)-induced whole-cell currents. At the single-channel level, ethanol increased the channel open probability and prolonged the channel open time and burst duration. In this study, we examined the detailed mechanism of the inhibitory action of the long-chain alcohol n-octanol on the neuronal nicotinic AChR. METHODS: Single-channel currents induced by application of 30 nm ACh were recorded with the patch-clamp technique from human embryonic kidney cells stably expressing the human alpha4beta2 AChR. RESULTS: Several single-channel parameters were markedly changed by octanol. At least two conductance-state currents were induced by low concentrations of ACh, and octanol increased the proportion of the low-conductance-state current relative to the high-conductance-state current without changing the current amplitude. Major analyses of temporal properties of single-channel currents were performed on the
Octanol decreased the burst duration and duration of openings within burst and prolonged the mean closed time. All of these changes contributed to the decrease in the open probability in a concentration-dependent manner. CONCLUSIONS: Several aspects of octanol action on neuronal AChRs at the single-channel level are compatible with an atypical open channel block model reported with muscle nicotinic AChRs. The potentiating action of short-chain alcohols and the inhibitory action of long-chain alcohols on the neuronal nicotinic AChR are mediated through different mechanisms.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15547451


BACKGROUND: We have previously reported that ethanol potentiates the acetylcholine-induced currents of the alpha4beta2 neuronal nicotinic acetylcholine receptors in rat cortical neurons and of those that are stably expressed in human embryonic kidney cells. The potentiation of the maximal currents evoked by high concentrations of acetylcholine suggests that ethanol affects the channel gating. METHODS: We performed single-channel patch-clamp experiments to elucidate the detailed mechanism of ethanol modulation of the alpha4beta2 receptor that is stably expressed in human embryonic kidney cells. RESULTS: At least two conductance states, 40.5 pS and 21.9 pS, were activated by acetylcholine. Acetylcholine at 30 nM predominantly induced the high conductance state currents (85% of total). Ethanol did not affect the single-channel conductance but selectively modulated the high-conductance state currents. The high-conductance state currents exhibited two open time constants. Both time constants were increased by 100 mM ethanol, from 1.9 msec to 2.8 msec and from 9.0 msec to 15.5 msec, respectively. Ethanol also prolonged the burst duration and the open time within burst and increased the probability of channel opening. CONCLUSIONS: These changes in single-channel parameters indicate that ethanol stabilizes the alpha4beta2 receptor-channel in the opening state, explaining how the maximum acetylcholine-induced whole-cell currents are further potentiated by ethanol.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15166642


Paraoxonase1 (PON1) gene polymorphisms were implicated as risk factors for Parkinson's disease (PD), but the results of case-control studies that investigated these associations were controversial. In order to provide an answer to these contradictory results, a meta-analysis of all available studies relating the PON1-55M/L and PON1-192Q/R polymorphisms to the risk of developing PD was conducted. The racial descent of the populations in these studies was Caucasian and Asian. The meta-analysis revealed that there was an association of the PON1-55M allele and the risk of developing PD relative to the L allele: fixed effects pooled odds ratio (OR)=1.32 [95%CI (1.10-1.59)]. In addition, there was evidence of association for the genotypic contrast PON1-55MM+LM relative to PON1-55LL: fixed effects OR=1.50 [95%CI (1.16-1.95)]. There was no significant association between PON1-192Q/R alleles and risk of developing PD: OR=1.09 [95%CI (0.93-1.26)]. There was no evidence for an association between the genotypic contrasts of PON1-192 and development of PD. The heterogeneity between studies and the publication bias were not significant (P> or =0.10) in either polymorphism. Therefore, the pooled results of the meta-analysis supported that there was an association between PON1-55M/L polymorphism and PD and that PON1-192Q/R polymorphism was unlikely to be a major risk factor for susceptibility to PD.


In this paper a case of good tolerance to benzathine benzylpenicillin, but benzylpenicillin potassium allergy in subject with history of multidrug hypersensitivity was described. The same therapeutic agent is contained in both commercial drugs and dosage formulation can cause the unpredictable adverse drug reactions (ADRs). This thesis was confirmed by positive intradermal test with the same, but negative with other commercial product of benzylpenicillin potassium. Later chromatographic analysis shows drug contaminations. Thus an exclusion of allergy to drug impurities (and additives) is necessary for correct diagnosis benzylpenicillin allergy (and any active constituent). Furthermore, allergy to drug impurities (and additives) closely resemble cross-reactions or multiple chemical sensitivity syndrome (MCSS).

We examine Gulf War illnesses—which include the fatigue, joint pain, dermatitis, headaches, memory loss, blurred vision, diarrhea, and other symptoms reported by Gulf War veterans—in relation to other medically unexplained physical symptoms such as multiple chemical sensitivity, chronic fatigue syndrome, and fibromyalgia. Our intent is to examine the diagnosis negotiations involved in these mysterious diseases, by showing the different forms of legitimacy involved in such interactions. Factors involved in diagnostic legitimacy are: diagnostic legitimacy in the medical community, lay acceptance of the diagnosis, uncertainty in looking for causes, and social mobilization. We conclude by noting that research may not be able to find any cause for these diseases/conditions; hence, it may be necessary to embrace medical uncertainty, and also to accept patient experience in order to facilitate diagnosis, treatment, and recovery process. Such a change can alter patients' expectations and taken-for-granted assumptions about medicine, and perhaps in turn reduce the frequency with which dissatisfied individuals form illness groups that mobilize to challenge what they see as an unresponsive medical system.

http://www.sciencedirect.com/science/article/B6T4S-4BDM465-1/26997a207cf057563f4b58106a001b633

Young, EA and Breslau, N Journal/Biological Psychiatry. 56: 205-209.
http://www.sciencedirect.com/science/article/B6T4S-4CS4PN6-3/2da10762a2254b0c7b9f1bc7707cd43a7

Young, EA, Abelson, JL and Cameron, OG Journal/Biological Psychiatry. 56: 113-120.
(2004) Structure/function analyses of human serum paraoxonase (HuPON1) mutants designed from a DFPase-like homology model.

Human serum paraoxonase (HuPON1) is a calcium-dependent enzyme that hydrolyzes esters, including organophosphates and lactones, and exhibits anti-atherogenic properties. A few amino acids have been shown to be essential for the enzyme's arylesterase and organophosphatase activities. Until very recently, a three-dimensional model was not available for HuPON1, so functional roles have not been assigned to those residues. Based on sequence-structure alignment studies, we have folded the amino acid sequence of HuPON1 onto the sixfold beta-propeller structure of squid diisopropylfluorophosphatase (DFPase). We tested the validity of this homology model by circular dichroism (CD) spectroscopy and site-directed mutagenesis. Consistent with predictions from the homology model, CD data indicated that the structural composition of purified HuPON1 consists mainly of beta-sheets. Mutants of HuPON1 were assayed for enzymatic activity against phenyl acetate and paraoxon. Substitution of residues predicted to be important for substrate binding (L69, H134, F222, and C284), calcium ion coordination (D54, N168, N224, and D269), and catalytic mechanism of HuPON1 (H285) led to enzyme inactivation. Mutants F222Y and H115W exhibited substrate-binding selectivity towards phenyl acetate and paraoxon, respectively. The homology model presented here is very similar to the recently obtained PON1 crystal structure, and has allowed identification of several residues within the enzyme active site.


Tracking incidence or prevalence of diseases and using that information to target interventions is a well-established strategy for improving public health. The need to track environmentally mediated chronic diseases is increasingly recognized. Trends in childhood illnesses are 1 element of a framework for children's environmental health indicators, which also includes trends in contaminants in the environment and in concentrations of contaminants in bodies of children and their mothers. This article presents data on 3 groups of important childhood diseases or disorders that seem to be caused or exacerbated, at least in part, by exposure to environmental agents and
for which nationally representative data are available. They are asthma, childhood cancers, and neurodevelopmental disorders. Data were used from the National Health Interview Survey for asthma and neurodevelopmental disorders; the Surveillance, Epidemiology, and End Results Program for childhood cancer incidence; and the National Vital Statistics System for childhood cancer mortality. The prevalence of children with asthma doubled between 1980 and 1995, from 3.6% in 1980 to 7.5% in 1995. The annual incidence of childhood cancer increased from 1975 until approximately 1990 and seems to have become fairly stable since. Childhood cancer mortality has declined substantially during the past 25 years. Incidence of certain types of cancers has increased since 1974, including acute lymphoblastic leukemia, central nervous system tumors, and non-Hodgkin's lymphoma. Approximately 6.7% of children aged 5 to 17 were reported to have attention-deficit/hyperactivity disorder in 1997-2000, and approximately 6 of every 1000 children were reported to have received a diagnosis of mental retardation during the same period.


Two experiments were conducted regarding the culturability and toxicity of fungi located on building materials over time and the efficacy of seven laboratory techniques in recovering culturable fungi from sample swabs. In the first experiment, eight sections of drywall were inoculated with Stachybotrys chartarum and stored at 25 +/- 5 degrees Celsius and 20-60% relative humidity (RH) for up to two years. Another eight sections of ceiling tile were stored at 100% RH for 1 year. Six sections of ceiling tile and 15 swabs were also inoculated with Penicillium chrysogenum and S. chartarum respectively and stored under the same conditions for 8 months and 3.3 years. All materials were tested for culturability at the end of the storage period. S. chartarum-inoculated samples were also tested for toxicity. In the second experiment (replicated twice), S. chartarum and Chaetomium globosum were inoculated onto 84 swabs each. Storage was up to 266 days at 25 +/- 5 degrees Celsius and 20-60% RH. Seven techniques were compared regarding the recovery of culturable fungi from the swabs over different time points. Results for Experiment 1 showed that all samples were culturable after the storage period and that the S. chartarum-inoculated drywall samples were toxic. In Experiment 2, all techniques showed high rates of recovery. These data show that despite being without a water source, these organisms can be culturable and toxic after long periods of time under conditions similar to human-occupied dwellings and that a number of preparation techniques are suitable for the recovery of these fungi from inoculated swabs.

Air treatment with a compact biological membrane filter, and air quality monitoring with an electronic nose were tested in the laboratory on air from a cage containing six mice. Additional analyses of air to and from the filter were performed using olfactometry and ammonia and hydrogen sulphide gas detection tubes. The biological air filter is a module containing biofilm-coated membrane fibres that separate a closed liquid loop from a gas phase. Odour compounds and oxygen diffuse through the membranes from the gas phase to the biofilm, where they are degraded to carbon dioxide and water. The prototype "ENQBE" electronic nose is based on an array of eight thickness shear mode resonators (TSMR), also known in the literature as quartz microbalance sensors. The chemical sensitivity is given by molecular films of metalloporphyrins and similar compounds. Chemical interaction of compounds in the air with the vibrating sensors induces a frequency change of the vibration that can be measured as a signal. The air from the mouse cage had a strong odour (3490 OUE/m3). The biological membrane filter performed well, achieving over 80% odour and ammonia reduction. The electronic nose signal could be correlated with the inlet and outlet air-quality of the biological filter, making it a promising method for monitoring air quality in closed environments.

Wilkie, B Journal/Environ Health Perspect. 112: A266.

We reported previously that insecticide exposures were widespread among minority women in New York City during pregnancy and that levels of the organophosphate chlorpyrifos in umbilical cord plasma were inversely associated with birth weight and length. Here we expand analyses to include additional insecticides (the organophosphate diazinon and the carbamate propoxur), a larger sample size (n = 314 mother-newborn pairs), and insecticide measurements in maternal personal air during pregnancy as well as in umbilical cord plasma at delivery. Controlling for potential confounders, we found no association between maternal personal air insecticide levels and birth weight, length, or head circumference. For each log unit increase in cord plasma chlorpyrifos levels, birth weight decreased by 42.6 g [95% confidence interval (CI), -81.8 to -3.8, p = 0.03] and birth length decreased by 0.24 cm (95% CI, -0.47 to -0.01, p = 0.04). Combined measures of (ln)cord plasma chlorpyrifos and diazinon (adjusted for relative potency) were also inversely associated with birth weight and length (p < 0.05). Birth weight averaged 186.3 g less (95% CI, -375.2 to -45.5) among newborns with the highest compared with lowest 26% of exposure levels (p = 0.01). Further, the associations between birth weight and length and cord plasma chlorpyrifos and diazinon were highly significant (p < or = 0.007) among newborns born before the 2000-2001 U.S. Environmental Protection Agency’s regulatory actions to phase out residential use of these insecticides. Among newborns born after January 2001, exposure levels were substantially lower, and no association with fetal growth was apparent (p > 0.8). The propoxur metabolite 2-isopropoxyphenol in cord plasma was inversely associated with birth length, a finding of borderline significance (p = 0.05) after controlling for chlorpyrifos and diazinon. Results indicate that prenatal chlorpyrifos exposures have impaired fetal growth among this minority cohort and that diazinon exposures may have contributed to the effects. Findings support recent regulatory action to phase out residential uses of the insecticides.

Watson, WP and Mutti, A Journal/Biomarkers. 9: 211-42.

Biomarkers are becoming increasingly important in toxicology and human health. Many research groups are carrying out studies to develop biomarkers of exposure to chemicals and apply these for human monitoring. There is considerable interest in the use and application of biomarkers to identify the nature and amounts of chemical exposures in occupational and environmental situations. Major research goals are to develop and validate biomarkers that reflect specific exposures and permit the prediction of the risk of disease in individuals and groups. One important objective is to prevent human cancer. This review presents a commentary and consensus views about the major developments on biomarkers for monitoring human exposure to chemicals. A particular emphasis is on monitoring exposures to carcinogens. Significant developments in the areas of new and existing biomarkers, analytical methodologies, validation studies and field trials together with auditing and quality
assessment of data are discussed. New developments in the relatively young field of toxicogenomics possibly leading to the identification of individual susceptibility to both cancer and non-cancer endpoints are also considered. The construction and development of reliable databases that integrate information from genomic and proteomic research programmes should offer a promising future for the application of these technologies in the prediction of risks and prevention of diseases related to chemical exposures. Currently adducts of chemicals with macromolecules are important and useful biomarkers especially for certain individual chemicals where there are incidences of occupational exposure. For monitoring exposure to genotoxic compounds protein adducts, such as those formed with haemoglobin, are considered effective biomarkers for determining individual exposure doses of reactive chemicals. For other organic chemicals, the excreted urinary metabolites can also give a useful and complementary indication of exposure for acute exposures. These methods have revealed 'backgrounds' in people not knowingly exposed to chemicals and the sources and significance of these need to be determined, particularly in the context of their contribution to background health risks.


Introduction - Oxidative stress has been implicated in a number of disease processes. There is evidence suggesting that vitamin C, a major water-soluble antioxidant, may reduce oxidative stress. The effects of dietary polyphenols, water-soluble compounds with potent antioxidant activity in vitro, on oxidative stress are unclear. Objectives - The objectives of this study were to investigate the effect of supplementation with grape-seed polyphenols on oxidative stress, and to compare any effects to those of vitamin C. Design- Following a 3-week washout, participants were randomised to receive (i) 500mg/day vitamin C + matched placebo (n = 19), (ii) 1000mg /day polyphenols + matched placebo (n= 16), (iii) 500mg/day vitamin C + 1000mg/day polyphenols (n = 16), or (iv) matched placebos (n = 18). Plasma and urinary F(2)-isoprostanes and oxidised low-density lipoproteins were analysed as markers of oxidative damage. Outcomes - Supplementation with grape-seed polyphenols resulted in a significant increase in urinary excretion of specific phenolic acids (3-hydroxyphenylpropionic acid), but did not alter F(2)-isoprostane concentrations or oxidised low-density lipoproteins. The phenolic acid metabolites, markers of exposure to grape-seed polyphenols, were not related to changes in markers of oxidative stress. Plasma vitamin C levels increased significantly following supplementation. Plasma F(2)-isoprostane concentrations fell following supplementation with vitamin C (p=0.056). There was no change in urinary F(2)-isoprostane concentrations or oxidised low-density lipoproteins. There was no relationship between increases in plasma vitamin C and changes in markers of oxidative stress. Conclusions - These results
support the suggestion that supplementation with vitamin C may reduce in vivo lipid peroxidation. However, supplementation with grape-seed polyphenols and exposure to phenolic acid metabolites had no effect on in vivo lipid peroxidation.


The Cdc14 family of protein phosphatases is conserved within eukaryotes and antagonizes the action of cyclin-dependent kinases, thereby promoting mitotic exit and cytokinesis. We performed a detailed kinetic and mechanistic study of the Cdc14 phosphatases with both small molecule aryl phosphates and a physiological protein substrate hCdh1. We found that Cdc14 displays a strong preference for two-ringed aryl phosphates over smaller one-ringed or larger, multi-ringed substrates, a finding that may have important implications for inhibitor design. Results from both leaving group and pH dependence of the Cdc14-catalyzed reaction are consistent with a general acid-independent mechanism for substrates with leaving group pKa < 7 and a general acid-dependent mechanism for substrates with leaving group pKa > 7. The use of both low and high leaving group pKa substrates, in combination with steady-state and pre-steady-state kinetic techniques enabled the isolation and analysis of both the phosphoenzyme (E-P) formation and hydrolysis step. We established the requirement of general acid catalysis for E-P formation in reactions with high leaving group pKa substrates, and the presence of general base catalysis in E-P hydrolysis. Mutational study of invariant acidic residues in Cdc14 identified Asp253 as the general acid during E-P formation and the general base in E-P hydrolysis. We also identified several residues including Asp50, Asp129, Glu168, Glu171, and Asp177 in the Cdc14 active site cleft that are required for efficient dephosphorylation of hCdh1.


Wagner, BM Journal/Inhal Toxicol. 16: 113; author reply 114.

The paper describes some results of the activities of the centers of the sanitary-and-epidemiological service of the Ministry of Republic of Uzbekistan in controlling the quality of tap water, the pollution of atmospheric air, soil, raw food and foodstuffs under the reforms of the public health system (according to the 2001 data).


http://www.sciencedirect.com/science/article/B6T4S-4CBW1K6-3/2 3278d3326195dcd6b54012c18f67ca93


Ethanol (EtOH) stimulates peptidergic primary sensory neurons via the activation of the transient receptor potential vanilloid-1 (TRPV1). EtOH is also known to trigger attacks of asthma in susceptible individuals. Our aim was to investigate whether EtOH produces airway inflammation via a TRPV1-dependent mechanism and to verify whether this effect is produced via a mechanism distinct from that of acetaldehyde.
(AcH). EtOH caused a Ca(2+)-dependent release of neuropeptides from guinea pigs airways, an effect that was inhibited by both capsaicin pretreatment and the TRPV1 antagonist capsazepine (CPZ). Furthermore, EtOH contracted isolated guinea pig bronchi, showing efficacy similar to that of carbachol: this effect of EtOH was sensitive to capsaicin pretreatment, tachykinin receptor blockade, and TRPV1 antagonism. The EtOH metabolite AcH also contracted isolated guinea pig bronchi, but this action was not affected by capsaicin pretreatment, tachykinin receptor, or TRPV1 antagonism. EtOH by intravenous or intragastric route of administration caused bronchoconstriction and increased plasma extravasation in the guinea pig airways, effects that were abolished selectively by CPZ. In conclusion, we have demonstrated that EtOH stimulates peptidergic primary sensory neurons in the guinea pig airways by TRPV1 activation. This excitatory effect of EtOH, distinct from that of AcH, results in neurogenic inflammatory responses that may contribute to the mechanism of EtOH-induced asthma.


OBJECTIVE: A new concept for the out-patient clinic for environmental diseases (Umweltambulanz) of Augsburg central hospital was devised in July 1999. METHOD: By April 2003 441 patients with environment-related disorders were examined. In a retrospective analysis the proportion and type of mental disorders were assessed as well as acceptance of the psychiatric therapy recommended. RESULTS: 5 % of patients received a psychiatric diagnosis - in most cases a somatoform disorder. Half of the patients did not accept the therapy recommended. CONCLUSIONS: In contrast to other studies the prevalence of mental disorders is low and has therefore to be discussed critically.


Three mechanisms for disease caused by mold-infection, allergy, and toxicity-are established and well recognized by clinicians. In each case the corresponding diseases are specific to a particular fungus. The mechanisms involved include a recognized inflammatory pathology that leads to objective clinical evidence of disease. Recent widespread litigation has arisen out of an unproved assertion that exposure to indoor molds causes an ill-defined illness. This illness is characterized by the absence of objective evidence of disease and by the lack of a defined pathology. There is usually
no specificity for the involved fungus purported to cause the illness. Those publications that claim such an illness are reviewed. They are found to lack scientific validity, often on the basis of faulty methodology and insufficient information. There is no coherent clinical description for the presumed illness. Recommendations are offered for published reports and studies to address this problem.


CONTEXT: The rotary diversified diet, which involves food elimination and rotation of remaining allowed foods, is commonly used in the management of environmental illness. No studies have considered patient adherence while evaluating the effectiveness of the diet in controlling symptoms. OBJECTIVE: The study examined the severity of patients' perceived symptoms and dietary adherence during treatment with a rotary diversified diet. DESIGN: A prospective and exploratory study using purposive sampling and the following data collection methods: personal interviews, symptom severity questionnaires, and food records to assess dietary adherence. SETTING: Private clinic of a Toronto, Ontario physician specializing in environmental medicine. PATIENTS OR OTHER PARTICIPANTS: Twenty-five female residents of Toronto, Ontario (aged 25-67 years) diagnosed with environmental illness. INTERVENTION: Patients were treated with a rotary diversified diet for 16 weeks. MAIN OUTCOME MEASURES: Symptom severity and dietary adherence were assessed after 4, 10, and 16 weeks of treatment. Adherence was assessed by comparing food records to the diet prescription. RESULTS: At 16 weeks, patients reported a 50% decline in symptom severity for 5 of the 6 symptom categories assessed and for all categories combined. Those with closer elimination and rotation adherence reported a greater decline in gastrointestinal symptoms at 4 and 10 weeks of treatment, respectively. Improvement in total symptom severity was associated with closer rotation adherence at 10 weeks. Patients experienced difficulties in adhering to the diet. CONCLUSIONS: Results suggest that the diet, if followed, is beneficial, especially in improving gastrointestinal symptoms. Further evaluation of its effectiveness is limited by its complexity and the nature of environmental illness. Because the diet is difficult to follow over time, patients require extensive nutritional counseling and support.
Multiple-chemical sensitivity (MCS) patients are presumed to be compelled to lead inconvenient and difficult lives, because unpleasant and multiorgan symptoms are caused by very small amounts of various chemicals in the living environment. Therefore we conducted a questionnaire survey of MCS patients who are members of support groups to elucidate the problems of MCS patients in using medicinal drugs. In this report, we selected 205 persons who stated that they had been "diagnosed with MCS by a physician" or "a physician suspected a diagnosis of MCS" on the questionnaire as the reason they judged themselves to have MCS. The questionnaire results showed that about 60% of MCS patients have difficulty in using medicinal drugs and that the difficulties are more likely to occur in women, in people 40-59 years old, and in patients who developed MCS in reaction to pesticides or medicinal drugs. The prescribed drugs and OTC drugs noted as usable or unusable by patients in the questionnaire were analyzed from the viewpoint of their medicinal constituents. The results indicated that lidocaine is likely to be unusable by MCS patients. In addition, caffeine, aspirin, chlorphenylamine maleate, minocycline hydrochloride, levofloxacin, etc. were also likely to be unusable by MCS patients. Many patients who recorded drugs containing the above-mentioned remedies as unusable had a past history of allergy, suggesting that allergy is involved in the difficulties of MCS patients in using medicinal drugs.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15297726

Sutherland, ER, Brandorff, JM and Martin, RJ Journal/J Asthma. 41: 863-8.

The role of respiratory infections in asthma is poorly understood. Atypical bacteria Mycoplasma pneumoniae and Chlamydia pneumoniae are present in the lower airways of approximately 50% of asthmatics. This study tested the hypothesis that early life community-acquired pneumonia caused by Mycoplasma pneumoniae or Chlamydia pneumoniae is associated with increased asthma prevalence. Thirty-five subjects with a history of community-acquired pneumonia (22 due to atypical bacteria, 13 due to nonatypical pathogens) were evaluated by questionnaire 7-9 years after the episode of pneumonia. Subjects with a history of either typical or atypical pneumonia demonstrated increased asthma prevalence. Current or past asthma prevalence was 55% in subjects with atypical bacterial pneumonia and 61.5% in subjects with
nonatypical bacterial pneumonia. Significant between-group differences were not
demonstrated with regard to asthma prevalence (risk ratio=0.89; 95% confidence
interval=0.49-1.61), current bronchodilator use [1.18 (0.44-3.17)], and family history of
atopy [1.18 (0.73-1.91)], or asthma [1.63 (0.68-3.88)]. These data suggest that atypical
bacterial pneumonia confers a risk of asthma similar to that seen with nonatypical
bacterial pneumonia. Prospective studies are warranted to more fully evaluate the
importance of atypical bacterial pneumonia as an asthma risk factor.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15641636

(2004) [Assessing the risk from the effects of ambient air pollution on health in
the sociohygienic monitoring system].
Surzhikov, DV, Surzhikov, VD and Oleshchenko, AM Journal/Gig Sanit. 64-6.

(2004) [The health status of children under poor ecological and social
conditions].
Sukharev, AG and Mikhailova, SA Journal/Gig Sanit. 47-51.

In the Republic of Altai, the past decades are marked by poor trends in the children's
health status: lower birth rates, a rise in general and infantile mortality and morbidity
and worse physical development. The districts and areas that differ in environmental
and social characteristics have been identified. Their comparison has determined the
influence of environmental and social factors on the health status of children. There is
a relationship of the children’s health to environmental and social factors. It has been
found that social factors much more influence than do environmental ones. A
combination of environmental and social factors exerts the greatest impact on the
basic health indices. In the area exposed to a combination of negative effects of these
factors where natives predominantly live, there are negative changes in the children's
health status. The leading social factors are maternal working conditions, familial
financial position, a child's dietary habits, and living conditions.

(2004) Monitoring the transition from the T to the R state in E.coli aspartate
transcarbamoylase by X-ray crystallography: crystal structures of the E50A
mutant enzyme in four distinct allosteric states.
A detailed description of the transition that allosteric enzymes undergo constitutes a major challenge in structural biology. We have succeeded in trapping four distinct allosteric states of a mutant enzyme of Escherichia coli aspartate transcarbamoylase and determining their structures by X-ray crystallography. The mutant version of aspartate transcarbamoylase in which Glu50 in the catalytic chains was replaced by Ala destabilizes the native R state and shifts the equilibrium towards the T state. This behavior allowed the use of substrate analogs such as phosphonoacetamide and malonate to trap the enzyme in T-like and R-like structures that are distinct from the T-state structure of the wild-type enzyme (as represented by the structure of the enzyme with CTP bound and the R-state structure as represented by the structure with N-(phosphonacetyl)-L-aspartate bound). These structures shed light on the nature and the order of internal structural rearrangements during the transition from the T to the R state. They also suggest an explanation for diminished activity of the E50A enzyme and for the change in reaction mechanism from ordered to random for this mutant enzyme.

(2004) Is chronic fatigue syndrome an autoimmune disorder of endogenous neuropeptides, exogenous infection and molecular mimicry?

Chronic fatigue syndrome is a disorder characterised by prolonged fatigue and debility and is mostly associated with post-infection sequelae although ongoing infection is unproven. Immunological aberration is likely and this may prove to be associated with an expanding group of vasoactive neuropeptides in the context of molecular mimicry and inappropriate immunological memory. Vasoactive neuropeptides including vasoactive intestinal peptide (VIP) and pituitary adenylate activating polypeptide (PACAP) belong to the secretin/glucagon superfamily and act as hormones, neurotransmitters, immune modulators and neurotrophes. They are readily catalysed to smaller peptide fragments by antibody hydrolysis. They and their binding sites are immunogenic and are known to be associated with a range of autoimmune conditions. Vasoactive neuropeptides are widely distributed in the body particularly in the central, autonomic and peripheral nervous systems and have been identified in the gut, adrenal gland, reproductive organs, vasculature, blood cells and other tissues. They have a vital role in maintaining vascular flow in organs, and in thermoregulation, memory and concentration. They are co-transmitters for acetylcholine, nitric oxide, endogenous opioids and insulin, are potent immune regulators with primarily anti-inflammatory activity, and have a significant role in protection of the nervous system to toxic assault, promotion of neural development and the maintenance of homeostasis. This paper describes a biologically plausible mechanism for the development of CFS based on loss of immunological tolerance to the vasoactive neuropeptides following infection, significant physical exercise or de novo. It is proposed that release of these substances is accompanied by a loss of tolerance either to them or their receptor binding sites in CFS. Such an occurrence would have predictably serious consequences resulting from
compromised function of the key roles these substances perform. All documented symptoms of CFS are explained by vasoactive neuropeptide compromise, namely fatigue and nervous system dysfunction through impaired acetylcholine activity, myalgia through nitric oxide and endogenous opioid dysfunction, chemical sensitivity through peroxynitrite and adenosine dysfunction, and immunological disturbance through changes in immune modulation. Perverse immunological memory established against these substances or their receptors may be the reason for the protracted nature of this condition. The novel status of these substances together with their extremely small concentrations in blood and tissues means that clinical research into them is still in its infancy. A biologically plausible theory of CFS causation associated with vasoactive neuropeptide dysfunction would promote a coherent and systematic approach to research into this and other possibly associated disabling conditions.


Multiple chemical sensitivity (MCS) is an ill-defined disorder in humans attributed to exposure to volatile organic compounds. This study draws on apparent parallels between individuals with posttraumatic stress disorder (PTSD) and panic disorder and a subset of those reporting MCS, using a conditioned fear task in rats. Male and female Sprague-Dawley rats were given repeated exposure to 2 ppm formaldehyde (Form) (1 h/day x 5 days/week x 4 week) or air, and after 2-3 weeks, rats were trained on the conditioned fear task. One half of Air and Form rats were given odor (orange oil, the conditioned stimulus, CS) paired with footshock (PRD) and the other half was given the same stimuli in an unpaired manner (UNP). After 24 h, rats were placed into the same context without the CS or footshock. Male and female PRD groups demonstrated contextual freezing 5-15% of the time, while the UNP groups showed freezing 30-50% of the time, with no effect of Air or Form pretreatment. For the next 5 days, rats were placed into a novel context and tested for freezing in the absence or presence of the CS. In male rats, Form pretreatment produced a significantly greater freezing response in both UNP and PRD groups in the presence of the CS, with no differences in freezing in the absence of the CS. In female rats, no significant differences between Form pretreated rats and Air controls were observed in either the PRD or UNP groups. The increase in conditioned fear responding to the CS after Form exposure in males suggests that repeated low-level Form may act as a stressor to produce sensitized responding within olfactory/limbic pathways, and may help explain the panic-like responses observed in a subset of individuals reporting MCS. Furthermore, the male female differences suggest a gonadal hormonal contribution to this behavior.


The appropriate regulation of drugs, chemicals and environmental contaminants requires the establishment of clear and accepted guidelines for developmental neurotoxicity. Ideally, these guidelines should encompass the ability to assess widely disparate classes of compounds through routine tests, with high throughput and low cost. Increasingly, however, the progress in primary research from academic laboratories deviates from this goal, focusing instead on categorizing novel effects of toxicants, development of new testing paradigms, and extension of techniques into molecular biology. The differing objectives of academic science as opposed to those of regulatory agencies or industry, are driven in part, by the priorities of the agencies that fund primary research. Recent work on organophosphate pesticides (OPs) such as chlorpyrifos (CPF) illustrate this dichotomy. Originally, OPs were thought to affect brain development through their ability to elicit cholinesterase inhibition and consequent cholinergic hyperstimulation. This common mechanism allowed for parallels to be drawn between standard measures of systemic toxicity, gross morphological examinations, and exposure testing utilizing an easily-assessed surrogate endpoint, plasma cholinesterase activity. In the past decade, however, it has become increasingly evident that CPF, and probably other OPs, have direct effects on cellular processes that are unique to brain development, and that these effects are mechanistically unrelated to inhibition of cholinesterase. The identification and pursuit of these mechanisms and their consequences for brain development represent new and exciting scientific findings, while at the same obscuring the ability to sustain a uniform approach to neurotoxicity guidelines or biomarkers of exposure. In the future, a new set of test paradigms, relying on primary work in cell culture, invertebrates, or non-mammalian models, followed by more targeted examinations of specific processes in mammalian models, may unite cutting-edge academic research with the need for establishing flexible guidelines for developmental neurotoxicity.


The authors studied dependence of various parameters (morbidity, physical development) in infants and toddlers on environmental state of major industrial city.

CONTEXT: Acute asthma causes nearly 2 million hospital emergency department (ED) visits in the United States annually, and hospitalization after an ED visit and relapse after ED discharge are common. OBJECTIVE: To evaluate the adding of therapy with zafirlukast to standardized care for patients with acute asthma in the ED and a 28-day follow-up period. DESIGN AND PATIENTS: A total of 641 patients presenting to the ED with acute asthma were randomized to receive either single-dose zafirlukast, 160 mg (Z160) [162 patients], zafirlukast, 20 mg (Z20) [158 patients]), or placebo (321 patients) as adjunct treatment to standard care in this double-blind, multicenter trial. Assessments, including spirometry and symptom scores, were obtained before each albuterol treatment and at 4 h. Patients who were discharged from the ED after 4 h continued outpatient therapy over a 28-day period and received either Z20 bid (276 patients) or placebo (270 patients) in addition to prednisone, albuterol, and their previous asthma medications. FEV(1) was measured at clinic visits on days 10 and 28. Patients recorded outpatient clinical data twice daily on a home diary card. MAIN OUTCOME MEASURES: the effect of zafirlukast on relapse after ED discharge. Other assessments were the rate of extended care (ie, ED stay for > 4 h or hospitalization), FEV(1), and symptoms. RESULTS: At the end of the outpatient period, 65 of 276 patients (23.6%) treated with zafirlukast and 78 of 270 patients (28.9%) treated with placebo relapsed (p = 0.047; absolute reduction, 5.3%; relative reduction, 18.3%). At the end of the ED period, 16 of 162 patients (9.9%) treated with Z160, 26 of 158 patients (16.5%) treated with Z20, and 48 of 321 patients (15.0%) treated with placebo required extended care (p = 0.052; absolute reduction with Z160 compared to placebo, 5.1%; relative reduction, 34%). These findings were supported by a significant improvement in FEV(1) and dyspnea in the ED with the use of Z160 therapy, and by greater improvement in FEV(1) and symptoms during the outpatient period for patients treated with Z20. CONCLUSIONS: When added to standardized care, therapy with Z20 bid reduced the risk of relapse compared with placebo over a 28-day treatment period. One dose of Z160 in the ED also reduced the rate of extended care.


Multiple chemical sensitivity (MCS) has become a serious problem as a result of airtight techniques in modern construction. The mechanism of the MCS, however, has
not been clarified. Responsible chemicals and their exposure levels for patient's hypersensitive reactions need to be identified. We measured the exposure of 15 MCS patients to both carbonyl compounds and volatile organic compounds (VOCs) that may induce hypersensitive reactions. The exposures of those not suffering from MCS (non-MCS individuals) were also measured at the same time. To characterize the chemicals responsible for MCS symptoms, we applied a new sampling strategy for the measurement of carbonyls and VOCs using active and passive sampling methods. The results of our study clearly demonstrated that the chemicals responsible for such hypersensitive reactions varied from patient to patient. Moreover, the concentrations during hypersensitive symptoms, which were apparent in some of the MCS patients, were far below both the WHO and the Japanese indoor guidelines. The average exposure levels of MCS patients within a 7-day period were lower than those of paired non-MCS individuals except for a few patients who were exposed to chemicals in their work places. This result indicates that the MCS patients try to keep away from exposures to the chemical compounds that cause some symptoms.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14726947

(2004) Ambient, indoor and personal exposure relationships of volatile organic compounds in Mexico City Metropolitan Area.

Air pollution standards and control strategies are based on ambient measurements. For many outdoor air pollutants, individuals are closer to their sources (especially traffic) and there are important indoor sources influencing the relationship between ambient and personal exposures. This paper examines the relationship between volatile organic compounds (VOCs) measured at central site monitoring stations and personal exposures in the Mexico City Metropolitan Area. Over a 1-year period, personal exposures to 34 VOCs were measured for 90 volunteers from 30 families living close to one of five central monitoring stations. Simultaneous 24-h indoor, outdoor and central site measurements were also taken. Dual packed thermal desorption tubes and C(18) DNPH-coated cartridges were used for sampling VOCs and these were analyzed by GC/MS and HPLC, respectively. A factor analysis of the personal exposure data aided in grouping compounds by the most likely source type: vehicular (BTEX, styrene and 1,3-butadiene), secondary formed or photochemical (most aldehydes), building materials and consumer products (formaldehyde and benzaldehyde), cleaning solvents (tetrachloroethene and 1,1,1-trichloroethane), volatilization from water (chloroform and trichloroethene) and deodorizers (1,4-dichlorobenzene). Mean ambient, indoor and personal concentrations were 7/7/14 microg/m(3) for benzene, 1/3/3 for 1,3-butadiene, 6/20/20 for formaldehyde and 3/9/50 for 1,4-dichlorobenzene. Geometric mean (GM) ambient concentrations of trichloroethene and carbon tetrachloride were similar to GM personal exposures. While
outdoor and indoor home GM concentrations for most vehicular related compounds (benzene, MTBE, xylenes and styrene) were comparable, the GM personal exposures were twice as high. Indoor concentrations of 1,3-butadiene, 1,1,1-trichloroethane, tetrachloroethane, chloroform, formaldehyde, valeraldehyde, propionaldehyde and n-butyraldehyde were comparable to personal exposures. For certain compounds, such as chloroform, aldehydes, toluene, 1,3-butadiene and 1,4-dichlorobenzene, GM personal exposures were more than two times greater than GM ambient measurements.


Multiple Chemical Sensitivity (MCS) is characterized by an increased sensitivity towards chemicals. Many patients with severed unspecific symptoms ascribe these to MCS. At present there is neither a generally accepted diagnosis nor a therapeutic concept. The ENT doctor should look at the nasal airflow resistance, nasal mucosa and olfactory system.


OBJECTIVE: To measure health care providers' capacity to detect biofields before and after bioenergy awareness training in relation to individual differences in the personality trait of absorption. METHODS: Twenty-seven (27) physicians, psychologists, and nurses participated in a 5-day intensive bioenergy healing training course with Rev. Rosalyn Bruyere. The course was part of the Associate Fellows Program in the Program in Integrative Medicine at the University of Arizona. Blindfolded participants received a 24-trial hand biofield detection test (HBDT) pretraining and post-training. The experimenter placed his or her dominant hand a few inches above the participant's left or right hand for 30-second trials. After each trial, the participant guessed which hand was being tested. Blocks contained two right- and two left-hand trials in different orders. Participants filled out Tellegen's Absorption Scale, a measure of the capacity to focus attention in tasks. RESULTS: Percent HBDT accuracy for the entire sample was 50.8% (standard deviation [SD] = 12.24) at pretraining (50% is chance); accuracy
increased to 55.5% (SD = 12.38) at post-training (t = p = 2.08, p < 0.05). Pretraining absorption (mean = 23.9; SD = 5.52) was significantly correlated with degree of detection accuracy increase (r = 0.42, n = 22, p < 0.05). High absorption (mean = 28.2 n = 11) participants increased to 58.3% compared to 52.7% for low absorption (mean = 19.2 n = 11) participants. CONCLUSION: The findings support claims of energy healers that (1) training can improve bioenergy awareness, and (2) there are substantial individual differences in response to training.


(2004) [Interdisciplinary diagnostics in the outpatient treatment department of an environmental medical centre - report on experience with 400 patients].

The medical diagnostics of 400 patients of an interdisciplinary environmental medical centre is presented. The basic diagnostics included a special environmental medical history using a questionnaire, physical examination, allergological examinations and human biomonitoring. The latter was carried out in order to quantify the internal exposure to environmental pollutants. The main focus was on the differential diagnostics which was supported by special medical divisions of the hospital. Allergic illnesses as well as results of human biomonitoring exceeding the reference ranges were found frequently. Unfortunately a link between external exposure, internal dose and symptoms can hardly be established in environmental medicine. However, in several cases we found a considerably increased internal exposure which allowed to identify the sources of exposure (for example, usage of dichlorobenzene, permethrin, pentachlorophenol). Eliminating the sources obviously improved the health status of some of the patients concerned.

(2004) Influence of GSTT1, mEH, CYP2E1 and RAD51 polymorphisms on diepoxybutane-induced SCE frequency in cultured human lymphocytes.
1,3-Butadiene (BD) is a common chemical in the human environment. Diepoxybutane (DEB) is the most reactive epoxide metabolite of BD. The aim of the present study was to evaluate the influence of polymorphisms in enzymes operating in DEB-metabolism (epoxide hydrolase mEH, CYP2E1 and GSTT1), as well as in the DNA-repair enzyme RAD51, on the frequency of sister chromatid exchange (SCE) induced by DEB in lymphocyte cultures from 63 healthy donors. Their genotypes were determined using PCR and restriction fragment length polymorphism (RFLP)-PCR techniques. The analysis of xenobiotic-metabolizing genes revealed that GSTT1 and CYP2E1 polymorphisms have an influence on DEB-induced SCE frequency. Individuals with the GSTT1 null genotype and CYP2E1 c2 variant allele heterozygotes were observed to have significantly higher SCE frequency than individuals with more common genotypes. A correlation between sensitivity to DEB and GSTT1 null genotype indicates that this pathway is a major detoxification step in DEB metabolism in whole-blood lymphocyte cultures, which has been shown in many studies. The analysis of combined polymorphisms indicated that, in the presence of GSTT1, a significantly higher DEB-induced SCE frequency is observed in the CYP2E1 c2 variant allele heterozygotes than in individuals with the most common CYP2E1 genotype. In the absence of GSTT1, however, the CYP2E1 polymorphism has no influence on DEB-induced SCEs. A significant difference was also observed between individuals characterized by low and high mEH activity, but only in subjects with the GSTT1 null genotype. Lack of GSTT1 resulted in higher SCE frequency in individuals with mEH high-activity genotypes than in individuals with mEH low-activity genotype. In the present study no statistically significant difference in DEB-induced SCEs was observed for the RAD51 polymorphism. The influence of GSTT1 genotype on SCE-frequency in RAD51 variant allele carriers was not analysed as all individuals in this group (except one person) had the GSTT1 gene present. Our study shows that the combined analysis of polymorphisms in metabolizing enzymes may lead to a better understanding of their contribution to an individual's susceptibility to DEB.


We examine the effect on the hypothalamus-pituitary-adrenal gland (HPA) axis of prolonged exposure to low levels of formaldehyde in female C3H/He mice, using immunocytochemical and RT-PCR methods. Two groups of female mice were exposed to differing concentrations (0, 80, 400, 2000 ppb) of formaldehyde inhalation for 16 h day, 5 days/week, for 12 weeks. The corticotropin releasing hormone (CRH)-immunoreactive (ir) neurons in the hypothalamus were then examined, together with the adrenocorticotropic hormone (ACTH)-ir cells and ACTH mRNA in the pituitary. One group comprised sham control mice. The other group was made allergic by
injection of ovalbumin (OVA) and alum prior to exposure to formaldehyde, since most sick building syndrome (SBS) sufferers are women with allergic disease. These animals were further exposed to aerosolized OVA as a booster four times during the exposure period. Our results showed a dose-dependent increase in the number of CRH-ir neurons in the non-allergy (NAG) group. A similar pattern was found in ACTH-ir cells and ACTH mRNA. The allergy (AG) model group showed an increase in basal levels of all markers of HPA activity. Moreover, the AG mice appeared to respond to the lowest concentration of formaldehyde, and all indices of HPA activity were reduced at the highest concentrations of formaldehyde. These results relate to an important clinical issue and also have implications in the broader area of HPA regulation. We conclude that our experimental system may be a suitable animal model for SBS and/or multiple chemical sensitivity (MCS).


The role of pet keeping during infancy for the development of allergy and asthma is still controversial. The objective of this population-based birth cohort study was to assess the development of atopy and different wheezing phenotypes during the first 4 yr of life in relation to heredity and early pet keeping. The cohort comprised all 1228 infants living in a Swedish county who were born over a 1-yr period. The parents replied to repeated questionnaires and 817 of the children were skin prick tested both at 1 and 4 yr. Cat keeping during the first year of life was associated with an increased risk of a positive skin prick test to cat at 1 yr of age [odds ratio (OR) 2.2, 95% confidence interval (CI) 0.9-5.6], but neither with sensitivity nor clinical symptoms of allergy at 4 yr. Dog keeping during the first year of life was associated with an increased risk of early-onset transient wheezing, but only in children with parental asthma (adjusted OR 4.3, 95% CI 1.5-12.1). In contrast, early dog keeping had an inverse association with sensitivity to pollen allergen at 4 yr (adjusted OR 0.3, 95% CI 0.1-0.9) and late-onset wheezing (adjusted OR 0.4, 95% CI 0.2-1.0). Thus, pet keeping during the first year of life was not associated with an increased risk of atopy at 4 yr, although a positive SPT to cat was more common at 1 yr. Our findings may even suggest that dog keeping during the first year of life might provide some protection from pollen allergy and late-onset wheezing and increase the risk of early-onset transient wheezing in children with heredity for asthma.

Housing hazards contribute to considerable morbidity and mortality among millions of children each year in the US, but few interventions are proven to control asthma and lead poisoning. Moreover, there is little evidence that many of the current recommendations to control residential hazards are safe and efficacious. The only interventions that have been found to work consistently are home visitation programs and home modification, such as installment of window guards and carpet removal. Altering the environment to protect the health of children requires pediatrician intervention. New models of cooperation between pediatricians and public health agencies must deal with residential hazards in an integrated manner and cannot be focused on one disease process or one method at a time. With research in more effective environmental interventions and pediatric-public-health partnerships, primary and secondary prevention of diseases from residential hazards may become a reality in the future.


Low-frequency sounds presented at high nontraumatizing levels induce temporary hyperacusis in humans and animals. One explanation of this finding is that the basilar membrane operating point may be disturbed by an endolymph volume change. This possibility was investigated using volume and flow markers iontophoresed into the endolymphatic space of guinea pigs. Marker concentrations were measured with ion-selective microelectrodes placed apically and basally to the iontophoresis site during exposure of the ear to low-frequency tones. Concentration changes were interpreted quantitatively using a finite-element model of the endolymphatic space that allowed changes of endolymph cross-sectional area and flow to be derived. Stimulation with a 200 Hz tone at 115 dB SPL for 3 min produced marker concentration changes consistent with the induction of transient endolymphatic hydrops and a basally directed displacement of endolymph. Endocochlear potentials were greater than normal after the exposure when hydrops was present. During identical tone exposures of animals without marker, we found that action potential (AP) threshold changes and endolymph potassium changes associated with the hydropic state were small. Marker concentration changes were compared with changes in endocochlear potential and AP thresholds for a range of exposure frequencies and levels. AP hypersensitivity occurred with 200 Hz exposure levels below those inducing endolymph volume disturbances. Endolymph volume changes are thought to be the result of, rather than the cause of, changes in operating point of the cochlear transducer. The observations that auditory threshold and endolymph potassium changes are minimal under conditions where substantial endolymphatic hydrops is present is relevant to our understanding of the hearing loss in patients with Meniere’s disease.
(2004) **Lewy body-related alpha-synucleinopathy in aging.**

To clarify the significance of Lewy body (LB)-related alpha-synucleinopathy in aging, we investigated the incidence of LBs in 1,241 consecutive autopsy cases (663 males and 578 females). LB pathology was identified histologically in sections stained with hematoxylin and eosin and with anti-ubiquitin and anti-alpha-synuclein antibodies. Cases without LBs were classified as LB stage 0 (987 cases). Cases with LBs were classified as follows: LB stage I = incidental LBs (149 cases); LB stage II = LB-related degeneration without attributable clinical symptoms (47 cases); LB stage III = Parkinson disease without dementia (10 cases); LB stage IV = dementia with Lewy bodies (DLB) transitional (limbic) form (25 cases); and LB stage V = DLB neocortical form (23 cases). The average age at death was greater for those cases with LBs. There were no gender differences in the LB pathology. G842A polymorphism in the paraoxonase 1 gene was associated with men in LB stage II or above and suggests a gender-specific risk factor. LB stage V had higher stages of neurofibrillary tangle and senile plaque involvement and also had a higher frequency of apolipoprotein E epsilon4. Our findings indicate that LBs are associated with cognitive decline, either independently or synergistically with neurofibrillary tangles and senile plaques.

(2004) **Pulmonary function decay in women ice hockey players: is there a relationship to ice rink air quality?**
Rundell, KW Journal/Inhal Toxicol. 16: 117-23.

Fossil-fueled ice rink resurfacing machines emit high levels of ultrafine and fine particulate matter (PM(1)) and may be related to asthmalike symptoms in skaters. We examined PM(1) exposure and airway status in elite women ice hockey players over 4 training years. Lung function, asthma symptoms, and rink PM(1) were evaluated. Pre- and postexercise spirometry was performed on 14 female hockey players and 9 female control nordic skiers 4 times over 4 yr. Baseline lung functions were normalized to height cubed (Ht(3)) and recalculated to subject mean height (1.69 m) to evaluate change. Venue CO, NO(2), and PM(1) were measured. Training history for hockey players included 2 yr in a low-[PM(1)] rink, followed by transition to high-[PM(1)] fossil fuel machine resurfaced rinks; [PM(1)] for control ski venue was low. [CO] and [NO(2)] were acceptable at all venues. Controls showed no baseline function change over 4 yr. For hockey players, 1997 lung function values at the low-[PM(1)] venue were significantly higher than 2001 high-[PM(1)] venue values (p <.05); decay per year between 1997 and 2001 was greater for FEF(25-75) (251 +/- 185, 83 +/- 40, 109 +/- 58, 109 +/- 187 ml yr(-1), mean +/- SD for FEF(25-75), FVC, FEV1, PEF, respectively;
p < .05). No relationships between baseline lung functions and airway hyperresponsiveness or symptoms were identified. Five of 9 controls had symptoms, and 10 of 14 subjects had symptoms. This preliminary study suggests [PM(1)] is related to airway function decay in ice rink athletes.


d8e8aa11a83fd296a1646efdf78bb09


Numerous time-series studies have investigated the association between daily mortality and daily ambient particulate air pollution concentrations (PM). The consensus from these studies is that increases in PM are associated with increases in daily mortality. However, it may be that increases in PM only hasten the deaths of individuals in a small, frail subset of the population whose longevity is short even in the absence of particulate air pollution. This hypothesis has been termed mortality displacement or harvesting. Distributed lag models (DLM) have been used to explore mortality effects of air pollution that are spread over multiple days, and DLM coefficients have been proposed as indicators of mortality displacement. We investigate statistical properties of DLM coefficients in the context of mortality displacement using simulation studies with frail population models. Our simulations use actual PM time series, as well as actual weather time series included as confounders. Our simulations show that DLM coefficients can have large bias when the mean lifetime of individuals in the frail subset of the population is more than a few weeks, and that the magnitude of this bias increases as the mean lifetime of individuals in the frail subset of the population increases. We conclude that DLM coefficients may be misleading as an indicator of mortality displacement, in the context of the frail population models that we explored.

BACKGROUND: Medically unexplained physical symptoms (MUPS) and related syndromes are common in medical care and the general population, are associated with extensive morbidity, and have a large impact on functioning. Much of medical practice emphasizes specific pharmacological and surgical intervention for discrete disease states. Medical science, with its emphasis on identifying etiologically meaningful diseases comprised of homogeneous groups of patients, has split MUPS into a number of diagnostic entities or syndromes, each with its own hypothesized pathogenesis. However, research suggests these syndromes may be more similar than different, sharing extensive phenomenological overlap and similar risk factors, treatments, associated morbidities, and prognoses. Examples of syndromes consisting of MUPS include chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivities, somatoform disorders, and 'Gulf War Syndrome.' REVIEW SUMMARY: This paper is a narrative review of the increasing body of evidence suggesting that MUPS and related syndromes are common, disabling, and costly. It emphasizes that MUPS occur along a continuum of symptom count, severity, and duration and may be divided into acute, subacute (or recurrent), and chronic types. Predisposing, precipitating, and perpetuating factors influence the natural history of MUPS. CONCLUSIONS: Effective symptom management involves collaborative doctor-patient approaches for identification of problems based on a combination of medical importance and patient readiness to initiate behavioral change, negotiated treatment goals and outcomes, gradual physical activation and exercise prescription. Additionally, efforts should be made to teach and support active rather than passive coping with the symptoms.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14720312

----------------------------------------------------------------------


The neurochemical effects in developing rats exposed during gestation to the anticholinesterase organophosphorus insecticide chlorpyrifos (CPS) were determined. Pregnant rats were dosed daily with CPS (0, 3, or 7 mg/kg) in corn oil from gestation days (GD) 6-20. Pups were euthanized on postnatal days (PND) 1, 3, 6, 9, 12, and 30 for the determination of brain cholinesterase (ChE) and choline acetyltransferase (ChAT) activities, along with muscarinic receptor (mACHR) densities, the levels of the high-affinity choline uptake (HACU) system, and the vesicular acetylcholine transporter (VACHT). ChE activities were inhibited about 15 and 30% on PND 1, in the low- and high-dosage groups, respectively, and were not different from control values by PND 6.
mACHR densities on PND 1 were reduced in the high-dosage group by about 18, 21, and 17%, using 3H-N-methylscopolamine, 3H-quinuclidinyl benzilate, and 3H-4-DAMP, respectively, as ligands, and were not different from control levels by PND 6. ChAT activity was decreased by approximately 12% in the high-dosage group on PND 9, 12, and 30. HACU levels, using 3H-hemicholinium-3 as the ligand, were reduced by approximately 25% on PND 6 in the low- and high-dosage groups, and by approximately 14 and 21% on PND 12 and 30, only in the high-dosage group. Levels of the VACHT were reduced by a range of 13-31% on PND 3 through 30 in the high-dosage group, using 3H-AH5183 (vesamicol) as the ligand. These data suggest that gestational exposure to 7 mg/kg/day CPS results in long-term alterations of presynaptic cholinergic neurochemistry.


A 55-year-old practitioner from an island in the northern sea felt an increasing hypersensitivity of his entire body to various ambient and nutritional allergens and toxics. He started to treat himself with increasing doses of glucocorticoids and moved to a southern climate in Lanzarote and later on to the Swiss mountains in the grisons. On admission to our hospital in December he was in a disastrous psychotic condition, trying to cool down his body by laying naked on his bed at ambient temperatures around the freezing point. He had consumed on average 250 mg prednisone daily over weeks. As we found out later his personal assistant travelling with him was giving him glucocorticoids through the infusion during his hospital stay. He developed a necrotizing septic phlebitis at the infusion site followed by a Pseudomonas aeruginosa sepsis with fatal multiorgan failure. This case illustrates the dangers of self-treatment by doctors and the difficulties in treating a physician.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15651166


The article is aimed at discussing the theoretical grounds which support the diagnosis of solvent-related chronic encephalopathy in the field of the worker’s mental health, having it as a target in this area. The psychiatric, neurological and labor health postulates which contribute to the multidisciplinary description of such diagnostic category are presented.
(2004) [The assortment index of pesticide load of areas in the sociohygienic monitoring system].
Rakitskii, VN and Sinitskaia, TA Journal/Gig Sanit.  38-40.

(2004) [Study of the influence of chemical pollution of the environment on the health status of children by noninvasive biochemical diagnosis].

The paper presents the results of a complex biochemical study of the health status of children from Moscow, the Moscow Region, Yaroslavl, Cherepovets, the Voronezh Region, etc. The presented results allowed the authors to detect renal protective dysfunction in children in relation to environmental pollution. The greatest deviations of the studied parameters were observed in Moscow (Garden Ring, Central Administration Okrug (CAO)) and in the industrial town of Cherepovets (the area in vicinity of the Severostal enterprise). The results of a complex biomedical examination of 486 children in the Moscow CAO were first analyzed. The spread of changes was established in the studied parameters over a time, which indicates the presence of immunodeficiency, immunopathology, renal detoxifying dysfunction, and nasal and oral mucosal changes.


Neighbours of intensive livestock production facilities frequently complain of odour annoyance. They are also concerned about potential negative health effects of environmental exposures to livestock emissions. Quality of life (QoL) was assessed in residents of a rural community neighbouring an area with high concentration of animal farms. A postal cross-sectional survey was carried out among the 4,537 residents, aged 18-44 years. Of these, 3,112 (69 %) responded to questions on annoyance by livestock odours (4-point scale), on QoL (assessed by the short form 12, SF-12), and on potential confounders (age, gender, respiratory symptoms, smoking, living on or close to a farm, and employment status). SF-12 scores were available for 2745 (88 %) subjects. Sixty-one percent of the respondents complained about unpleasant odours, 91 % of these accused livestock as source of these odours. Physical and emotional
SF-12 scores were inversely related to annoyance scores. Better risk communication might improve QoL in concerned neighbours of intensive livestock production facilities.

Prusakov, VM, Verzhbitskaia, EA, Basaraba, IN and Tkachenko, AV Journal/Gig Sanit. 74-7.

(2004) [Combined effect of detergents and priority pollutants on the body and quality of environment (review of literature)].

The paper deals with the topical problem in the combined effect of detergents and priority pollutants (pesticides, mineral fertilizers, and heavy pollutants) on the body and the quality of the environment. Under combined man-made environmental pollution, surfactants may substantially alter the behavior and toxicity of many chemical substances, which requires that these studies should be continued.

(2004) [Basing the problem of contemporary hygienic regulation of ambient air pollution].
Privalova, LI, Katsnel'son, BA, Kuz'min, SV, Chiburaev, VI, Nikonor, BI, Gurvich, VB, Voronin, SA, Kosheleva, AA and Malykh, OL Journal/Med Tr Prom Ekol. 41-4.


Irritable bowel syndrome (IBS) is a group of functional bowel disorders with different pathophysiological mechanisms but some common clinical features. It can be conceptualized within the biopsychosocial model of illness as a dysregulation of brain-gut axis and its relationships with psychosocial and environmental variables.
Using advanced neuro-imaging techniques, it has been found that some brain centers (anterior cingulate cortex, limbic system, locus ceruleus) are active in mediating gut signals and that visceral hyperalgesia mediates perceptual sensitivity. Using new criteria for diagnosing psychosocial components of somatic illnesses, persistent somatization has been found as one of the main psychological factors that contributes to persistence of symptoms and poor treatment outcome in patients with IBS. Other psychological variables influencing symptom reporting have been identified in the constructs of health-care seeking, abuse, somatosensory amplification, and alexithymia. From a psychological viewpoint, IBS may be conceived as an abnormal cognitive processing of emotional and visceral stimuli, a tendency to perceive somatic stimuli as evidence of symptoms of disease, and to seek repeated and often unnecessary medical care.


In a series of 50 consecutive cases in the outpatients' unit of Environmental Medicine (UEM) at the University Hospital of Aachen, Germany, five patients with the diagnosis of schizophrenia presented delusions of being poisoned by environmental factors. This case report illustrates the clinical features of the paranoid type of schizophrenic psychoses. Schizophrenia represents an important differential diagnosis in the interdisciplinary diagnosis and management of health problems attributed to environmental factors.


Human exposure research has consistently shown that, for most volatile organic compounds (VOCs), personal exposures are vastly different from outdoor air concentrations. Therefore, risk estimates based on ambient measurements may over- or under-estimate risk, leading to ineffective or inefficient management strategies. In the present study we examine the extent of exposure misclassification and its impact on risk for exposure estimated by the U.S. Environmental Protection Agency (U.S. EPA) Assessment System for Population Exposure Nationwide (ASPEN) model relative to monitoring results from a community-based exposure assessment conducted in Baltimore, Maryland (USA). This study is the first direct comparison of the ASPEN model (as used by the U.S. EPA for the Cumulative Exposure Project and subsequently the National-Scale Air Toxics Assessment) and human exposure data to estimate health risks. A random sampling strategy was used to recruit 33 nonsmoking adult community residents. Passive air sampling badges were used to assess 3-day time-weighted-average personal exposure as well as outdoor and indoor residential concentrations of VOCs for each study participant. In general, personal exposures were greater than indoor VOC concentrations, which were greater than outdoor VOC concentrations. Public health risks due to actual personal exposures were estimated. In comparing measured personal exposures and indoor and outdoor VOC concentrations with ASPEN model estimates for ambient concentrations, our data suggest that ASPEN was reasonably accurate as a surrogate for personal exposures (measured exposures of community residents) for VOCs emitted primarily from mobile sources or VOCs that occur as global "background" source pollutant with no indoor source contributions. Otherwise, the ASPEN model estimates were generally lower than measured personal exposures and the estimated health risks. ASPEN's lower exposures resulted in proportional underestimation of cumulative cancer risk when pollutant exposures were combined to estimate cumulative risk. Median cumulative lifetime cancer risk based on personal exposures was 3-fold greater than estimates based on ASPEN-modeled concentrations. These findings demonstrate the significance of indoor exposure sources and the importance of indoor and/or personal monitoring for accurate assessment of risk. Environmental health policies may not be sufficient in reducing exposures and risks if they are based solely on modeled ambient VOC concentrations. Results from our study underscore the need for a coordinated multimedia approach to exposure assessment for setting public health policy.


The vanilloid receptor (TRPV1 or VR1), widely distributed in the central and peripheral nervous system, is activated by a broad range of chemicals similar to those implicated in Multiple Chemical Sensitivity (MCS) Syndrome. The vanilloid receptor is reportedly hyperresponsive in MCS and can increase nitric oxide levels and stimulate N-methyl-D-aspartate (NMDA) receptor activity, both of which are important features in
the previously proposed central role of nitric oxide and NMDA receptors in MCS. Vanilloid receptor activity is markedly altered by multiple mechanisms, possibly providing an explanation for the increased activity in MCS and symptom masking by previous chemical exposure. Activation of this receptor by certain mycotoxins may account for some cases of sick building syndrome, a frequent precursor of MCS. Twelve types of evidence implicate the vanilloid receptor as the major target of chemicals, including volatile organic solvents (but not pesticides) in MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16241041


OBJECTIVES: This study investigated exposure- and subject-related determinants of annoyance and performance during the chemical odor provocation of healthy persons with self-reported environmental annoyance. METHODS: Persons with self-reported annoyance attributed to (i) chemicals or smells (smell-annoyed, SA, N=29), (ii) electrical equipment (electrically annoyed, EA, N=16), and (iii) both smells and electricity (generally annoyed, GA, N=39) were, together with referents (N=54), challenged with n-butyl acetate in an exposure chamber at levels far below the threshold values for neurotoxic effects and trigeminal irritation. A sequence of three air concentrations, 0.37, 1.5, and 6 ppm (1.8, 7.1, and 28 mg/m3) was used, counterbalanced within groups, together with intermittent periods of room air between each exposure level. The response measures comprised ratings of annoyance and smell intensity and reaction-time tests. RESULTS: Only the GA group showed clearly elevated ratings of smell annoyance, mucous membrane irritation, and fatigue, as well as longer reaction times, compared with the referents, in response to the challenge. No group difference was found for the smell-intensity ratings. During intermittent periods without exposure, only the GA group maintained higher ratings for mucous membrane irritation and fatigue. Reaction time and all the rating dimensions showed a positive relationship with momentary n-butyl acetate concentration, while cumulative exposure had a more limited impact on the ratings and reaction time. A suggestion effect by the chamber environment before exposure could not be demonstrated. CONCLUSIONS: The results suggest that self-reported annoyance generalized to both electrical equipment and smells is a better predictor of chemical intolerance than self-reported annoyance to smells only.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15633599

Onishchenko, GG Journal/Gig Sanit. 3-7.

(2004) [Risk of ecologically conditioned diseases (review of literature)].
Omirbaeva, SM Journal/Med Tr Prom Ekol. 28-32.

(2004) [Hypersensitivity to chemical substances].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15552917


OBJECTIVES: A short version of the 21-item Chemical Sensitivity Scale (CSS), called the Chemical Sensitivity Scale for Sensory Hyperreactivity (CSS-SHR), was developed and evaluated for the quantifying of self-reported affective reactions to and behavioral disruptions in daily activities by odorous/pungent substances among patients with sensory hyperreactivity (SHR) for clinical and epidemiological studies. METHODS: Twenty-two patients with clinically diagnosed SHR and 124 control participants responded to the CSS and to additional questions about chemical sensitivity for the evaluation of the CSS-SHR. RESULTS: Eleven of the 21 items of the CSS were
selected, on statistical grounds, to constitute the CSS-SHR, which was found to
generate approximately normal distributions, have good test-retest reliability
\( (r(xy)=0.87) \), satisfying internal consistency \( (r(\alpha)=0.76-0.84) \) and predictive and
concurrent validity, and to be uni-dimensional. The metric properties of the CSS-SHR
were, despite its few items, comparable with those of the CSS. A proposed diagnostic
cut-off score for SHR demonstrated a high correct classification rate (92\%) for the
CSS-SHR. CONCLUSIONS: The favorable metric properties of the CSS-SHR and its
sensitivity/specificity suggests that it is useful for clinical diagnosis and epidemiological
study of sensory hyperreactivity in combination with other diagnostic tools.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15024570


Toxic encephalopathy is a rarely described side effect of 5-fluorouracil which usually
presents with cerebellar, neuropsychiatric, and focal neurological symptoms. Magnetic
resonance imaging findings are described as patchy white matter alterations. We
report the 1st case of capecitabine-induced toxic encephalopathy with epilepsy-like
symptoms and diffuse white matter alterations on magnetic resonance imaging.

(2004) [The specific features of sociohygienic monitoring in an area of
liquidation of former chemical weapons production objects].
Nagornyi, SV, Maimulov, VG, Tsybul'skaia, EA, Lomtev, A, Trofimov, ON and
Oleinikova, EV Journal/Gig Sanit. 51-4.

application of the Slick criteria.

(2004) Short-term fluoxetine treatment enhances baroreflex control of
sympathetic nervous system activity after hindlimb unloading.
Moffitt, JA and Johnson, AK Journal/Am J Physiol Regul Integr Comp Physiol. 286: R584-90.

Data in humans indicate that individuals with orthostatic hypotension that are refractory to other traditional forms of therapy are responsive to selective serotonin reuptake inhibitor (SSRI) treatment. We tested the hypothesis that SSRI administration would help correct the attenuated baroreflex control of sympathetic nervous system activity in the hindlimb-unloaded (HU) rat model of cardiovascular deconditioning. An initial study was conducted to determine the time course of effects of fluoxetine (Flu) administration on baroreflex control of lumbar sympathetic nerve activity (LSNA) in conscious, chronically instrumented rats. Animals received either vehicle (Veh, sterile water) or 10 mg/kg Flu for 1, 4, or 16 days of treatment. Data indicate that while 1-day and 16-day Flu administration did not affect baroreflex function, baroreflex control of LSNA was enhanced after 4-day (short term) Flu administration. HU rats were then treated with Flu for 4 days and compared with HU rats receiving Veh and to casted control rats maintained in the normal posture that received either Veh or short-term Flu treatment. Similar to pilot data, short-term Flu treatment enhanced baroreflex control of LSNA in both HU rats and control rats. These data taken together indicate that baroreflex control of sympathetic nervous system activity is a possible mechanism responsible for the successful treatment of orthostatic intolerance with Flu.

----------------------------------------------------------------------------------


BACKGROUND: It is well known that some patients with allergy complain of airway symptoms from chemicals (ASCs) and strong odours. However, the importance of such information for the treatment of allergic disease is not known. Such symptoms in non-allergic patients have previously been shown to be related to increased sensory nerve reactivity, which is expressed as increased cough sensitivity to inhaled capsaicin. OBJECTIVE: The aim of this study was to examine ASC in atopic patients and relate it to cough reaction to capsaicin inhalation. MATERIALS AND METHODS: Fifty-seven consecutively chosen, skin prick-positive patients with symptoms of the upper and/or lower airways completed a questionnaire concerning ASC. The patients were then divided into two groups, those with and those without such symptoms. Both groups were provoked with inhaled capsaicin in three increments and compared with 73 healthy control subjects. RESULTS: Out of 57 atopic patients, 34 reported ASC agents and 23 did not. The patients with ASC were older (P<0.01) and coughed significantly more on capsaicin provocations (P<0.001), but did not differ from them with respect to the allergic disease or its treatment or to smoking habits. Patients with atopy but without ASC did not differ from healthy controls with regard to sensitivity to capsaicin inhalation. The scored degree of ASC was directly related to the number of coughs during the capsaicin provocation. CONCLUSION: ASC in atopic patients are related to
increased airway sensory nerve reactivity. There is still no explanation for this in certain patients with atopy, but age may be a confounding factor.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15080816

(2004) [Major environmental factors that influence human health in the Novosibirsk Region].
Mikheev, VN, Otroshchenko, VA and Iagudin, BI Journal/Gig Sanit. 50-1.

(2004) Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR.

BACKGROUND: Impaired metabolism of toxic chemicals is a postulated mechanism underlying multiple chemical sensitivity (MCS). Because genetic variation alters the rate of chemical metabolism, this study was designed to determine if MCS cases differed from controls for genetic polymorphisms in drug-metabolizing enzymes. METHODS: Female Caucasian participants (203 cases and 162 controls) were drawn from a larger case-control study based on a reproducible and validated case definition. Common polymorphisms for CYP2D6, NAT1, NAT2, PON1, and PON2 were genotyped. RESULTS: Comparing cases and controls, significant differences were found in genotype distributions for CYP2D6 (P = 0.02) and NAT2 (P = 0.03). Compared with the referent homozygous inactive (CYP2D6) or slow (NAT2) metabolizers, the odds for being CYP2D6 homozygous active (OR = 3.36, P = 0.01) and NAT2 rapid (OR = 4.14, P = 0.01) were significantly higher in cases than controls. The odds for being heterozygous for PON1-55 (OR = 2.05, P = 0.04) and PON1-192 (OR = 1.57, P = 0.04) were also significantly higher in cases. CONCLUSIONS: A genetic predisposition for MCS may involve altered biotransformation of environmental chemicals. The CYP2D6 enzyme activates and inactivates toxins; the NAT2 enzyme bioactivates arylamines to protein-binding metabolites. A gene-gene interaction between CYP2D6 and NAT2 suggested that rapid metabolism for both enzymes may confer substantially elevated risk (OR = 18.7, P = 0.002). Our finding parallels others' observation of a link between PON1 heterozygosity and neurological symptoms in Gulf War syndrome. This first demonstration of genetic variation in drug-metabolizing enzymes in association with MCS requires replication. However, it suggests new research directions on genetically variable toxin pathways that might be important in MCS.

The purpose of this paper is the exploration and explication of the complex phenomena of "healing presence" and of appropriately supportive theoretical approaches to integrate emerging models for research design. Healing presence is described as an interpersonal, intrapersonal, and transpersonal to transcendent phenomenon that leads to a beneficial, therapeutic, and/or positive spiritual change within another individual (healee) and also within the healer. An integrated framework merging knowledge from diverse fields of research develops the multiple elements of healing presence, the healer, the healee's capacity for response and the healing effect as an entangled phenomenon. A conceptual systemic model is presented, and questions and dilemmas that emerge are delineated. An integrated qualitative-quantitative research design is proposed. A systemic relationship model, which includes the healer, the healee, and persons within the healee's environment is presented. The challenges are substantial, but the research questions are meaningful and worthwhile. The goal is to foster healing at bio-psycho-social-spiritual levels of the human being.


The data of hygienic monitoring of the Saint Petersburg environment suggest that the soil of the megapolis is greatly polluted with heavy metals among which lead is of priority. The studies performed indicate that under the environmental and hygienic conditions, the level of lead in the hair of children is a qualitative and quantitative criterion for the negative impact of chemical pollution of the environment. The threshold level at which there are higher morbidity rates in children is 5.8 micrograms/g. The findings suggest that there is a reduction in the earlier accepted critical level 8 micrograms/g. (V. Lukovenko, 1990; B.A. Revich, 1999). When its level is 8 micrograms/g, the children are found to have retarded mental and physical development. The results of examination of the nonspecific resistance system in children living under the conditions of the megapolis show that the level of nonspecific defense decreases when the hair content of lead is 5 micrograms/g.

---

(2004) **Nrf2, An Antioxidant Activated Cnc Bzip Transcription Factor: Mechanism Of Action And Role In Autoimmune Function.**
Ma, Q Journal/Toxicologist. 78: 252.

NF-E2 related factor 2 (Nrf2) is a member of the cap n collar, basic leucine zipper family of transcription factors. Nrf2 mediates gene regulation by a range of chemicals with diverse structures. Activation of Nrf2 by phenolic and other antioxidants involves redox signaling. Induction of phase 2 drug-metabolizing enzyme NQO1, which catalyzes two electron reductions of quinone and quinoid chemicals, is used as a model for analyzing mechanism of gene transcription by Nrf2. Biochemical and genetic evidence demonstrate Nrf2 is required for three types of transcription of the gene: the basal expression, induction by antioxidants, and induction by AhR ligands, suggesting it serves as a master regulator of multiple signal transduction pathways in the transcription of target genes. Loss of Nrf2 function by targeted gene knock out increases the sensitivity of mice and cells to toxicity of oxidative chemicals. Moreover, Nrf2 null mice develop an early-onset, Lupus-like, autoimmune syndrome, characterized by appearance of anti-double strand DNA antibodies in young adulthood (as early as 2 month of age), multi-organ inflammatory lesions, enhanced proliferation of lymphoid cells, deposition of immunoglobulin complexes in glomerular membranes, and death due to rapid progressing, diffuse membranogluomerular nephritis. Taken together, these findings suggest Nrf2 plays critical roles in maintaining cellular homeostasis to oxidative toxicants and in physiological surveillance of autoimmune functions.

---

(2004) **Multiple chemical sensitivities: stigma and social experiences.**
Multiple Chemical Sensitivity (MCS), an intolerance to everyday chemical and biological substances in amounts that do not bother other people, is a medically contested condition. In addition to symptoms and the ongoing difficulties of living with this condition, this hidden and stigmatized disability strongly impacts social relationships and daily life. Based on an ethnographic study, this article introduces the context of MCS in terms of cultural themes, the media, and the economic power of industries that manufacture the products that make people with MCS sick. Participants’ experiences with family members and friends, in work and school settings, and with physicians exemplify the difficulties of living with MCS. I dedicate this article to Joan Ablon, my professor and mentor, whose work has always inspired my thinking and research topics.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15272804


http://www.sciencedirect.com/science/article/B6T4S-4BWYH51-1/2
45369bdd2609a2056d9d0de59c298966


BACKGROUND: Children in urban public housing are at high risk for asthma, given elevated environmental and social exposures and suboptimal medical care. For a multifactorial disease like asthma, design of intervention studies can be influenced by the relative prevalence of key risk factors. To better understand risk factors for asthma morbidity in the context of an environmental intervention study, we conducted a detailed baseline evaluation of 78 children (aged 4-17 years) from three public housing developments in Boston. METHODS: Asthmatic children and their caregivers were recruited between April 2002 and January 2003. We conducted intake interviews that captured a detailed family and medical history, including questions regarding asthma symptom severity, access to health care, medication usage, and psychological stress. Quality of life was evaluated for both the child and caregiver with an asthma-specific scale. Pulmonary function was measured with a portable spirometer, and allergy testing for common indoor and outdoor allergens was conducted with skin testing using the prick puncture method. Exploratory linear and logistic regression models evaluating
predictors of respiratory symptoms, quality of life, and pulmonary function were conducted using SAS. RESULTS: We found high rates of obesity (56%) and allergies to indoor contaminants such as cockroaches (59%) and dust mites (59%). Only 36% of children with persistent asthma reported being prescribed any daily controller medication, and most did not have an asthma action plan or a peak flow meter. One-time lung function measures were poorly correlated with respiratory symptoms or quality of life, which were significantly correlated with each other. In multivariate regression models, household size, body mass index, and environmental tobacco smoke exposure were positively associated with respiratory symptom severity (p < 0.10). Symptom severity was negatively associated with asthma-related quality of life for the child and the caregiver, with caregiver (but not child) quality of life significantly influenced by caregiver stress and whether the child was in the intensive care unit at birth. CONCLUSION: Given the elevated prevalence of multiple risk factors, coordinated improvements in the social environment, the built environment, and in medical management would likely yield the greatest health benefits in this high-risk population.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15585065


Sequence-specific oligonucleotide probes play a crucial role in hybridization techniques including PCR, DNA microarray and RNA interference. Once the entire genome becomes the search space for target genes/genomic sequences, however, cross-hybridization to non-target sequences becomes a problem. Large gene families with significant similarity among family members, such as the P450s, are particularly problematic. Additionally, accurate single nucleotide polymorphism (SNP) detection depends on probes that can distinguish between nearly identical sequences. Conventional oligonucleotide probes that are perfectly matched to target genes genomic sequences are often unsuitable in such cases. Carefully designed mismatches can be used to decrease cross-hybridization potential, but implementing all possible mismatch probes is impractical. Our study provides guidelines for designing non-perfectly matched DNA probes to target DNA sequences as desired throughout the genome. These guidelines are based on the analysis of hybridization data between perfectly matched and non-perfectly matched DNA sequences (single-point or double-point mutated) calculated in silico. Large changes in hybridization temperature predicted by these guidelines for non-matched oligonucleotides fit independent experimental data very well. Applying the guidelines to find oligonucleotide microarray probes for P450 genes, we confirmed the ability of our point mutation method to differentiate the individual genes in terms of thermodynamic calculations of hybridization and sequence similarity.
(2004) [Evaluation of the impact of emissions from the oil-refining plants on human health].
Ledentsova, EE, Zaitseva, NV and Zemlianova, MA Journal/Gig Sanit. 10-2.

The entry of complexes of organic compounds, the components of the emissions from petrochemical and oil-refining plants into the environment leads to its quality and can have an adverse impact on the health status of the population in the area adjacent to the petrochemical plant. This paper deals with the formation of an evidence base for evaluating the etiopathogenetic role of the chemical components of emissions from a petrochemical plant in the development of diseases in the population under environmental conditions. The files of data accumulated in the period of 1994-2001 were analytically generalized in the electron database in accordance with the content of the priority chemical components of emissions in the body of 250 children living in the industrial area where the study plant is situated. The estimation of the level and time course of changes in toxicants in the blood of children identified health indicators to optimize monitoring and to evaluate the efficiency of environment-protective and therapeutic-and-prophylactic programs. The findings suggest that the elevated level of some organic compounds that exert a polytropic toxic effect on the vital organs and systems is a risk factor for diseases and requires a systemic monitoring.

(2004) [Evaluation of the influence of chemical factors of petroleum organic synthesis enterprises on the health status of their workers].
Ledentsova, EE, Zaitseva, NV and Zemlianova, MA Journal/Gig Sanit. 29-32.

Recent studies conducted by a number of authors have given a good idea of the toxic effects of petroleum and its products on man. The combined effects of chemical and physical factors are known to potentiate their toxic effects and to cause an increase in morbidity among the workers of oil-refining plants. The paper substantiates the basic health indices to reduce the risk of industrial influences of the chemical components of emissions from an oil-producing plant on its workers' health. The workers were examined in accordance with the developed algorithm of hygienic evaluation under the influence of a combination of chemical factors, which makes it possible to define health indicators to optimize monitoring and to evaluate the efficiency of therapeutic-and-prophylactic programs. The results of the study suggest that in the workers, the elevated blood level of organic compounds exerting a polytropic toxic effect on the vital organs and systems is a risk factor for diseases and requires a systemic monitoring. Thus, program-specific planning of therapeutic and prophylactic measures implemented at an oil-producing plant should be accomplished by taking into
account the optimum complex of diagnostic studies to evaluate the workers’ health status.


http://www.sciencedirect.com/science/article/B6T4S-4BG8VW2-9/2
4a3cd1e20c70082f7c1452c6cf9b317c


In addition to vitamin C (and other vitamins/antioxidants), clinical ecologists (functional medicine) recommend selenium supplementation as a fundamental therapeutic remedy for the treatment of environment associated health disorders. This recommendation is based on the postulation that the trace element selenium inhibits oxidative stress generated during endogenous detoxification of xenobiotics (phase 1) by increasing selenium-dependent glutathione peroxidase activity, and that it counteracts heavy metal toxicity by forming inert metal complexes. The objective of this review was to investigate whether there are any valid studies providing reliable evidence of the therapeutic benefits of selenium supplementation in potentially environment associated health disorders. A systematic review was conducted based on the rigorous and well-defined methods developed by the Cochrane Collaboration. To achieve the demanding standards for systematic review set by the Cochrane Collaboration, study selection, quality assessment and data abstraction were performed independently and in duplicate using a standardized protocol. Overall, 1290 studies were identified as being eligible for inclusion. Twelve of these met the inclusion criteria and their quality was evaluated individually. None of the studies included in the analysis provided evidence of the therapeutic benefits of selenium supplementation in environment associated health disorders.


Proteins that bind to specific sites on DNA often do so in order to carry out catalysis or specific protein-protein interaction while bound to the recognition site. Functional specificity is enhanced if this second function is coupled to correct DNA site recognition. To analyze the structural and energetic basis of coupling between recognition and catalysis in EcoRI endonuclease, we have studied stereospecific phosphorothioate (PS) or methylphosphonate (PMe) substitutions at the scissile phosphate GpAATTC or at the adjacent phosphate GApATTC in combination with molecular-dynamics simulations of the catalytic center with bound Mg2+. The results show the roles in catalysis of individual phosphoryl oxygens and of DNA distortion and suggest that a "crosstalk ring" in the complex couples recognition to catalysis and couples the two catalytic sites to each other.


Formaldehyde is a flammable, colorless and readily polymerized gas at ambient temperature, and is one of the major pollutants in indoor air. Medical students during their dissection course are exposed to formaldehyde, whose exposure is recently considered to be one of the causes of multiple chemical sensitivity. To understand the system that produces exposures and to plan for implementing control options, this study examined formaldehyde exposures that occurred in the gross anatomy laboratory. Formaldehyde in air was sampled by an active 2,4-dinitrophenylhydrazine (DNPH)-silica gel cartridge, extracted with acetonitrile and analyzed with an high performance liquid chromatograph-ultraviolet(HPLC-UV)detector. The geometric mean formaldehyde concentration was 20-93 ppb in the anatomy laboratory before starting the anatomy dissecting. After beginning the dissecting, however, the highest geometric mean concentrations were 1012-1380 ppb. Significant differences were observed.
during the exposed period for symptoms of "unusual thirst", "burning eyes", "itchy eyes", "bad feeling", "fatigue", etc. in comparison with the non-exposed period. These results show that medical schools should take more concrete measures to reduce exposure to formaldehyde.

(2004) [Quantitative and qualitative analyses in patients with environmentally related disorders].

BACKGROUND: Diagnostics and therapy of environmentally related disorders are hampered by one-sided assumptions and by discrepancies between therapists' and patients' assessments of the disease cause. OBJECTIVES: Discrepancies between patient and expert opinions are examined as to (1) whether the sample can be classified in subgroups according to the convergence or divergence between self and expert rating, (2) which features and (3) which disorder-related behaviour and concepts characterize these groups. METHODS: Medical, psychopathological and environmental symptoms were assessed and their relative influence evaluated. Four subgroups were defined by differentiating between high and low psychological stress according to self and expert judgment, and then compared using statistical and qualitative methods. RESULTS: 61 patients were assessed and assigned to four different subgroups according to the number of psychiatric diagnoses, psychological conflicts, personality structure, environmental exposure and psychosocial integration. CONCLUSIONS: Diagnostics of environmentally related disorders must be based on interdisciplinary tools. Treatment should incorporate the individual patient's conception of his or her disorder.

Kropp, TJ, Glynn, P and Richardson, RJ Journal/Biochemistry. 43: 3716-22.

Aging of organophosphorus (OP)-compound-inhibited neuropathy target esterase (NTE) is the critical event that initiates OP-compound-induced delayed neurotoxicity (OPIDN). Aging has classically been considered to involve side-group loss from phosphorylated NTE, rendering the enzyme refractory to reactivation. N,N'-Disisopropylphosphorodiamidofluoridate (mipafox, MIP)-inhibited NTE has been thought to age quickly; however, it can be reactivated under acidic conditions. The present study was undertaken to determine whether MIP-inhibited human recombinant NTE esterase domain (NEST) ages classically by isopropylamine loss.
Diisopropylphosphorofluoridate (DFP), the oxygen analogue of MIP, was used for comparison. Kinetic values for DFP against NEST were as follows: $k(i) = 17200 \pm 180\text{ M}^{-1}\text{ min}^{-1}$; reactivation $t(1/2)$ approximately 90 min at pH 8.0 and approximately 60 min at pH 5.2; $k(4) = 0.108 \pm 0.041 \text{ min}^{-1}$ at pH 8.0 and $0.181 \pm 0.034 \text{ min}^{-1}$ at pH 5.2. Kinetic values for MIP against NEST were as follows: $k(i) = 1880 \pm 61 \text{ M}^{-1}\text{ min}^{-1}$; reactivation $t(1/2) = 0$ min at pH 8.0 and approximately 60 min at pH 5.2; aging was complete at all time points tested at pH 8.0, but no aging occurred at pH 5.2. Mass spectrometry revealed a mass shift of $123.0 \pm 0.6$ Da for the active site peptide peak of aged DFP-inhibited NEST, corresponding to a monoisopropyl phosphate adduct. In contrast, the analogous mass shift for aged MIP-inhibited NEST was $162.8 \pm 0.6$ Da, corresponding to the intact N,N'-diisopropylphosphorodiamido adduct. Thus, MIP-inhibited NEST does not age by isopropylamine loss. However, because kinetically aged MIP-inhibited NEST yields an intact adduct capable of reversible deprotonation, aging could occur by proton loss. Indeed, MIP-inhibited NEST does not age at pH 5.2 but ages immediately and completely at pH 8.0. Therefore, we conclude that the MIP-NEST conjugate ages by deprotonation rather than classical side-group loss.

(2004) [Particle pollution and allergies in children. What relationships are found in epidemiological studies?].

Particles in the air influence mortality and morbidity even in concentrations which were considered harmless. This report examines their role in allergies. Studies on children from areas with different degrees of pollution show that the "classical" type of air pollution with high amounts of coarse particles apparently does not induce allergies. Nearly all studies, which characterized exposure on a smaller spatial scale, found that symptoms of asthma and allergic rhinitis were more common in children exposed to traffic-related pollution. Time series and panel studies demonstrate that particle pollution contributes to asthma aggravation. Whether this applies to eczema or allergic rhinitis has hardly been investigated. Overall the studies suggest a special role for traffic-related particles.

Kon'zhina, LG, Sergeeva, MV, Lipanova, LL and Solonin, AV Journal/Gig Sanit. 22-4.

The established tense ecological situation in the town of Orsk presents a serious human threat. The use of methods for assessing the risk has allowed the authors to determine the values of carcinogenic and noncarcinogenic risks. Due to the influence
of all environments polluted by industrial emissions, the total annual carcinogenic risk is 2.31 cases for the adult population of the town and 0.49 for its children. The greatest carcinogenic risk is associated with arsenic in water and foodstuffs, hexavalent chromium, cadmium, and formaldehyde in the air. The high concentrations of dust, phenol, nitrogen dioxide, and carbon oxide cause a major damage to human health. The established specific values of this risk are of relative significance.


In contrast to octaethylporphyrin, which forms a very labile bis-BF(2) complex, treatment of the hexa- and octapyrrolic expanded porphyrins amethyrin and [32]octaphyrin with BF(3).Et(2) under standard reaction and work-up conditions gives rise to stable, non-labile mono- and bis-BF(2) complexes; these were readily characterised by, inter alia, X-ray diffraction analyses.


A search of the scientific literature was carried out for physiochemical and biological data [i.e., IC50, LD50, Kp (cm/h) for percutaneous absorption, skin/water and tissue blood partition coefficients, inhibition ki values, and metabolic parameters such as Vmax and Km] on 31 organophosphorus pesticides (OPs) to support the development of predictive quantitative structure-activity relationship (QSAR) and physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) models for human risk assessment. Except for work on parathion, chlorpyrifos, and isofenphos, very few modeling data were found on the 31 OPs of interest. The available percutaneous absorption, partition coefficients and metabolic parameters were insufficient in number to develop predictive QSAR models. Metabolic kinetic parameters (Vmax, Km) varied according to enzyme source and the manner in which the enzymes were characterized. The metabolic activity of microsomes should be based on the kinetic activity of purified or cDNA-expressed cytochrome P450s (CYPs) and the specific content of each active CYP in tissue microsomes. Similar requirements are needed to assess the activity of
tissue A- and B-esterases metabolizing OPs. A limited amount of acetylcholinesterase (AChE), butryrylcholinesterase (BChE), and carboxylesterase (CaE) inhibition and recovery data were found in the literature on the 31 OPs. A program is needed to require the development of physicochemical and biological data to support risk assessment methodologies involving QSAR and PBPK/PD models.

(2004) Effect of exposure to volatile organic compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self-reported multiple chemical sensitivity.

Plasma levels of substance P, vasoactive intestinal peptide and nerve growth factor, but not histamine, were elevated in patients with self-reported multiple chemical sensitivity (sMCS). Exposure to volatile organic compounds (VOC) increased plasma levels of all parameters in these patients, while it had no effect in normal subjects or patients with atopic eczema/dermatitis syndrome (AEDS). Exposure to VOC also enhanced skin wheal responses induced by histamine in patients with sMCS, while it failed to do so in normal or AEDS subjects. These results indicate that exposure to VOC may enhance neurogenic inflammation with concomitant enhancement of histamine-induced responses.


Flight attendants (FAs) exposed to insecticide spray in an aircraft were compared with unexposed subjects for neurobehavioral function, pulmonary function, mood states, and symptoms. The 33 symptomatic FAs were self-selected, and 5 had retired for disability. Testing procedures included balance, reaction time, color discrimination, visual fields, grip strength, verbal recall, problem solving, attention and discrimination functions, and long-term memory functions. Measurements were expressed as a
percentage of their predicted values (derived from unexposed controls), and the author compared the means of the percentage predicted values by analysis of variance. Symptom frequencies and Profile of Mood States (POMS) scores were assessed. FAs were significantly more impaired than controls with respect to balance with eyes closed, grip strength, and color discrimination. Nearly half had 3 or more abnormal neurobehavioral functions, after adjustment was made for age, sex, and education level. Neither elevated POMS scores nor frequencies of average symptoms correlated with their numbers of abnormal measurements. Occupational exposure to synthetic pyrethrin insecticides on airliners was associated with neurobehavioral impairment and disability retirement.


The authors determined prospective directions in research on asbestos problem—risk evaluation, early diagnosis and physiotherapy of asbestos-related diseases; sanitary and epidemiologic well-being of population influenced by enterprises extracting and concentration of asbestos; evaluation of new production and development of legal regulation of safety for work with natural and artificial mineral fibers.


Wasabi, horseradish and mustard owe their pungency to isothiocyanate compounds. Topical application of mustard oil (allyl isothiocyanate) to the skin activates underlying sensory nerve endings, thereby producing pain, inflammation and robust hypersensitivity to thermal and mechanical stimuli. Despite their widespread use in both the kitchen and the laboratory, the molecular mechanism through which isothiocyanates mediate their effects remains unknown. Here we show that mustard oil depolarizes a subpopulation of primary sensory neurons that are also activated by capsaicin, the pungent ingredient in chilli peppers, and by Delta(9)-tetrahydrocannabinol (THC), the psychoactive component of marijuana. Both allyl isothiocyanate and THC mediate their excitatory effects by activating ANKTM1, a member of the TRP ion channel family recently implicated in the detection of noxious cold. These findings identify a cellular and molecular target for the pungent action of
mustard oils and support an emerging role for TRP channels as ionotropic cannabinoid receptors.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14712238


Moisture, microbial and in particular mold related indoor exposure and health problems in homes, offices, and public buildings (Kindergartens, schools, library, and hospitals) have been gaining recognition as one of the most common indoor environmental health issues. Proper recognition of microbial related health problems and the differential diagnosis of sick building syndrome (SBS) or building related illness (BRI) are important for early and effective exposure intervention, treatment, referral and prevention of more serious illness.


The problem of communication in treating multiple chemical sensitivity (MCS) was analysed and evaluated using the documentation of an MCS chatroom which was set up in April 2001 following the TV programme Gesundheitsmagazin Praxis (Health Magazine: Practice). Approaches were developed for solving communication problems in the chatroom. A total of 490 cases were evaluated, most of which (355) were directly or indirectly affected, 76 came from self-help groups and 10 were from 4 guest experts invited by ZDF (Zweites Deutsches Fernsehen, Second German TV channel). Of these 4 experts, 2 were environmental medicine specialists, 1 psychosomatics expert and 1 psychiatrist. Forty-nine of the cases included a petition for chatroom participants to join a class-action law. Aside from exchanging basic information on MCS, frequent topics of discussion on the air were the assessment of physicians, clinics, self-help groups and experts. The participants also expressed their views on problems with society, politics, the economy, science and social security. Another common topic was communication in the chatroom itself, which for the most part consisted of sarcasm and insults, which were cause for conflicts in the chatroom. These communication problems led to the conclusion that a chatroom is not the best medium for discussing MCS. If a chatroom is to be used profitably to this end, it is imperative to have a well-defined organisational framework which allows the exchange of current,
scientifically accurate information while keeping discussions from escalating and degenerating into arguments.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15729837

---------------------------------------------------------------

(2004) [Efficiency of sanitary measures in oil-producing areas].
Ivanov, AV and Tafeeva, EA Journal/Gig Sanit. 22-5.

The paper presents the results of an analysis of the efficiency of sanitary and environment-protective measures relating the ambient atmosphere in the oil-producing areas of the Republic of Tatarstan. It characterizes the environment-protective activity of the PJSC "Tatneft", gives a sanitary evaluation of the quality of the ambient air in the oil-producing areas. It has been ascertained that the improvement of manufacturing technology and the construction of gas and dust catching units on the oil-producing facilities reduce atmospheric pollutant emissions. The levels of hydrocarbons, nitric oxide, and hydrogen sulfide have been substantially decreased. At present, the influence of oil-producing facilities on the quality of the ambient air is 17-19%; the main source of atmospheric pollution is motor transport (its influence on atmospheric pollution is 40-56%). At present versus 1989-1995, the degree of pollution and the mutagenic potential of the ambient air are reduced, which suggests the efficiency of sanitary and environment-protective measures implemented by the PJSC "Tatneft".

---------------------------------------------------------------


For several decades, neuroscientists have provided many clues that point out the involvement of de novo gene expression during the formation of long-lasting forms of memory. However, information regarding the transcriptional response networks involved in memory formation has been scarce and fragmented. With the advent of genome-based technologies, combined with more classical approaches (i.e., pharmacology and biochemistry), it is now feasible to address those relevant questions--which gene products are modulated, and when that processes are necessary for the proper storage of memories--with unprecedented resolution and scale. Using one-trial inhibitory (passive) avoidance training of rats, one of the most studied tasks so far, we found two time windows of sensitivity to transcriptional and translational inhibitors infused into the hippocampus: around the time of training and 3-6 h after training. Remarkably, these periods perfectly overlap with the involvement of hippocampal cAMP/PKA (protein kinase A) signaling pathways in memory consolidation. Given the complexity of transcriptional responses in the brain,
particularly those related to processing of behavioral information, it was clearly necessary to address this issue with a multi-variable, parallel-oriented approach. We used cDNA arrays to screen for candidate inhibitory avoidance learning-related genes and analyze the dynamic pattern of gene expression that emerges during memory consolidation. These include genes involved in intracellular kinase networks, synaptic function, DNA-binding and chromatin modification, transcriptional activation and repression, translation, membrane receptors, and oncogenes, among others. Our findings suggest that differential and orchestrated hippocampal gene expression is necessary in both early and late periods of long-term memory consolidation. Additionally, this kind of studies may lead to the identification and characterization of genes that are relevant for the pathogenesis of complex psychiatric disorders involving learning and memory impairments, and may allow the development of new methods for the diagnosis and treatment of these diseases.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15325958


The self-reported prevalence of asthma in the United States increased by 75% from 1980 to 1994, a trend found to be significant and evident in every region of the country. The increase was most marked in children from birth to 14 years of age; and growing evidence indicates that, as with lead poisoning, inner-city and urban populations are most at risk. Attention has turned to the role of indoor environmental risk factors, especially in homes and schools. Such factors include moisture and mold growth, pest infestation, dust mites, the building envelope, heating systems, inadequate ventilation, nitrogen dioxide, and environmental tobacco smoke. The Healthy Public Housing Initiative (HPHI) is a Boston-based community-centered research and intervention project designed to engage Boston Housing Authority residents in a collaborative process to improve respiratory health, quality of life, building conditions, and building maintenance in public housing. This article summarizes the significant research findings from four pilot studies in housing developments that laid the foundation for the larger HPHI asthma-related environmental intervention study. The research design for the pilot projects is informed by principles of community-collaborative research. The strengths of this model of research for our work are also discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15742674

PROBLEM: To assess symptoms attributed to the environment from an interdisciplinary perspective and to evaluate the plausibility of the participants’ individual theory of a causal relationship between exposure and health impairment.
METHOD: We assessed the medical, psychiatric and environmental background in every participant in an environmental medicine project and discussed the explanatory value of our findings for each reported symptom.
RESULTS: Every second participant had at least one symptom that could be plausibly explained by simultaneously occurring medical, psychological or environmental findings. In 40% of the participants the research team rated the association between an environmental exposure and the health complaints to be ‘plausible’. Psychiatric disorders were frequent, but did not exclude environmentally caused symptoms.
CONCLUSION: Only an interdisciplinary structure including medical, psychiatric and environmental expertise is likely to adequately diagnose and advise persons with environmentally related symptoms.


The extracellular signal-regulated protein kinase 2 (ERK2) plays a central role in cellular proliferation and differentiation. Full activation of ERK2 requires dual phosphorylation of Thr183 and Tyr185 in the activation loop. Tyr185 dephosphorylation by the hematopoietic protein-tyrosine phosphatase (HePTP) represents an important mechanism for down-regulating ERK2 activity. The bisphosphorylated ERK2 is a highly efficient substrate for HePTP with a kcat/Km of 2.6 x 10(6) m(-1) s(-1). In contrast, the kcat/Km values for the HePTP-catalyzed hydrolysis of Tyr(P) peptides are 3 orders of magnitude lower. To gain insight into the molecular basis for HePTP substrate specificity, we analyzed the effects of altering structural features unique to HePTP on the HePTP-catalyzed hydrolysis of p-nitrophenyl phosphate, Tyr(P) peptides, and its physiological substrate ERK2. Our results suggest that substrate specificity is conferred upon HePTP by both negative and positive selections. To avoid nonspecific
tyrosine dephosphorylation, HePTP employs Thr106 in the substrate recognition loop as a key negative determinant to restrain its protein-tyrosine phosphatase activity. The extremely high efficiency and fidelity of ERK2 dephosphorylation by HePTP is achieved by a bipartite protein-protein interaction mechanism, in which docking interactions between the kinase interaction motif in HePTP and the common docking site in ERK2 promote the HePTP-catalyzed ERK2 dephosphorylation (approximately 20-fold increase in kcat/Km) by increasing the local substrate concentration, and second site interactions between the HePTP catalytic site and the ERK2 substrate-binding region enhance catalysis (approximately 20-fold increase in kcat/Km) by organizing the catalytic residues with respect to Tyr(P)185 for optimal phosphoryl transfer.


Environmental medicine outpatient clinics, counseling centers, and practicing physicians have observed environment-related health disorders in patient groups of mixed age as well as for groups consisting only of adults or children. Practicing physicians suspected correlations between environmental factors and health disorders in 36-45% of cases, environmental medicine outpatient clinics and counseling centers in 4-34% for mixed-age groups, 0-24% for adults, and 9-13% for children. A comparison of these data is difficult due to differences in data acquisition, evaluation methods, and descriptive statistics used. Furthermore, data on children are insufficient. Patient-oriented environmental medicine faces a number of problems regarding determination of exposure, effects, and susceptibility, including a lack of scientifically verified cause-and-effect models as well as incorrect diagnoses, attributions, and conclusions. In view of the scope and intensity of environment-related health disorders, the topic cannot be ignored. A functioning program of environmental medicine counseling and patient care is needed for practicing physicians, universities and/or the public sector to deliver effective primary medical care in this field. As always, the building blocks of environmental medicine counseling are medical history, physical examination, differential diagnosis, human biomonitoring, and on-site inspection with environmental monitoring while also taking gender differences into account. Uniform basic documentation procedures and health science analyses will help to optimize patient care in environmental medicine. The value of a diagnostic algorithm in the care of patients with environment-related health disorders is beyond dispute. Last but not least, quality assurance and control are a sine qua non of patient-oriented environmental medicine.

Inhalation of toxins commonly found in air pollution contributes to the development and progression of asthma and environmental airway injury. In this study, we investigated the requirement of toll-like receptor 4 (TLR4) in mice for pulmonary responses to three environmental toxins: aerosolized lipopolysaccharide, particulate matter (residual oil fly ash), and ozone. The physiologic and biologic responses to these toxins were evaluated by the extent of airway responsiveness, neutrophil recruitment to the lower respiratory tract, changes in inflammatory cytokines, and the concentration of protein in the lavage fluid. Genetically engineered, TLR4-deficient mice (C57BL/6(TLR4-/-)) were unresponsive to inhaled lipopolysaccharide, except for minimal increases in some inflammatory cytokines. In contrast, C57BL/6(TLR4-/-) mice did not differ from wild-type mice in their airway response to instilled residual oil fly ash or acute ozone exposure; however, we found that, despite a robust inflammatory response, C57BL/6(TLR4-/-) mice are protected against the development of airway hyperresponsiveness after subchronic ozone exposure. These data demonstrate in the mouse that the requirement of TLR4 for pulmonary inflammation depends on the nature of the toxin and appears specific to toxin and exposure conditions.

-------------------------------------------------------------------------------------------------------------------------------


BACKGROUND: Despite the recognition of chemical emergencies, terrorist events, and ongoing threats, little practical guidance exists for healthcare facilities. METHODS: An approach and materials developed by the Veterans Health Administration in a five-element program over the last 2 years to enhance the existing emergency management program is outlined. Nine steps to the development of a comprehensive all-hazards, emergency plan and program, with auditing and improvement tools are offered. RESULTS: Cognitive aids for clinical use are available on-line and in hard copy. A hazard assessment modeled patients as emission sources documenting the operations strategies under which level C personal protective equipment will protect healthcare workers. The development of this response program appears to support a broader, long-standing VHA approach to problem solving. This involves bringing together individual talented field staff, representing specific skills, geographic regions, and work styles; investing in face-to-face consensus development; and developing programs with extensive internal peer-review ("field-based," "bottom-up and top-down," and external reviews). CONCLUSIONS: Comprehensive and effective programs can be constructed at low cost with reasonable speed within large systems with a public mandate, leading to responsible use of public funds internally, and as models for
private sector programs. It is the long-term operational cost implications, under budget constraints in health care, which often present the true challenge.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15490478


PROBLEM: In patients attributing their chronic, medically unexplained complaints to environmental factors the greatest challenge is to overcome their disabling belief in toxicogenic explanations. METHOD: Patients presenting with health complaints that they attributed to environmental causes in an environmental outpatient department (EOPD) within a university medical center in Germany were studied. An interdisciplinary review of previously diagnosed medical conditions, current clinical consultations, personal risk communication and therapeutic advice is presented. Additionally, patient contentedness, complaint development, and belief in environmental attribution in a follow-up interview are given. RESULTS: The open, prospective study comprises 51 patients reporting more than one complaint. Symptoms had lasted for more than 3 years in 63% of the cases. Seventy percent attributed their complaints to more than one environmental cause. The clinical diagnostic procedure reduced the number of prediagnosed clinical conditions by 50%. Numerous foregoing environmental laboratory analyses had overestimated toxicologically relevant findings. These were not confirmed in 80% (8/10) of the cases. In 8% (n = 4) of the patients a relevant environmental or occupational medical condition was found. A mental or behavioral condition was not considered to have first priority in explaining all complaints in 43% (22/51) of the patients. Among these, mostly respiratory or skin-related diseases were found. All patients contacted participated in a follow-up study after a minimum of 21 months. Sixty-seven percent reported having felt that they were taken seriously, 38% felt better after the beginning of the study, and 45% were no longer certain about the importance of the environmental attribution. Since 83% of the patients with a preceding residential diagnosis of MCS or SBS still believed in environmental causes of their complaints in the follow-up study, we conclude that these prediagnoses appear to be a risk for persisting attribution of the environmental factor. About one third (37%) of these patients with complaints that had not been medically explained by an organic condition during interdisciplinary diagnostics had meanwhile consulted a psychotherapist. CONCLUSIONS: Interdisciplinary diagnostics and scientifically based risk assessment in a specialized clinical center were effective and mostly well accepted by the patients and resulted in reduced attribution of complaints to environmental conditions. No indication was found that patients with complaints not medically explained by organic conditions were managed less
successfully by this approach. Considering the high costs that these patients have previously caused, it appears valuable to apply an interdisciplinary diagnostic strategy.


Multiple chemical sensitivity (MCS) in response to a long-term low-level chemical exposure is as yet an unclarified disorder. To determine the role of olfactory function in the induction of MCS, immunocytochemical analysis of the main olfactory bulb (MOB) was performed after exposure of mice to low levels of formaldehyde. A long-term exposure resulted in an increase in the number of tyrosine hydroxylase-immunopositive periglomerular cells and may affect the neuronal function of the MOB.


PURPOSE: To test the hypothesis that subtle abnormalities of the autonomic nervous system underlie the chronic symptoms reported by many Gulf War veterans, such as chronic diarrhea, dizziness, fatigue, and sexual dysfunction. METHODS: Twenty-two ill Gulf War veterans and 19 age-, sex-, and education-matched control veterans underwent measurement of circadian rhythm of heart rate variability by 24-hour electrocardiography, ambulatory blood pressure recording, Valsalva ratio testing, sympathetic skin response evaluation, sweat imprint testing, and polysomnography. Investigators were blinded to case- or control-group status. RESULTS: High-frequency spectral power of heart rate variability increased normally 2.2-fold during sleep in controls but only 1.2-fold in ill veterans (P <0.0001). In ill veterans as compared with controls, it was lower at night (P = 0.0006), higher during the morning (P = 0.007), but no different during the rest of the day (P = 0.8). The mean heart rate of ill veterans also declined less at night (P = 0.0002), and their corrected QT intervals tended to be longer over the full 24 hours (P = 0.07), particularly at night (P = 0.03). Blunting of the nocturnal heart rate dip in ill veterans was confirmed by 24-hour automatic ambulatory blood pressure monitoring (P = 0.05) and polysomnography (P = 0.03). These differences remained significant after adjusting for potential confounders. Cases and
controls were similar on measures of sympathetic adrenergic and sudomotor function, sleep architecture, respiratory function, and circadian variation in blood pressure and body temperature. CONCLUSION: Some symptoms of Gulf War syndrome may be due to subtle autonomic nervous system dysfunction.


"Chronoastrobiology: are we at the threshold of a new science? Is there a critical mass for scientific research?" A simple photograph of the planet earth from outer space was one of the greatest contributions of space exploration. It drove home in a glance that human survival depends upon the wobbly dynamics in a thin and fragile skin of water and gas that covers a small globe in a mostly cold and vast universe. This image raised the stakes in understanding our place in that universe, in finding out where we came from and in choosing a path for survival. Since that landmark photograph was taken, new astronomical and biomedical information and growing computer power have been revealing that organic life, including human life, is and has been connected to invisible (non-photic) forces, in that vast universe in some surprising ways. Every cell in our body is bathed in an external and internal environment of fluctuating magnetism. It is becoming clear that the fluctuations are primarily caused by an intimate and systematic interplay between forces within the bowels of the earth— which the great physician and father of magnetism William Gilbert called a 'small magnet'— and the thermonuclear turbulence within the sun, an enormously larger magnet than the earth, acting upon organisms, which are minuscule magnets. It follows and is also increasingly apparent that these external fluctuations in magnetic fields can affect virtually every circuit in the biological machinery to a lesser or greater degree, depending both on the particular biological system and on the particular properties of the magnetic fluctuations. The development of high technology instruments and computer power, already used to visualize the human heart and brain, is furthermore making it obvious that there is a statistically predictable time structure to the fluctuations in the sun's thermonuclear turbulence and thus to its magnetic interactions with the earth's own magnetic field and hence a time structure to the magnetic fields in organisms. Likewise in humans, and in at least those other species that have been studied, computer power has enabled us to discover statistically defined endogenous
physiological rhythms and further direct effects that are associated with these invisible geo- and heliomagnetic cycles. Thus, what once might have been dismissed as noise in both magnetic and physiological data does in fact have structure. And we may be at the threshold of understanding the biological and medical meaning and consequences of these patterns and biological-astronomical linkages as well. Structures in time are called chronomes; their mapping in us and around us is called chronomics. The scientific study of chronomes is chronobiology. And the scientific study of all aspects of biology related to the cosmos has been called astrobiology. Hence we may dub the new study of time structures in biology with regard to influences from cosmo- helio- and geomagnetic rhythms chronoastrobiology. It has, of course, been understood for centuries that the movements of the earth in relation to the sun produce seasonal and daily cycles in light energy and that these have had profound effects on the evolution of life. It is now emerging that rhythmic events generated from within the sun itself, as a large turbulent magnet in its own right, can have direct effects upon life on earth. Moreover, comparative studies of diverse species indicate that there have also been ancient evolutionary effects shaping the endogenous chronomic physiological characteristics of life. Thus the rhythms of the sun can affect us not only directly, but also indirectly through the chronic patterns that solar magnetic rhythms have created within our physiology in the remote past. For example, we can document the direct exogenous effects of given specific solar wind events upon human blood pressure and heart rate. We also have evidence of endogenous internal rhythms in blood pressure and heart rate that are close to but not identical to the period length of rhythms in the solar wind. These were installed genetically by natural selection at some time in the distant geological past. This interpretive model of the data makes the prediction that the internal and external influences on heart rate and blood pressure can reinforce or cancel each other out at different times. A study of extensive clinical and physiological data shows that the interpretive model is robust and that internal and external effects are indeed augmentative at a statistically significant level. Chronoastrobiological studies are contributing to basic science—that is, our understanding is being expanded as we recognize heretofore unelaborated linkages of life to the complex dynamics of the sun, and even to heretofore unelaborated evolutionary phenomena. Once, one might have thought of solar storms as mere transient 'perturbations' to biology, with no lasting importance. Now we are on the brink of understanding that solar turbulences have played a role in shaping endogenous physiological chronomes. There is even documentation for correlations between solar magnetic cycles and psychological swings, eras of belligerence and of certain expressions of sacred or religious feelings. Chronoastrobiology can surely contribute to practical applications as well as to basic science. It can help develop refinements in our ability to live safely in outer space, where for example at the distance of the moon the magnetic influences of the sun will have an effect upon humans unshielded by the earth's native magnetic field. We should be better able to understand these influences as physiological and mechanical challenges, and to improve our estimations of the effects of exposure. Chronoastrobiology moreover holds great promise in broadening our perspectives and powers in medicine and public health right here upon the surface of the earth. Even the potential relevance of chronoastrobiology for practical environmental and agricultural challenges cannot be ruled out at this early stage in our
understanding of the apparently ubiquitous effects of magnetism and hence perhaps of solar magnetism on life. The evidence already mentioned that fluctuations in solar magnetism can influence gross clinical phenomena such as rates of strokes and heart attacks, and related cardiovascular variables such as blood pressure and heart rate, should illustrate the point that the door is open to broad studies of clinical implications. The medical value of better understanding magnetic fluctuations as sources of variability in human physiology falls into several categories: 1) The design of improved analytical and experimental controls in medical research. Epidemiological analyses require that the multiple sources causing variability in physiological functions and clinical phenomena be identified and understood as thoroughly as possible, in order to estimate systematic alterations of any one variable. 2) Preventive medicine and the individual patients' care. There are no flat 'baselines', only reference chronomes. Magnetic fluctuations can be shown statistically to exacerbate health problems in some cases. The next step should be to determine whether vulnerable individuals can be identified by individual monitoring. Such vulnerable patients may then discover that they have the option to avoid circumstances associated with anxiety during solar storms, and/or pay special attention to their medication or other treatments. Prehabilitation by self-help can hopefully complement and eventually replace much costly rehabilitation. 3) Basic understanding of human physiological mechanisms. The chronomic organization of physiology implies a much more subtle dynamic integration of functions than is generally appreciated. All three categories of medical value in turn pertain to the challenges for space science of exploring and colonizing the solar system. The earth's native magnetic field acts like an enormous umbrella that offers considerable protection on the surface from harsh solar winds of charged particles and magnetic fluxes. The umbrella becomes weaker with distance from the earth and will offer little protection for humans, other animals, and plants in colonies on the surface of the moon or beyond. Thus it is important before more distant colonization is planned or implemented to better understand those magnetism-related biological-solar interactions that now can be studied conveniently on earth. Thorough lifelong maps of chronomes should be generated and made available to the scientific world. Individual workers should not have to rediscover cycles and rhythms, which can be a confusing source of variation when ignored. By contrast, once mapped, the endpoints of a spectral element in chronomes can serve everybody, for instance for the detection of an elevation of vascular disease risk. Chronomic cartography from birth to death is a task for governments to implement, thereby serving the interests of transdisciplinary science and the general public alike. Governments have supported the systematic gathering of physical data for nearly two centuries on earth in order to serve exploration, trade, and battle on land and on the seas, and indeed agriculture. These government functions have been augmented enormously with satellite technology in more recent decades. The biological comparison with regard to government support and chronomic needs would be the mapping of the human genome. The complete sequences of DNA might have eventually become available due simply to countless individual laboratories publishing piecemeal results in scattered journals. But there would have been enormous redundancy and confusion in assembling and piecing the information together. The waste of time and money involved in the redundancy and confusion would have been considerable. (ABSTRACT TRUNCATED)
(2004) [Dynamic morbidity of children as a evaluation criterion for renovation of aluminum manufacturing industries].

Negative pollution effects from atmospheric discharges by aluminium facilities exerted on population health can be traced by the parameters of the reproductive function in women, physical development of newborns, general and differential morbidity of children aged below one year as well as by anthropometric signs in birth, morbidity of children and adults, mortality, including due to oncology. The introduction of modern technologies including the preliminarily fire anode treatment and the use of highly effective methods of purification of industrial wastes cut the concentration (in atmospheric air) of anhydrous hydrogen fluoride and of solid fluorides as well as of aluminium to maximum permissible concentration; it also essentially reduced the content of benzapilene. A better atmospheric air observed yet in the course of renovation contributed to a lower morbidity of children, aged below one year, as well as to the prevalence of diseases affecting the eyes, respiratory and digestive organs, skin and subcutaneous cellular tissue; it also cuts the number of congenital anomalies versus the data obtained in a neighboring district.


Occupational exposures to pesticides may increase parental risk of infertility and adverse pregnancy outcomes such as spontaneous abortion, preterm delivery, and congenital anomalies. Less is known about residential use of pesticides and the risks they pose to reproduction and development. In the present study we evaluate environmentally relevant, low-dose exposures to agrochemicals and lawn-care pesticides for their direct effects on mouse preimplantation embryo development, a period corresponding to the first 5-7 days after human conception. Agents tested were those commonly used in the upper midwestern United States, including six herbicides [atrazine, dicamba, metolachlor, 2,4-dichlorophenoxyacetic acid (2,4-D)], pendimethalin, and mecoprop], three insecticides (chlorpyrifos, terbufos, and permethrin), two fungicides (chlorothalonil and mancozeb), a desiccant (diquat), and a fertilizer (ammonium nitrate). Groups of 20-25 embryos were incubated 96 hr in vitro with either individual chemicals or mixtures of chemicals simulating exposures encountered by handling pesticides, inhaling drift, or ingesting contaminated groundwater. Incubating embryos with individual pesticides increased the percentage
of apoptosis (cell death) for 11 of 13 chemicals (p \leq 0.05) and reduced development to blastocyst and mean cell number per embryo for 3 of 13 agents (p \leq 0.05). Mixtures simulating preemergent herbicides, postemergent herbicides, and fungicides increased the percentage of apoptosis in exposed embryos (p \leq 0.05). Mixtures simulating groundwater contaminants, insecticide formulation, and lawn-care herbicides reduced development to blastocyst and mean cell number per embryo (p \leq 0.05). Our data demonstrate that pesticide-induced injury can occur very early in development, with a variety of agents, and at concentrations assumed to be without adverse health consequences for humans.


In this study, we characterized the pharmacology and physiology of the automodulation of ACh release at the lizard neuromuscular junction (NMJ). The activation of muscarinic ACh receptors generated a biphasic modulation of synaptic transmission. Muscarine-induced activation of M3 receptors (0-12 min) decreased release, whereas M1 activation (> 12 min) enhanced release. Both phases of the biphasic effect are dependent on nitric oxide. However, cAMP acting via protein kinase A is also necessary for the M1 effect. In summary, we present a novel biphasic role for muscarine and implicate M3 receptors in the inhibition and M1 receptors in the enhancement of transmitter release at the cholinergic lizard NMJ.

Grant, MK and El-Fakahany, EE Journal/Life Sci. 74: 1701-21.

Nitric oxide is involved in a countless number of physiological processes and is known to have cytoprotective as well as cytotoxic effects. Increased knowledge about the multifaceted role of nitric oxide in a variety of disease states has led to the design of multiple treatment strategies involving the nitric oxide system. The current review focuses on recent research advances in the fields of obstetrics, bone disease and erectile dysfunction that have led to current or potential future therapies involving nitric oxide.


BACKGROUND: Hospitals distant from the immediate site of an incident involving a hazardous materials (HAZMATs) release which could include chemical warfare agents, must develop emergency response plans (ERPs) to protect healthcare professionals if they receive potentially contaminated victims. The ERP must address OSHA, EPA, and JCAHO requirements. METHODS: The VHA convened groups to develop a hazard and exposure assessment, identify actions for compliance with existing regulatory standards, and review site and operational planning issues. Exposure modeling results were used to derive relationships between operational parameters (time and distance from sites/sources) and potential exposure for healthcare workers. RESULTS: According to exposure modeling, level C personal protective equipment is adequate to protect hospital staff distant from the chemical release site. Decontamination runoff and contaminated clothing should also be controlled to limit exposure. CONCLUSIONS: Development and coordination of ERPs must include the local emergency planning committee, with clear assignment of tasks, locations, and training in order to prevent exposures to healthcare workers.


OBJECTIVE: A significant proportion of Gulf War veterans (GWVs) report chemical sensitivity, fatigue, and unexplained symptoms resulting in ongoing disability. GWVs frequently recall an association between diesel and petrochemical fume exposure and symptoms during service. The purpose of the present study among GWVs was to evaluate the immediate health effects of acute exposure to chemicals (diesel vapors with acetaldehyde) with and without stress. METHODS: In a single, controlled exposure to 5 parts per million (ppm) diesel vapors, symptoms, odor ratings, neurobehavioral performance, and psychophysiologic responses of 12 ill GWVs
(GWV-I) were compared with 19 age- and gender-matched healthy GWVs (GWV-H).

RESULTS: Relative to baseline and to GWV-H, GWV-I reported significantly increased symptoms such as disorientation and dizziness and displayed significantly reduced end-tidal CO(2) just after the onset of exposure. As exposure increased over time, GWV-I relative to GWV-H reported significantly increased symptoms of respiratory discomfort and general malaise. GWV-I were also physiologically hyporeactive in response to behavioral tasks administered during but not before exposure.

CONCLUSIONS: Current symptoms among GWV-I may be exacerbated by ongoing environmental chemical exposures reminiscent of the Gulf War. Both psychologic and physiologic mechanisms contribute to current symptomatic responses of GWV-I.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15272108

(2004) [The role of mineral composition of drinking water in the development of non-communicable diseases among the population].
Fetisova, GK Journal/Gig Sanit. 20-2.


Although pesticide use is widespread, little is known about potential adverse health effects of in utero exposure. We investigated the effects of organophosphate pesticide exposure during pregnancy on fetal growth and gestational duration in a cohort of low-income, Latina women living in an agricultural community in the Salinas Valley, California. We measured nonspecific metabolites of organophosphate pesticides (dimethyl and diethyl phosphates) and metabolites specific to malathion (malathion dicarboxylic acid), chlorpyrifos [O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) phosphoro-thioate], and parathion (4-nitrophenol) in maternal urine collected twice during pregnancy. We also measured levels of cholinesterase in whole blood and butyryl cholinesterase in plasma in maternal and umbilical cord blood. We failed to demonstrate an adverse relationship between fetal growth and any measure of in utero pesticide exposure. In fact, we found increases in body length and head circumference associated with some exposure measures. However, we did find decreases in gestational duration associated with two measures of in utero pesticide exposure: urinary dimethyl phosphate metabolites [beta(adjusted) = -0.41 weeks per log10 unit increase; 95% confidence interval (CI), -0.75 -- -0.02; p = 0.02], which reflect exposure to dimethyl organophosphate compounds such as malathion, and umbilical
cord cholinesterase (beta(adjusted) = 0.34 weeks per unit increase; 95% CI, 0.13-0.55; p = 0.001). Shortened gestational duration was most clearly related to increasing exposure levels in the latter part of pregnancy. These associations with gestational age may be biologically plausible given that organophosphate pesticides depress cholinesterase and acetylcholine stimulates contraction of the uterus. However, despite these observed associations, the rate of preterm delivery in this population (6.4%) was lower than in a U.S. reference population.


INTRODUCTION: This review argues that "subjective health complaints" is a better and neutral term for "unexplained medical symptoms." The most common complaints are musculoskeletal pain, gastrointestinal complaints and "pseudoneurology" (tiredness, sleep problems, fatigue, and mood changes). These complaints are common in the general population, but for some these complaints reach a level that requires care and assistance. THEORETICAL ASSUMPTIONS: We suggest that these complaints are based on sensations from what in most people are normal physiological processes. In some individuals these sensations become intolerable. In some cases it may signal somatic disease, in most cases not. Cases without somatic disease, or with minimal somatic findings, occur under diagnoses like burnout, epidemic fatigue, multiple chemical sensitivity, chronic musculoskeletal pain, chronic low back pain, chronic fatigue syndrome, and fibromyalgia. These complaints are particularly common in individuals with low coping and high levels of helplessness and hopelessness. CONCLUSION: The psychobiological mechanisms for this is suggested to be sensitization in neural loops maintained by sustained attention and arousal.

(2004) [Immunologic criteria of health changes caused by chemicals polluting environment in infants and pregnant women].

The authors revealed relations-hip between pregnancy disorders and changed humoral immunity parameters including production of anti-hapten antibodies to chemical pollutants (formaldehyde, nickel and lead). The authors disclosed reliable correlations between immune disorders in pregnancy and specific diseases in newborns and infants.
(2004) **Ozone and asthma.**

---


BACKGROUND: The purpose of this report is to identify self-reported health problems and functional impairment associated with screening positive for posttraumatic stress disorder (PTSD) in women seen for care at a Department of Veterans Affairs (VA) medical center. METHODS: A survey was mailed to all women (N = 1935) who received care at the VA Puget Sound Health Care System between October 1996 and January 1998. The survey inquired about health history and habits. It included the PTSD Checklist-Civilian Version (PCL-C) and validated screening measures for other psychiatric disorders. The veteran's version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36-V) was included to assess health-related quality of life. RESULTS: Of the 1259 eligible women who completed the survey, 266 women (21%) screened positive for current PTSD (PCL-C score > or = 50). In age-adjusted bivariate analyses, women who screened positive for PTSD reported more psychiatric problems, substance abuse, and lifetime exposure to domestic violence. They were significantly more likely to endorse physical health problems including obesity, smoking, irritable bowel syndrome, fibromyalgia, chronic pelvic pain, polycystic ovary disease, asthma, cervical cancer, and stroke. In fully adjusted multivariate models, a PCL-C score of 50 or greater was independently associated with scoring in the lowest quartile on SF-36-V subscales and composite scales. CONCLUSIONS: Symptoms of PTSD are common in women treated at VA facilities. In addition, PTSD is associated with self-reported mental and physical health problems and poor health-related quality of life in these patients. These findings have implications for the design of VA primary care services for the growing population of female veterans.

---

(2004) **[Genetic state of population living on soils polluted with heavy metals].**

The study covered heavy metals content of soil at various distances from industrial enterprises. The parameters studied are level of micronuclei in peripheral RBC, frequency and spectrum of chromosomal aberrations in WBC of residents. Finding is
increased mutation pace induced by mutagens. Soil pollution with heavy metals appeared a risk factor for genetic instability.


BACKGROUND: We investigated the effects of worrying information about chemical pollution on subjective symptoms in response to an odor that was previously associated with symptom episodes. METHODS: Ammonia and butyric acid in harmless concentrations were used as odor cues, and 10% CO2-enriched air was used to induce symptoms. One of two odors was consistently mixed with CO2-enriched air while the other odor was presented in room air during 80 s breathing trials (three trials of each). Next, information framing the experiment in the context of possible health-damaging effects of chemical pollution of our environment was presented to half the participants, whereas no information was given to the other half. Finally, both odor cues were presented with room air. Symptom scores were used as the dependent variable. RESULTS: Unexpectedly, participants reported more symptoms in response to the odor previously presented with air than to the odor previously presented with CO2-enriched air. Post-hoc analyses suggested a crucial role for perceived rather than actual contingencies between odor and symptom episodes. Information manipulation had no effect. CONCLUSIONS: Believing that a specific odor cue was associated with a symptom episode was more important than the actual association in order to provoke symptoms in response to harmless odor cues.


PURPOSE: Chemical defunctionalization of C-fiber bladder afferents with intravesical vanilloids such as capsaicin (CAP) or resiniferatoxin (RTX) improves detrusor hyperreflexia in humans and animals. The little existing data comparing the efficacy and tolerance of these 2 vanilloid agents seem to favor RTX in 10% alcohol over CAP, which is usually diluted in 30% alcohol. We compared the efficacy and tolerability of the 2 vanilloid agonists in what to our knowledge is the first randomized, controlled
study comparing non-alcohol CAP vs RTX in 10% alcohol in neurogenic patients with detrusor hyperreflexia. MATERIALS AND METHODS: This single-center, randomized, double-blind, parallel groups study included 39 spinal cord injured adults with detrusor hyperreflexia. On day 0 patients were randomized to receive 1, 100 ml intravesical instillation of 100 nMol/l RTX diluted in 10% ethanol or 1 mmol/l CAP diluted in glucidic solvent. Efficacy (voiding chart and cystomanometry) and tolerability were evaluated during a 3-month follow-up. RESULTS: On day 30 clinical and urodynamic improvement was found in 78% and 83% of patients with CAP vs 80% and 60% with RTX, respectively, without a significant difference between the 2 treated groups. The benefit remained in two-thirds of the 2 groups on day 90. There were no significant differences in regard to the incidence, nature or duration of side effects in CAP vs RTX treated patients. CONCLUSIONS: Our results strongly argue for the importance of accounting for the role of vanilloid solute when interpreting the efficacy and tolerance of vesical vanilloid instillation in detrusor hyperreflexia cases. They suggest that a glucidic solute is a valuable solvent for vanilloid instillation.


Depleted uranium (DU) is a by-product from the chemical enrichment of naturally occurring uranium. Natural uranium is comprised of three radioactive isotopes: (238)U, (235)U, and (234)U. This enrichment process reduces the radioactivity of DU to roughly 30% of that of natural uranium. Nonmilitary uses of DU include counterweights in airplanes, shields against radiation in medical radiotherapy units and transport of radioactive isotopes. DU has also been used during wartime in heavy tank armor, armor-piercing bullets, and missiles, due to its desirable chemical properties coupled with its decreased radioactivity. DU weapons are used unreservedly by the armed forces. Chemically and toxicologically, DU behaves similarly to natural uranium metal. Although the effects of DU on human health are not easily discerned, they may be produced by both its chemical and radiological properties. DU can be toxic to many bodily systems, as presented in this review. Most importantly, normal functioning of the kidney, brain, liver, and heart can be affected by DU exposure. Numerous other systems can also be affected by DU exposure, and these are also reviewed. Despite the prevalence of DU usage in many applications, limited data exist regarding the toxicological consequences on human health. This review focuses on the chemistry, pharmacokinetics, and toxicological effects of depleted and natural uranium on several systems in the mammalian body. A section on risk assessment concludes the review.

Paraoxonase 1 (PON1) is involved in the metabolism and detoxification of insecticides and pesticides. Two polymorphisms within the gene affect the enzyme activity. One is a methionine to leucine change at position 54 (M54L) and the other is a glutamine to arginine variant at position 192 (Q192R). There are contrasting reports assessing the role of these variants in Parkinson's disease (PD). We performed a case-control association study in order to elucidate the possible contribution of variability within PON1 to the risk of sporadic PD in a Finnish population. There was no statistically significant association of the allele, genotype or haplotype distribution with PD (all P values > 0.75). Our results suggest that the M54L and Q192R polymorphisms are not major risk factors for PD in the Finnish population.

(2004) [Human health risk factors of the intradwelling environment].
Chubirko, MI, Pichuzhkina, NM, Rusin, VI and Masailova, LA Journal/Gig Sanit. 67-8.


Cardiac parasympathetic activity reduces susceptibility to potentially lethal ventricular arrhythmias in heart failure and ischemic heart disease. This influence is mediated in large part by antagonism of the adverse cardiac effects of sympathetic overactivity ("indirect" parasympathetic activity) in addition to the "direct" effects of muscarinic stimulation. Nitric oxide modulates parasympathetic cardiac signaling in some animal models, but human data are lacking. We have investigated the influence of endogenous nitric oxide on cardiac responses to parasympathetic stimulation in healthy humans. In 18 volunteers, we studied chronotropic and inotropic responses to muscarinic stimulation, both before and after prestimulation with isoproterenol. Cardiac muscarinic stimulation was achieved using an intravenous bolus of the short-acting cholinesterase inhibitor, edrophonium. Responses were assessed during a background infusion of a nitric oxide synthase inhibitor (N(G)-monomethyl-L-arginine [L-NMMA]), placebo (saline), or phenylephrine (vasoconstrictor control) in a single-blind, random order, crossover protocol. L-NMMA did not affect chronotropic responses to edrophonium alone (direct parasympathetic activity). The decrease in heart rate attributable to "indirect" parasympathetic activity (derived by comparison with the effect
of edrophonium during concurrent adrenergic stimulation) was substantially attenuated by L-NMMA in comparison to both control infusions. No modification of muscarinic inotropic responses by L-NMMA was apparent in comparison to the vasoconstrictor control. Nitric oxide exerts a powerful facilitating influence on indirect (antiadrenergic) but not direct human cardiac parasympathetic control. Stimulation of the endogenous nitric oxide pathway might enhance parasympathetic protection against the adverse influences of cardiac sympathetic overactivity.


The article covers follow-up of 7 patients suffering from occupational argyrosis and 1 patient with domestic argyrosis. Clinical signs of the disease are presented. Mainly skin and mucous membranes are involved. Conclusions concern diagnosis and treatment of the condition.


The organophosphate poison mevinphos (Mev) elicits cardiovascular responses via nitric oxide (NO) produced on activation of M2 muscarinic receptors (M2R) in the rostral ventrolateral medulla (RVLM), where sympathetic vasomotor tone originates. This study further evaluated the contribution of nitric oxide synthase (NOS) isoforms at the RVLM to this process, using adult Sprague-Dawley rats. Bilateral co-microinjection into the RVLM of the selective NOS I inhibitor (250 pmol), 7-nitroindazole or N(omega)-propyl-L-arginine antagonized the initial sympatohexcitatory cardiovascular responses to Mev (10 nmol). Co-administration of a selective NOS II inhibitor, N6-(1-iminoethyl)-L-lysine (250 or 500 pmol) further enhanced these cardiovascular responses and reversed the secondary sympathoinhibitory actions of Mev. A potent NOS III inhibitor, N5-(1-iminoethyl)-L-ornithine (46 or 92 nmol) was ineffective. We also
found that M2R co-localized only with NOS I- or NOS II-immunoreactive RVLM neurons. Furthermore, only NOS I or II in the ventrolateral medulla exhibited an elevation in mRNA or protein levels during the sympathoexcitatory phase, with further up-regulated synthesis of NOS II during the sympathoinhibitory phase of Mev intoxication. We conclude that whereas NOS III is not engaged, NO produced by NOS I and II in the RVLM plays, respectively, a sympathoexcitatory and sympathoinhibitory role in the cardiovascular responses during Mev intoxication.


Type 2 diabetes is a worldwide increasing disease resulting from the interaction between a subject's genetic makeup and lifestyle. In genetically predisposed subjects, the combination of excess caloric intake and reduced physical activity induces a state of insulin resistance. When beta cells are no longer able to compensate for insulin resistance by adequately increasing insulin production, impaired glucose tolerance appears, characterized by excessive postprandial hyperglycemia. Impaired glucose tolerance may evolve into overt diabetes. These 3 conditions, ie, insulin resistance, impaired glucose tolerance, and overt diabetes, are associated with an increased risk of cardiovascular disease. Because all these conditions are also accompanied by the presence of an oxidative stress, this article proposes oxidative stress as the pathogenic mechanism linking insulin resistance with dysfunction of both beta cells and endothelium, eventually leading to overt diabetes and cardiovascular disease. This hypothesis, moreover, may also contribute to explaining why treating cardiovascular risk with drugs, such as calcium channel blockers, ACE inhibitors, AT-1 receptor antagonists, and statins, all compounds showing intracellular preventive antioxidant activity, results in the onset of new cases of diabetes possibly being reduced.

(2004) One size does not fit all: aptitude x treatment interaction (ATI) as a conceptual framework for complementary and alternative medicine outcome research. Part 1--what is ATI research?

When multiple treatment choices are available, the question is not just "which treatment is the best?" but more importantly "best or better for whom, when, and why?" Aptitude (or attribute) by treatment interaction (ATI) is a research paradigm that attempts to examine exactly that--how outcome depends on the match or mismatch between patients' specific characteristics and the treatment they receive. The purpose...
of this two-part paper is to introduce ATI methods as a conceptual framework into complementary and alternative medicine/integrative medicine (CAM/IM) outcome research. Part 1 presents key concepts in ATI research. Part 2 will present ATI research designs and discusses their applications to the examination of the relationships between individuals and therapies, and the illumination of the mechanisms that make therapies differentially effective. Based on this examination, we conclude that ATI research offers invaluable insights into the multifaceted package of care typically delivered in contemporary medicine and therefore should be included in the portfolio of all CAM/IM outcome research.


When multiple treatment choices are available, the question is not just "which treatment is the best?" but more importantly "best or better for whom, when, and why?" Aptitude (or attribute) by treatment interaction (ATI) is a research paradigm that attempts to examine exactly that--how outcome depends on the match or mismatch between patients' specific characteristics and the treatments they receive. The purpose of this two-part paper is to introduce ATI methods as a conceptual framework into complementary and Alternative medicine/integrative medicine (CAM/IM) outcome research. Part I presented key concepts in ATI research. Part II presents ATI research designs and discusses their applications to the examination of the relationships between individuals and therapies, and the illumination of the mechanisms that make therapies differentially effective. Based on this examination, we conclude that ATI research offers invaluable insights into the multifaceted package of care typically delivered in contemporary medicine and therefore should be included in the portfolio of all CAM/IM outcome research.


The authors conducted a telephone survey of 1054 randomly selected individuals within the continental United States to determine the prevalence of chemical hypersensitivity and the medical diagnosis of multiple chemical sensitivity (MCS) in the American population. The etiology and symptomatology of MCS also were investigated. Results produced a 95% confidence level and a +/-3% margin of error. The authors found that 11.2% of Americans reported an unusual hypersensitivity to
common chemical products such as perfume, fresh paint, pesticides, and other petrochemical-based substances, and 2.5% reported they had been medically diagnosed with MCS. Additionally, 31.1% of those sampled reported adverse reactions to fragranced products, and 17.6% experienced breathing difficulties and other health problems when exposed to air fresheners. Although chemical hypersensitivity was more common in women, it affected individuals in all demographic groups studied.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16238164


We examined the prevalence of multiple chemical sensitivities (MCS), a hypersensitivity to common chemical substances. We used a randomly selected sample of 1582 respondents from the Atlanta, Ga, standard metropolitan statistical area. We found that 12.6% of our sample reported the hypersensitivity and that, while the hypersensitivity is more common in women, it is experienced by both men and women of a variety of ages and educational levels. Our prevalence for MCS is similar to that (15.9%) found by the California Department of Health Services in California and suggests that the national prevalence may be similar.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15117694


BACKGROUND: Risk factors for acute wheezing among children in subtropical areas are largely unknown. OBJECTIVE: To investigate the role of viral infections, allergen sensitization, and exposure to indoor allergens as risk factors for acute wheezing in children 0 to 12 years old. METHODS: One hundred thirty-two children 0 to 12 years of age who sought emergency department care for wheezing and 65 children with no history of wheezing were enrolled in this case-control study. Detection of respiratory syncytial virus antigen, rhinovirus and coronavirus RNA, adenovirus, influenza, and parainfluenza antigens was performed in nasal washes. Total IgE and specific IgE to mites, cockroach, cat, and dog were measured with the CAP system. Major allergens from mites, cockroach, cat, and dog were quantified in dust samples by ELISA.
Univariate and multivariate analyses were performed by logistic regression. RESULTS: In children under 2 years of age, infection with respiratory viruses and family history of allergy were independently associated with wheezing (odds ratio, 15.5 and 4.2; \( P = .0001 \) and \( P = .008 \), respectively). Among children 2 to 12 years old, sensitization to inhalant allergens was the major risk factor for wheezing (odds ratio, 2.7; \( P = .03 \)). High-level allergen exposure, exposure to tobacco smoke, and lack of breast-feeding showed no association with wheezing. CONCLUSIONS: Some risk factors for wheezing previously identified in temperate climates were present in a subtropical area, including respiratory syncytial virus infection in infants and allergy in children older than 2 years. Rhinovirus was not associated with wheezing and did not appear to be a trigger for asthma exacerbations.


-----------------------------------------------


BACKGROUND: A toxic encephalopathy (or 'lead encephalopathy') may arise from leaded gasoline abuse that is characterised by tremor, hallucinations, nystagmus, ataxia, seizures and death. This syndrome requires emergency and intensive hospital treatment. METHODS: We compared neurological and cognitive function between chronic gasoline abusers with \((n=15)\) and without \((n=15)\) a history of leaded gasoline encephalopathy, and with controls who had never abused gasoline \((n=15)\). RESULTS: Both groups of chronic gasoline abusers had abused gasoline for the same length of time and compared to controls, showed equivalently elevated blood lead levels and cognitive abnormalities in the areas of visuo-spatial attention, recognition memory and paired associate learning. However, where gasoline abusers with no history of leaded gasoline encephalopathy showed only mild movement abnormalities, gasoline abusers with a history of leaded gasoline encephalopathy showed severe neurological impairment that manifest as higher rates of gait ataxia, abnormal rapid finger tapping, finger to nose movements, dysdiadochokinesia and heel to knee movements, increased deep tendon reflexes and presence of a palmomental reflex. CONCLUSIONS: While neurological and cognitive functions are disrupted by chronic gasoline abuse, leaded gasoline encephalopathy is associated with additional and long-lasting damage to cortical and cerebellar functions.

-----------------------------------------------

The crystal structure of the binary complex of trimeric purine nucleoside phosphorylase (PNP) from calf spleen with the acyclic nucleoside phosphonate inhibitor 2,6-diamino-(S)-9-[2-(phosphonomethoxy)propyl]purine ((S)-PMPDAP) is determined at 2.3Å resolution in space group P2(1)2(1)2(1). Crystallization in this space group, which is observed for the first time with a calf spleen PNP crystal structure, is obtained in the presence of calcium atoms. In contrast to the previously described cubic space group P2(1)3, two independent trimers are observed in the asymmetric unit, hence possible differences between monomers forming the biologically active trimer could be detected, if present. Such differences would be expected due to third-of-the-sites binding documented for transition-state events and inhibitors. However, no differences are noted, and binding stoichiometry of three inhibitor molecules per enzyme trimer is observed in the crystal structure, and in the parallel solution studies using isothermal titration calorimetry and spectrofluorimetric titrations. Presence of phosphate was shown to modify binding stoichiometry of hypoxanthine. Therefore, the enzyme was also crystallized in space group P2(1)2(1)2(1) in the presence of (S)-PMPDAP and phosphate, and the resulting structure of the binary PNP/(S)-PMPDAP complex was refined at 2.05Å resolution. No qualitative differences between complexes obtained with and without the presence of phosphate were detected, except for the hydrogen bond contact of Arg84 and a phosphonate group, which is observed only in the former complex in three out of six independent monomers. Possible hydrogen bonds observed in the enzyme complexed with (S)-PMPDAP, in particular a putative hydrogen bonding contact N(1)-H \cdots, three dots, centered Glu201, indicate that the inhibitor binds in a tautomeric or ionic form in which position N(1) acts as a hydrogen bond donor. This points to a crucial role of this hydrogen bond in defining specificity of trimeric PNPs and is in line with the proposed mechanism of catalysis in which this contact helps to stabilize the negative charge that accumulates on O(6) of the purine base in the transition state. In the present crystal structure the loop between Thr60 and Ala65 was found in a different conformation than that observed in crystal structures of trimeric PNPs up to now. Due to this change a new wide entrance is opened into the active site pocket, which is otherwise buried in the interior of the protein. Hence, our present crystal structure provides no obvious indication for obligatory binding of one of the substrates before binding of a second one; it is rather consistent with random binding of substrates. All these results provide new data for clarifying the mechanism of catalysis and give reasons for the non-Michaelis kinetics of trimeric PNPs.

BACKGROUND: Quantification of variations of human gene expression is complicated by the small differences between different alleles. Recent work has shown that variations do exist in the relative allelic expression levels in certain genes of heterozygous individuals. Herein, we describe the application of an immobilized polymerase chain reaction technique as an alternative approach to measure relative allelic differential expression. RESULTS: Herein, we report a novel assay, based on immobilized polymerase colonies, that accurately quantifies the relative expression levels of two alleles in a given sample. Mechanistically, this was accomplished by PCR amplifying a gene in a cDNA library in a thin polyacrylamide gel. By immobilizing the PCR, it is ensured that each transcript gives rise to only a single immobilized PCR colony, or "polony". Once polony amplified, the two alleles of the gene were differentially labeled by performing in situ sequencing with fluorescently labeled nucleotides. For these sets of experiments, silent single nucleotide polymorphisms (SNPs) were used to discriminate the two alleles. Finally, a simple count was then performed on the differentially labeled polonies in order to determine the relative expression levels of the two alleles. To validate this technique, the relative expression levels of PKD2 in a family of heterozygous patients bearing the 4208G/A SNP were examined and compared to the literature. CONCLUSIONS: We were able to reproduce the results of allelic variation in gene expression using an accurate technology known as polymerase colonies. Therefore, we have demonstrated the utility of this method in human gene expression analysis.

(2004) Polymorphisms in glutathione S-transferases GSTM1, GSTT1 and GSTP1 and cytochromes P450 CYP2E1 and CYP1A1 and susceptibility to cirrhosis or pancreatitis in alcoholics.

Excessive alcohol consumption may cause the development of pathologies in the liver and pancreas and various digestive tract cancers. The enzymes GSTM1, GSTT1, GSTP1, CYP1A1 and CYP2E1 are involved in the bioactivation and detoxification of a variety of xenobiotics present in food, organic solvents, tobacco smoke, drugs, pesticides, environmental pollutants and alcoholic drinks. Polymorphisms in the genes coding for these enzymes have been associated with susceptibility to different diseases, including ethanol-related diseases. To investigate whether these polymorphisms represent risk-modifying factors for ethanol-related diseases, a study was conducted involving 120 Brazilian alcoholics and 221 controls with similar ethnic backgrounds. The distribution of alcoholics groups was as follows: 65 with liver cirrhosis, 14 with chronic pancreatitis and 41 without cirrhosis or pancreatitis. The data revealed that carriers of the rare GSTP1 Val allele were at higher risk of liver cirrhosis and pancreatitis, since we found higher frequencies of the Val/Val genotype in
alcoholics with liver cirrhosis (15.4%) and pancreatitis (28.6%) in comparison with alcoholics without disease (7.3%). No differences were found in the prevalences of the GSTM1 and GSTT1 null genotypes between alcoholics and the controls and no association was found between the rare CYP2E1 c2 allele and liver cirrhosis and pancreatitis. However, when the mutant CYP1A1 allele was compared between alcoholics and controls, the m2/m2 genotype was more prevalent in the liver cirrhosis alcoholics (7.7%) than in the controls (1.4%) and this difference was statistically significant (P = 0.03, OR = 5.33). In conclusion, our data indicate an association between occurrence of the Val/Val GSTP1 genotype and chronic pancreatitis and an association between the m2/m2 CYP1A1 genotype and alcoholic liver cirrhosis. This could indicate that persons with these genotypes are genetically more prone to the development of alcoholic pancreatitis and alcoholic cirrhosis, respectively.

(2004) Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma.

In the United States, Puerto Ricans and Mexicans have the highest and lowest asthma prevalence, morbidity, and mortality, respectively. To determine whether ethnicity-specific differences in therapeutic response, clinical response, and/or genetic factors contribute to differences in asthma outcomes, we compared asthma-related clinical characteristics among 684 Mexican and Puerto Rican individuals with asthma recruited from San Francisco, New York City, Puerto Rico, and Mexico City. Puerto Ricans with asthma had reduced lung function, greater morbidity, and longer asthma duration than did Mexicans with asthma. Bronchodilator responsiveness, measured as percentage change from baseline FEV1, was significantly lower among Puerto Ricans with asthma than among Mexicans with asthma. Puerto Ricans with asthma had on average 7.3% (95% confidence interval [CI], 4.6 to 9.9; p < 0.001) lower bronchodilator reversibility in FEV1, higher risk of an emergency department visit in the previous year (odds ratio, 2.63; 95% CI, 1.6 to 4.3; p < 0.001), and of previous hospitalization for asthma (odds ratio, 1.94; 95% CI, 1.2 to 3.2; p = 0.009) than Mexicans. Subgroup analysis corroborated that Puerto Ricans with asthma had more severe disease than did Mexicans on the basis of lung function measurements, responsiveness to beta2-adrenergic agonists, and health care use. We conclude that Puerto Ricans with asthma respond less to albuterol than do Mexicans with asthma. These findings underscore the need for additional research on racial/ethnic differences in asthma morbidity and response to therapy.
Xenoestrogens can mimic or antagonize the activity of physiological estrogens, and the suggested mechanism of xenoestrogen action involves binding to estrogen receptors (ERs). However, the failure of various in vitro or in vivo assays to show strong genomic activity of xenoestrogens compared with estradiol (E2) makes it difficult to explain their ability to cause abnormalities in animal (and perhaps human) reproductive functions via this pathway of steroid action. E2 has also been shown to initiate rapid intracellular signaling, such as changes in levels of intracellular calcium, cAMP, and nitric oxide, and activations of a variety of kinases, via action at the membrane. In this study, we demonstrate that several xenoestrogens can rapidly activate extracellular-regulated kinases (ERKs) in the pituitary tumor cell line GH3/B6/F10, which expresses high levels of the membrane receptor for ER-alpha (mER). We tested a phytoestrogen (coumestrol), organochlorine pesticides or their metabolites (endosulfan, dieldrin, and DDE), and detergent by-products of plastics manufacturing (p-nonylphenol and bisphenol A). These xenoestrogens (except bisphenol A) produced rapid (3-30 min after application), concentration (10^{-14}-10^{-8} M)-dependent ERK-1/2 phosphorylation but with distinctly different activation patterns. To identify signaling pathways involved in ERK activation, we used specific inhibitors of ERs, epidermal growth factor receptors, Ca2+ signaling, Src and phosphoinositide-3 kinases, and a membrane structure disruption agent. Multiple inhibitors blocked ERK activation, suggesting simultaneous use of multiple pathways and complex signaling web interactions. However, inhibitors differentially affected each xenoestrogen response examined. These actions may help to explain the distinct abilities of xenoestrogens to disrupt reproductive functions at low concentrations.
Brown, M, Beatty, J, O'Keefe, S, Bierenbaum, A, Scott, M, Hodgson, M and Wear, J 

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15286597

(2004) Utilization of juvenile animal studies to determine the human effects and risks of environmental toxicants during postnatal developmental stages. 

BACKGROUND: Toxicology studies utilizing animals and in vitro cellular or tissue preparations have been used to study the toxic effects and mechanism of action of drugs and chemicals and to determine the effective and safe dose of drugs in humans and the risk of toxicity from chemical exposures. Testing in animals could be improved if animal dosing using the mg/kg basis was abandoned and drugs and chemicals were administered to compare the effects of pharmacokinetically and toxicokinetically equivalent serum levels in the animal model and human. Because alert physicians or epidemiology studies, not animal studies, have discovered most human teratogens and toxicities in children, animal studies play a minor role in discovering teratogens and agents that are deleterious to infants and children. In vitro studies play even a less important role, although they are helpful in describing the cellular or tissue effects of the drugs or chemicals and their mechanism of action. One cannot determine the magnitude of human risks from in vitro studies when they are the only source of toxicology data. METHODS: Toxicology studies on adult animals is carried out by pharmaceutical companies, chemical companies, the Food and Drug Administration (FDA), many laboratories at the National Institutes of Health, and scientific investigators in laboratories throughout the world. Although there is a vast amount of animal toxicology studies carried out on pregnant animals and adult animals, there is a paucity of animal studies utilizing newborn, infant, and juvenile animals. This deficiency is compounded by the fact that there are very few toxicology studies carried out in children. That is one reason why pregnant women and children are referred to as "therapeutic orphans." RESULTS: When animal studies are carried out with newborn and developing animals, the results demonstrate that generalizations are less applicable and less predictable than the toxicology studies in pregnant animals. Although many studies show that infants and developing animals may have difficulty in metabolizing drugs and are more vulnerable to the toxic effects of environmental chemicals, there are exceptions that indicate that infants and developing animals may be less vulnerable and more resilient to some drugs and chemicals. In other words, the generalization indicating that developing animals are always more sensitive to environmental toxicants is not valid. For animal toxicology studies to be useful, animal studies have to utilize modern concepts of pharmacokinetics and toxicokinetics, as well
as "mechanism of action" (MOA) studies to determine whether animal data can be utilized for determining human risk. One example is the inability to determine carcinogenic risks in humans for some drugs and chemicals that produce tumors in rodents. When the oncogenesis is the result of peroxisome proliferation, a reaction that is of diminished importance in humans. CONCLUSIONS: Scientists can utilize animal studies to study the toxicokinetic and toxicodynamic aspects of drugs and environmental toxicants. But they have to be carried out with the most modern techniques and interpreted with the highest level of scholarship and objectivity. Threshold exposures, no-adverse-effect level (NOAEL) exposures, and toxic effects can be determined in animals, but have to be interpreted with caution when applying them to the human. Adult problems in growth, endocrine dysfunction, neurobehavioral abnormalities, and oncogenesis may be related to exposures to drugs, chemicals, and physical agents during development and may be fruitful areas for investigation. Maximum permissible exposures have to be based on data, not on generalizations that are applied to all drugs and chemicals. Epidemiology studies are still the best methodology for determining the human risk and the effects of environmental toxicants. Carrying out these focused studies in developing humans will be difficult. Animal studies may be our only alternative for answering many questions with regard to specific postnatal developmental vulnerabilities.


Increasing evidence suggests that glutamate activates the generation of lactate from glucose in astrocytes; this lactate is shuttled to neurons that use it as a preferential energy source. We explore this multicellular "lactate shuttle" with a novel dual-cell, dual-gene therapy approach and determine the neuroprotective potential of enhancing this shuttle. Viral vector-driven overexpression of a glucose transporter in glia enhanced glucose uptake, lactate efflux, and the glial capacity to protect neurons from excitotoxicity. In parallel, overexpression of a lactate transporter in neurons enhanced lactate uptake and neuronal resistance to excitotoxicity. Finally, overexpression of both transgenes in the respective cell types provided more protection than either therapy alone, demonstrating that a dual-cell, dual-gene therapy approach gives greater neuroprotection than the conventional single-cell, single-gene strategy.

Several illnesses expressed somatically that do not have clearly demonstrated pathophysiological origin and that are associated with neuropsychological complaints are reviewed. Among them are nonepileptic seizures, fibromyalgia, chronic fatigue syndrome, Persian Gulf War unexplained illnesses, toxic mold and sick building syndrome, and silicone breast implant disease. Some of these illnesses may be associated with objective cognitive abnormalities, but it is not likely that these abnormalities are caused by traditionally defined neurological disease. Instead, the cognitive abnormalities may be caused by a complex interaction between biological and psychological factors. Nonepileptic seizures serve as an excellent model of medically unexplained symptoms. Although nonepileptic seizures clearly are associated with objective cognitive abnormalities, they are not of neurological origin. There is evidence that severe stressors and PTSD are associated with immune system problems, neurochemical changes, and various diseases; these data blur the distinctions between psychological and organic etiologies. Diagnostic problems are intensified by the fact that many patients are poor historians. Patients are prone to omit history of severe stressors and psychiatric problems, and the inability to talk about stressors increases the likelihood of suffering from physiological forms of stress.


Infections by enteropathogenic microorganisms linked to agroenvironmental contamination represent a significant threat to urban and rural communities. To better characterize and manage this risk, it is necessary, not only to accurately describe enteric illnesses occurring over time or across regions, but also to correctly assess exposure attributable to this environmental pollution. New agroenvironmental hygienic pressure indicators (AHPIs) were developed to synthesise relevant data expressing this exposure. They were derived from a conceptual framework for developing sustainable agriculture indicators and specifically adapted for describing the microbial risk of water contamination by livestock operations. The proposed indicators include
two components, and five attributes whose values are calculated at the livestock operation level from a set of available data related to the fields of microbiology, animal production, agronomy, hydrology, and meteorology. They are then aggregated at a higher geographical level to better express exposure of human populations to potential of water contamination by zoonotic enteropathogens. The indicators are calculated separately by zoonotic enteropathogens, and by water source (surface or groundwater). They take into account the various animal species within each livestock operation. When validated, the proposed indicators will allow decision-makers and public health officials to better manage crucial issues in the area of water safety and agriculture.

(2004) [Procedures for the quantitative determination of the significance of hygienic problems at the state level].
Belonog, AA Journal/Gig Sanit.  8-9.

A procedure has been developed to rank the regional problems of environmental hygiene on the basis of the modified risk-assessing model. The procedure has been tested, by using the regions of the Republic of Kazakhstan as an example. The priority problems and the country's regions requiring a particular attention have been identified in terms of the potential risks of environmental exposures on human health.


OBJECTIVES: To characterize initial central nervous system responses to olfactory administration of homeopathic remedies as biomarkers for subsequently exceptional, simillimum-like clinical outcomes at a systemic level (i.e., both locally and globally). DESIGN: Double-blinded, randomized, placebo-controlled clinical trial. SETTING: A private homeopathic clinic in Phoenix, AZ, and a university laboratory in Tucson, AZ. PATIENTS: Sixty-two (62) persons with physician-confirmed fibromyalgia (FM) (mean age, 49 years; 94% women) enrolled; 53 completed the 3-month assessment visit. Exceptional responders (n = 6, 23% of active treatment group; none on placebo) were those with improvements in the top one-third for both tender point pain and global health ratings after 3 months. INTERVENTION: Patients took daily oral doses of treatment solution in LM (1/50,000 dilution) potency (active group received individualized remedy; placebo group received plain solvent). Dependent measures: Baseline and 3-month difference scores for initial prefrontal electroencephalographic alpha frequency cordance (EEG-C, a correlate of functional brain activity) during 16
pairs of randomized, double-blinded bottle sniffs (treatment minus control solutions).

RESULTS: Exceptional responders versus other patients exhibited significantly more negative initial EEG-C difference scores at prefrontal sites. Right prefrontal cordance findings correlated with subsequently reduced pain ($r = 0.85$, $p = 0.03$), better global health ($r = -0.73$, $p = 0.10$), and trait absorption (genetically determined ability to focus attention selectively and fully) ($r = 0.91$, $p = 0.012$). CONCLUSIONS: These observations suggest prefrontal EEG-C as an early biomarker of individualized homeopathic medicine effects in patients with FM who later exhibit exceptional outcomes. Prefrontal cortex controls executive function, including ability to redirect attention. Interactions between executive function, absorption, and the simillimum remedy could facilitate exceptional responses.


Fibromyalgia (FM) patients show evidence of sensitizability in pain pathways and electroencephalographic (EEG) alterations. One proposed mechanism for the claimed effects of homeopathy, a form of complementary medicine used for FM, is time-dependent sensitization (TDS, progressive amplification) of host responses. This study examined possible sensitization-related changes in EEG relative alpha magnitude during a clinical trial of homeopathy in FM. A 4-month randomized, placebo-controlled double-blind trial of daily orally administered individualized homeopathy in physician-confirmed FM, with an additional 2-month optional crossover phase, included three laboratory sessions, at baseline, 3 and 6 months ($N = 48$, age $49.2 \pm 9.8$ years, $94\%$ women). Nineteen leads of EEG relative alpha magnitude at rest and during olfactory administration of treatment and control solutions were evaluated in each session. After 3 months, the active treatment group significantly increased, while the placebo group decreased, in global alpha-1 and alpha-2 during bottle sniffs over sessions. At 6 months, the subset of active patients who stayed on active continued to increase, while the active-switch subgroup reversed direction in alpha magnitude. Groups did not differ in resting alpha. Consistent with the TDS hypothesis, sniff alpha-1 and alpha-2 increases at 6 months versus baseline correlated with total amount of time on active remedy over all subjects ($r = 0.45$, $p = .003$), not with dose changes or clinical outcomes in the active group. The findings suggest initiation of TDS in relative EEG alpha magnitude by daily oral administration of active homeopathic medicines versus placebo, with laboratory elicitation by temporolimbic olfactory stimulation or sniffing.
Bell, IR, Lewis, DA, 2nd, Lewis, SE, Brooks, AJ, Schwartz, GE and Baldwin, CM

OBJECTIVE: To explore associations between a global rating for the classical homeopathic construct of vital force and clinician and patient ratings on previously validated bio-psycho-social-spiritual questionnaires. METHODS: Sixty-two (62) community-recruited patients with fibromyalgia (FM) were assessed at baseline prior to a clinical trial of individualized homeopathy. Two homeopaths jointly performed case-taking interviews. A conventional medical provider independently evaluated patients with a standardized history and physical examination. Homeopaths rated each patient's vital force (five-point Likert scale, with 1 = very weak to 5 = very strong). Homeopaths and the conventional medical provider rated their Clinical Global Impression (CGI) of the severity of illness (1 = normal; 7 = among the most extremely ill). Patients completed self-rating scales on pain, global health, mood, quality of life, coping style, health locus of control, multidimensional well-being, spirituality, sense of coherence, positive states of mind, and social desirability. RESULTS: Greater vital force ratings (mean 2.9 standard deviation [SD] 0.6) correlated moderately (p < or = 0.005) with less severe CGI illness ratings by the homeopaths (r =-0.59), decreased patient-rated mental confusion (r =-0.43), higher vigor (r = 0.38), and greater positive states of mind (r = 0.36). Vital force also showed correlations (p < 0.05) with lower CGI ratings by the conventional medical provider (r =-0.32), better self-rated quality of life (r = 0.33), lesser fatigue (r =-0.31), better global health (r = 0.29), greater sense of coherence (r = 0.28), powerful-others health locus of control (r = 0.27), increased emotional well-being (r = 0.27), and higher social desirability (r = 0.27), but not with age, pain, or illness duration. CONCLUSION: Homeopathic vital force ratings reflect better perceived mental function, energy, and positive dimensions of the individual, beyond absence of disease.

Bell, IR, Lewis, DA, 2nd, Brooks, AJ, Schwartz, GE, Lewis, SE, Walsh, BT and Baldwin, CM

OBJECTIVE: To assess the efficacy of individualized classical homeopathy in the treatment of fibromyalgia. METHODS: This study was a double-blind, randomized, parallel-group, placebo-controlled trial of homeopathy. Community-recruited persons (N = 62) with physician-confirmed fibromyalgia (mean age 49 yr, s.d. 10 yr, 94% women) were treated in a homeopathic private practice setting. Participants were randomized to receive oral daily liquid LM (1/50,000) potencies with an individually chosen homeopathic remedy or an indistinguishable placebo. Homeopathic visits involved joint interviews and concurrence on remedy selection by two experienced
homeopaths, at baseline, 2 months and 4 months (prior to a subsequent optional crossover phase of the study which is reported elsewhere). Tender point count and tender point pain on examination by a medical assessor uninvolved in providing care, self-rating scales on fibromyalgia-related quality of life, pain, mood and global health at baseline and 3 months, were the primary clinical outcome measures for this report.

RESULTS: Fifty-three people completed the treatment protocol. Participants on active treatment showed significantly greater improvements in tender point count and tender point pain, quality of life, global health and a trend toward less depression compared with those on placebo. CONCLUSIONS: This study replicates and extends a previous 1-month placebo-controlled crossover study in fibromyalgia that pre-screened for only one homeopathic remedy. Using a broad selection of remedies and the flexible LM dose (1/50,000 dilution factor) series, the present study demonstrated that individualized homeopathy is significantly better than placebo in lessening tender point pain and improving the quality of life and global health of persons with fibromyalgia.


OBJECTIVE: To assess individual difference characteristics of subgroups of patients with fibromyalgia (FM) patients with respect to the decision to stay in or switch from randomly-assigned verum or placebo treatment during an optional crossover phase of a double-blinded homeopathy study. DESIGN: Double-blinded, randomized, placebo-controlled, optional crossover clinical trial. PARTICIPANTS: Fifty-three (53) community-recruited patients with FM entered the optional crossover phase. INTERVENTION: Two homeopaths jointly selected an individualized homeopathic remedy for all patients. The pharmacy dispensed either verum LM remedy or indistinguishable placebo in accord with randomized assignment for 4 months and the patient's optional crossover decision for an additional 2 months. OUTCOME MEASURES: Patients completed a battery of baseline state/trait questionnaires, including mood, childhood neglect and abuse, and trait absorption. They rated global health (whole person-centered) and tender point pain on physical examination (disease-specific) at baseline, 3 months, and 6 months. RESULTS: Rates of optional crossover from verum to placebo or placebo to verum were comparable (p = 0.6; 31%, and 41%, respectively). The switch subgroups had greater baseline psychologic issues (emotional neglect in placebo-switch; depression and anger in verum-switch). The verum-stay subgroup scored highest on treatment helpfulness and included all six exceptional responders who fell, prior to crossover, into the top terciles for improvement in both global health and pain. Patients staying in their randomly assigned groups, active or placebo (n = 34), scored significantly higher in trait absorption than did those who switched groups (n = 19). CONCLUSION: Individual
difference factors may predict better and poorer responders with FM to specific and nonspecific effects of homeopathic and placebo treatment.

Bell, IR, Cunningham, V, Caspi, O, Meek, P and Ferro, L Journal/BMC Complement Altern Med. 4: 1.

BACKGROUND: Researchers are finding limitations of currently available disease-focused questionnaire tools for outcome studies in complementary and alternative medicine/integrative medicine (CAM/IM). METHODS: Three substudies investigated the new one-item visual analogue Arizona Integrative Outcomes Scale (AIOS), which assesses self-rated global sense of spiritual, social, mental, emotional, and physical well-being over the past 24 hours and the past month. The first study tested the scale’s ability to discriminate unhealthy individuals (n = 50) from healthy individuals (n = 50) in a rehabilitation outpatient clinic sample. The second study examined the concurrent validity of the AIOS by comparing ratings of global well-being to degree of psychological distress as measured by the Brief Symptom Inventory (BSI) in undergraduate college students (N = 458). The third study evaluated the relationships between the AIOS and positively- and negatively-valenced tools (Positive and Negative Affect Scale and the Positive States of Mind Scale) in a different sample of undergraduate students (N = 62). RESULTS: Substudy (i) Rehabilitation patients scored significantly lower than the healthy controls on both forms of the AIOS and a current global health rating. The AIOS 24-hours correlated moderately and significantly with global health (patients r = 0.50; controls r = 0.45). AIOS 1-month correlations with global health were stronger within the controls (patients r = 0.36; controls r = 0.50). Controls (r = 0.64) had a higher correlation between the AIOS 24-hour and 1-month forms than did the patients (r = 0.33), which is consistent with the presumptive improvement in the patients’ condition over the previous 30 days in rehabilitation. Substudy (ii) In undergraduate students, AIOS scores were inversely related to distress ratings, as measured by the global severity index on the BSI (rAIOS24h = -0.42, rAIOS1month = -0.40). Substudy (iii) AIOS scores were significantly correlated with positive affect (rAIOS24h = 0.56, rAIOS1month = 0.57) and positive states of mind (rAIOS24h = 0.42, rAIOS1month = 0.45), and inversely correlated with negative affect (rAIOS24h = -0.41, rAIOS1month = -0.59). CONCLUSIONS: The AIOS is able to distinguish relatively sicker from relatively healthier individuals; and correlates in expected directions with a measure of distress and indicators of positive and negative affect and positive states of mind. The AIOS offers a tool for CAM/IM research that extends beyond a disease emphasis.
Barshes, NR, Goodpastor, SE and Goss, JA Journal/Front Biosci. 9: 411-20.

Clinical organ transplantation only became a viable treatment option after the advent of effective pharmacologic immunosuppression. Azathioprine and steroids were among the first drugs available for pharmacologic immunosuppression allowed for the first long-term successes in kidney and liver transplantation, though survivors experienced significant adverse effects of the immunosuppression. Azathioprine is an antimetabolite which inhibits the de novo and salvage pathways of purine synthesis. This results in lymphocyte suppression but also toxicity to bone marrow, gastrointestinal tract, and liver. Mycophenolate mofetil (MMF), another antimetabolite drug, inhibits only the de novo purine synthesis pathway. Corticosteroids cause immunosuppression mainly by sequestration of CD4+ T-lymphocytes in the reticuloendothelial system and by inhibiting the transcription of cytokines. Corticosteroids have adverse effects on virtually every system in the body, producing many dose-limiting problems such as osteoporosis, obesity and glucose intolerance. The introduction of cyclosporine in 1983 allowed for further improvements in graft survival, and the incidence of acute rejection decreased. Cyclosporine and the more recently-introduced tacrolimus compose the class of immunosuppressive agents called calcineurin inhibitors. By binding calcineurin and preventing its translocation into the nucleus these drugs prevent transcription and subsequent secretion of IL-2. These drugs produce varying degrees of nephrotoxicity, neurotoxicity and glucose intolerance. Rapamycin also inhibits IL-2 expression, though by interaction with the mammalian Target of Rapamycin (mTOR) protein. The use of antibody to produce immunosuppression began with polyclonal sera developed in animals such as horses or goats. The mechanism by which polyclonal sera causes immunosuppression is not well understood, though cell-mediated cytotoxicity of lymphocytes in the circulation may be one major effect. In contrast, the monoclonal antibody OKT3 is specific for the T-cell receptor (TCR)/CD3 complex, thus preventing activation of T-lymphocytes. Most recently, human and chimeric murine monoclonal antibodies daclizumab and basiliximab have provided effective induction therapy with virtually no adverse effects. While the improved efficacy and decreased adverse effects immunosuppressive agents account for much of the progress in the field of transplantation, current immunosuppression medications not perfect. Ideally, medications would inducing graft tolerance while avoiding generalized immunosuppression and non-immunologic adverse effects. Future research will likely focus on molecular- and gene-level mechanisms to achieve this goal.

Rats were bilaterally implanted with indwelling cannulae in the CA1 region of the dorsal hippocampus. After recovery from surgery, they were trained in a one-trial, step-down inhibitory avoidance task using a 0.5 mA foot shock. The animals received intrahippocampal infusions of either vehicle or anandamide (100 microM, 0.5 microl side) 30 min before training. Then, either immediately post-training or 3 h later, they received infusions of saline, noradrenaline (0.5 microg/side), SKF 38393 (1.5 microg side), oxotremorine (0.6 microg/side) or Sp-cAMPs (0.5 microg/side) also in the hippocampus. All animals were tested for retention 24-h post-training. Anandamide produced anterograde amnesia. Immediate, but not delayed, post-training treatment with Sp-cAMPs and noradrenaline reversed this effect. SKF 38393 and oxotremorine had no influence on the amnesia caused by anandamide either when given immediately or 3 h after training. The results suggest that the amnesic effect of anandamide is related to the known noradrenergic regulation of cAMP-dependent protein kinase (PKA) activity previously described in the hippocampus immediately after avoidance training, which is crucial to long-term memory (LTM) formation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15234253

Baldwin, CM, Kroesen, K, Trochim, WM and Bell, IR Journal/BMC Complement Altern Med. 4: 2.

BACKGROUND: Despite the substantive literature from survey research that has accumulated on complementary and alternative medicine (CAM) in the United States and elsewhere, very little research has been done to assess conceptual domains that CAM and conventional providers would emphasize in CAM survey studies. The objective of this study is to describe and interpret the results of concept mapping with conventional and CAM practitioners from a variety of backgrounds on the topic of CAM. METHODS: Concept mapping, including free sorts, ratings, and multidimensional scaling was used to organize conceptual domains relevant to CAM into a visual "cluster map." The panel consisted of CAM providers, conventional providers, and university faculty, and was convened to help formulate conceptual domains to guide the development of a CAM survey for use with United States military veterans. RESULTS: Eight conceptual clusters were identified: 1) Self-assessment, Self-care, and Quality of Life; 2) Health Status, Health Behaviors; 3) Self-assessment of Health; 4) Practical Economic/ Environmental Concerns; 5) Needs Assessment; 6) CAM vs. Conventional Medicine; 7) Knowledge of CAM; and 8) Experience with CAM. The clusters suggest panelists saw interactions between CAM and conventional medicine as a critical component of the current medical landscape. CONCLUSIONS: Concept mapping provided insight into how CAM and conventional providers view the domain of health care, and was shown to be a useful tool in the formulation of CAM-related conceptual domains.
(2004) **Associations between chemical odor intolerance and sleep disturbances in community-living adults.**
Baldwin, CM, Bell, IR, Guerra, S and Quan, SF Journal/Sleep Med. 5: 53-9.

**OBJECTIVE:** To investigate associations between sleep disturbances and chemical odor intolerance (COI), which is the subjective report of feeling ill from common odors, such as carpet glue or pesticides. **METHODS:** This cross-sectional study consisted of government employees and their family members \(n=140\); 61% women, mean age=46.3 years) derived from a stratified cluster population living in Pima County, Tucson, AZ. Subjects completed a standard survey that included sleep symptoms, a validated measure of COI, and two questions regarding anxiety and depression. Odds ratios (OR) with 95% confidence intervals (CI) were computed to test the association between COI and sleep symptoms. Stratification according to the Mantel-Haenszel method and logistic regression models were used to test for confounding and/or effect modification. **RESULTS:** After adjusting for age and gender, subjects with COI were significantly more likely to report difficulty staying asleep (OR=3.06; CI=1.17-8.03), insufficient sleep (OR=3.93; CI=1.43-10.79), and nightmares (OR=3.17; CI=1.14-8.81) compared to persons without COI. Associations between COI, sleep maintenance problems and insufficient sleep were still significant after adjusting for gender and depression; however, the association between COI and nightmares became borderline. **CONCLUSIONS:** Compared to the non-COI, persons with COI are more likely to report sleep maintenance insomnia and insufficient sleep independent of self-reported depression. Nightmares appear to be related more to depression than to COI.

(2004) **Case-control study of multiple chemical sensitivity, comparing haematology, biochemistry, vitamins and serum volatile organic compound measures.**

**BACKGROUND:** Multiple chemical sensitivity (MCS), although poorly understood, is associated with considerable morbidity. **AIM:** To investigate potential biological mechanisms underlying MCS in a case-control study. **METHODS:** Two hundred and twenty-three MCS cases and 194 controls (urban females, aged 30-64 years) fulfilled reproducible eligibility criteria with discriminant validity. Routine laboratory results and serum levels of volatile organic compounds (VOCs) were compared. Dose-response relationships, a criterion for causality, were examined linking exposures to likelihood of case status. **RESULTS:** Routine laboratory investigations revealed clinically unimportant case-control differences in means. Confounder-adjusted odds ratios (OR) showed MCS was negatively associated with lymphocyte count and total plasma
homocysteine, positively associated with mean cell haemoglobin concentration, alanine aminotransferase and serum vitamin B6, and not associated with thyroid stimulating hormone, folate or serum vitamin B12. More cases than controls had detectable serum chloroform (P = 0.001) with the OR for detectability 2.78 (95% confidence interval = 1.73-4.48, P < 0.001). Chloroform levels were higher in cases. However, cases had significantly lower means of detectable serum levels of ethylbenzene, m&p-xylene, 3-methylpentane and hexane, and means of all serum levels of 1,3,5- and 1,2,3-trimethylbenzene, 2- and 3-methylpentane, and m&p-xylene. CONCLUSIONS: Our findings are inconsistent with proposals that MCS is associated with vitamin deficiency or thyroid dysfunction, but the association of lower lymphocyte counts with an increased likelihood of MCS is consistent with theories of immune dysfunction in MCS. Whether avoidance of exposures or different metabolic pathways in cases explain the observed lower VOC levels or the higher chloroform levels should be investigated.


Multiple Chemical Sensitivity (MCS) -- also known as Idiopathic Environmental Intolerances (IEI) -- is defined as a disorder with multiple somatic and psychological symptoms attributed to low levels of various, chemically unrelated substances in the environment. Self-reported chemical odor sensitivity is an important feature of MCS. We describe the construction and the reliability and validity properties of a short questionnaire for the assessment of chemical odor sensitivity (COSS). The 11 items of the COSS were factor analytically derived from the Questionnaire of Chemical and General Environmental Sensitivity (CGES). Test statistical properties of the COSS were examined in college students, unselected community members, environmental medicine outpatients and chemically sensitive subjects. The COSS achieved good internal consistency in all samples (Cronbach's alpha = 0.89 - 0.93). Women and subjects from samples with higher MCS risk showed elevated COSS scores. The scale showed adequate construct validity and proved useful as an economic screening instrument for persons at risk for MCS.


The Precautionary Principle is in sharp political focus today because: 1) the nature of scientific uncertainty is changing, and 2) there is increasing pressure to base governmental action on more "rational" schemes, such as cost-benefit analysis and quantitative risk assessment, the former being an embodiment of "rational choice theory" promoted by the Chicago School of Law and Economics. The Precautionary Principle has been criticized as being both too vague and too arbitrary to form a basis for rational decision making. The assumption underlying this criticism is that any scheme not based on cost-benefit analysis and risk assessment is both irrational and without secure foundation in either science or economics. This paper contests that view and makes explicit the rational tenets of the Precautionary Principle within an analytical framework as rigorous as uncertainties permit, and one that mirrors democratic values embodied in regulatory, compensatory, and common law. Unlike other formulations that reject risk assessment, this paper argues that risk assessment can be used within the formalism of tradeoff analysis--a more appropriate alternative to traditional cost-benefit analysis and one that satisfies the need for well-grounded public policy decision making. This paper will argue that the precautionary approach is the most appropriate basis for policy, even when large uncertainties do not exist, especially where the fairness of the distributions of costs and benefits of hazardous activities and products are a concern. Furthermore, it will offer an approach to making decisions within an analytic framework, based on equity and justice, to replace the economic paradigm of utilitarian cost-benefit analysis.


Chronic exposure to toxigenic molds in water-damaged buildings is an indoor environmental health problem to which escalating health and property insurance costs are raising a statewide concern in recent times. This paper reviews the structural and functional properties of mycotoxins produced by toxigenic molds and their interactive health implications with antifungal drugs. Fundamental bases of pathophysiological, neurodevelopmental, and cellular mechanisms of mycotoxic effects are evaluated. It is most likely that the interactions of mycotoxins with antifungal drugs may, at least in part, contribute to the observable persistent illnesses, antifungal drug resistance, and allergic reactions in patients exposed to chronic toxigenic molds. Safe dose level of mycotoxin in humans is not clear. Hence, the safety regulations in place at the moment remain inconclusive, precautionary, and arbitrary. Since some of the antifungal drugs are derived from molds, and since they have structural and functional groups similar to
those of mycotoxins, the knowledge of their interactions are important in enhancing preventive measures.


An extensive body of data demonstrates that diverse groups of mycotoxins can alter the structure and function of the nervous system in a variety of ways with notable human health consequences. Myconeurotoxicity refers to any adverse effects of exposure to mycotoxins or byproducts of primary and secondary mold metabolism, including volatile organic compounds (VOCs) on the structural or functional integrity of the developing or adult nervous system. Neuromycotoxic effects may involve a spectrum of biochemical, morphological, behavioral, and physiological abnormalities whose onset can vary from immediate to delayed action, following exposure to a mycotoxin, and whose duration may be transient or persistent and result in disability, while some may have life-threatening consequences. Myconeurotoxicity may result from effects of the mycotoxins acting directly on the elements of the nervous system or acting on other biological systems, which then adversely affect the nervous system. This paper reviews the application, effectiveness, and limitations of the electrophysiological diagnosis of myconeurotoxic effects of chronic environmental exposure to mycotoxins. The systemic targets of mycotoxic effects were reviewed for greater understanding as to why different neurophysiological test techniques have different levels of outcomes. Thus, nerve conduction velocity, sensory, motor, and evoked potentials, electroencephalographic techniques were evaluated using previously published papers and our clinical experience. Although, neuromycotoxic disorders can be established using clinical electrophysiological diagnosis, there is always the possibility of false positive and false negative results in some patients, which may be due to a multi-factorial etiopathogenesis of neuromycotoxicity. Detection of nervous system toxicity and other measures of toxicity could be achieved using a combination of these neurodiagnostic techniques.

(2004) [The use of rates of emergency care referral as early signs of ecological illness].
Agaev, FB and Meibaliev, MT Journal/Gig Sanit. 75-7.

-----------------------------------------------------------------------------------

Afram, R Journal/Yale J Health Policy Law Ethics. 4: 85-121.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15052861

-----------------------------------------------------------------------------------


BACKGROUND: National surveillance for chemical incidents is being developed in the UK. It is important to improve the quality of information collected, standardise techniques, and train personnel. OBJECTIVE: To define the extent to which eight National Poison Information Service specialists in poison information agree on the classification of calls received as "chemical incidents" based on the national definition. DESIGN: Blinded, inter-rater reliability measured using the kappa statistic for multiple raters. SETTING: National Poison Information Service and Chemical Incident Response Service, Guy's and St Thomas's NHS Trust, London. PARTICIPANTS: Eight specialists in poison information who are trained and experienced in handling poisons information calls and have been involved in extracting information for surveillance. RESULTS: The overall level of agreement observed was at least 69% greater than expected by chance (kappa statistic). Fire and incidents where chemicals were released within a property had a very good level of agreement with kappa statistic of 83% and 80% respectively. The lowest level of agreement was observed when no one or only one person was exposed to a chemical (33%) and when the chemical was released into the air (48%). CONCLUSION: High levels of agreement were observed. There is a need for more training and improvement in consistency of the data collected by all organisations.

-----------------------------------------------------------------------------------
Co-exposure to pyridostigmine bromide, DEET, and/or permethrin causes sensorimotor deficit and alterations in brain acetylcholinesterase activity.

Military personnel deployed in the Persian Gulf War (PGW) were exposed to a combination of chemicals, including pyridostigmine bromide (PB), DEET, and permethrin. We investigated the dose-response effects of these chemicals, alone or in combination, on the sensorimotor performance and cholinergic system of male Sprague-Dawley rats. Animals were treated with a daily dermal dose of DEET and/or permethrin for 60 days and/or PB (gavage) during the last 15 days. Neurobehavioral performance was assessed on day 60 following the beginning of the treatment with DEET and permethrin. The rats were sacrificed 24 h after the last treatment for biochemical evaluations. PB alone, or in combination with DEET, or DEET and permethrin resulted in deficits in beam-walk score and longer beam-walk times compared to controls. PB alone, or in combination with DEET, permethrin, or DEET and permethrin caused impairment in incline plane performance and forepaw grip strength. PB alone at all doses slightly inhibited plasma butyrylcholinesterase activity, whereas combination of PB with DEET or permethrin increased its activity. Brainstem acetylcholinesterase (AChE) activity significantly increased following treatment with combinations of either DEET or permethrin at all doses, whereas the cerebellum showed a significant increase in AChE activity following treatment with a combination of PB/DEET/permethrin. Co-exposure to PB, DEET, and permethrin resulted in significant inhibition in AChE in midbrain. PB alone or in combination with DEET and permethrin at all doses increased ligand binding for m2 muscarinic acetylcholine receptor in the cortex. In addition, PB and DEET together or a combination of PB, DEET, and permethrin significantly increased ligand binding for nicotinic acetylcholine receptor. These results suggest that exposure to various doses of PB, alone and in combination with DEET and permethrin, leads to sensorimotor deficits and differential alterations of the cholinergic system in the CNS.

Maternal exposure to nicotine and chlorpyrifos, alone and in combination, leads to persistently elevated expression of glial fibrillary acidic protein in the cerebellum of the offspring in late puberty.
Abdel-Rahman, A, Dechkovskaia, AM, Mehta-Simmons, H, Sutton, JM, Guan, X, Khan, WA and Abou-Donia, MB Journal/Arch Toxicol.  78: 467-76.

We previously showed that maternal exposure to nicotine, alone or in combination with chlorpyrifos, caused an increase in glial fibrillary acidic protein (GFAP) immunostaining in the CA1 subfield of hippocampus and cerebellum in postnatal day (PND) 30 offspring. In the present study, PND 60 offspring were evaluated for histopathological and cholinergic effects following maternal exposure to nicotine and chlorpyrifos, alone and in combination. Timed-pregnant Sprague-Dawley rats (300-350 g) were treated
daily with nicotine (1 mg/kg, s.c., in normal saline) or chlorpyrifos (0.1 mg/kg, dermal, in ethanol) or a combination of nicotine and chlorpyrifos from gestational days (GD) 4 to 20. Control animals were treated with saline and ethanol. On PND 60, the offspring were evaluated for cholinergic changes and pathological effects. Plasma butyrylcholinesterase (BChE) activity in the female offspring from chlorpyrifos treated mothers showed a significant increase (approximately 183% of control). Male offspring from mothers treated with either chlorpyrifos or nicotine alone showed a significant increase in the acetylcholinesterase (AChE) activity in the brainstem while female offspring from mothers treated with either nicotine or a combination of nicotine and chlorpyrifos showed a significant increase (approximately 134 and 126% of control, respectively) in AChE activity in the brainstem. No significant changes were observed in the ligand binding densities for alpha4beta2 and alpha7 nicotinic acetylcholine receptors in the cortex. Histopathological evaluation using cresyl violet staining showed a significant decrease in surviving Purkinje neurons in the cerebellum of the offspring from nicotine treated mothers. An increase in GFAP immunostaining in cerebellar white matter was observed in the offspring from the mothers treated with nicotine. These results suggest that maternal exposure to real-life levels of nicotine and/or chlorpyrifos causes differential regulation of brainstem AChE activity. Also, nicotine caused a decrease in the surviving neurons and an increased expression of GFAP in cerebellar white matter of the offspring on PND 60. These changes can lead to long-term neurological adverse health effects later in life.


Malathion (O,O-dimethyl-S-[1,2-carbethoxyethyl]phosphorodithionate), DEET (N,N-diethyl-m-toluamide), and permethrin [(+-)-cis trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid (3-phenoxyphenyl) methyl ester] are commonly used pesticides. To determine the effects of the dermal application of these chemicals, alone or in combination, the sensorimotor behavior, central cholinergic system, and histopathological alterations were studied in adult male Sprague-Dawley rats following a daily dermal dose of 44.4 mg/kg malathion, 40 mg/kg DEET, and 0.13 mg/kg permethrin, alone and in combination for 30 d. Neurobehavioral evaluations of sensorimotor functions included beam-walking score, beam walk time, inclined plane, and grip response assessments. Twenty-four hours after the last treatment with each chemical alone or in combination all behavioral measures were impaired. The combination of DEET and permethrin, malathion and permethrin, or the three chemicals together resulted in greater impairments in inclined performance than permethrin alone. Only animals treated with a combination of DEET and malathion or with DEET and permethrin exhibited significant increases in plasma butyrylcholinesterase (BChE) activity. Treatment with
DEET or permethrin alone, malathion and permethrin, or DEET and permethrin produced significant increases in cortical acetylcholinesterase (AChE) activity. Combinations of malathion and permethrin or of DEET and permethrin produced significant decreases in midbrain AChE activity. Animals treated with DEET alone exhibited a significant increase in cortical m2 muscarinic ACh receptor binding. Quantification of neuron density in the dentate gyrus, CA1 and CA3 subfields of the hippocampus, midbrain, brainstem, and cerebellum revealed significant reductions in the density of surviving neurons with various treatments. These results suggest that exposure to real-life doses of malathion, DEET, and permethrin, alone or in combination, produce no overt signs of neurotoxicity but induce significant neurobehavioral deficits and neuronal degeneration in brain.

(2004) Stress and combined exposure to low doses of pyridostigmine bromide, DEET, and permethrin produce neurochemical and neuropathological alterations in cerebral cortex, hippocampus, and cerebellum.

Exposure to a combination of stress and low doses of the chemicals pyridostigmine bromide (PB), DEET, and permethrin in adult rats, a model of Gulf War exposure, produces blood-brain barrier (BBB) disruption and neuronal cell death in the cingulate cortex, dentate gyrus, thalamus, and hypothalamus. In this study, neuropathological alterations in other areas of the brain where no apparent BBB disruption was observed was studied following such exposure. Animals exposed to both stress and chemical exhibited decreased brain acetylcholinesterase (AChE) activity in the midbrain, brainstem, and cerebellum and decreased m2 muscarinic acetylcholine (ACh) receptor ligand binding in the midbrain and cerebellum. These alterations were associated with significant neuronal cell death, reduced microtubule-associated protein (MAP-2) expression, and increased glial fibrillary acidic protein (GFAP) expression in the cerebral cortex and the hippocampal subfields CA1 and CA3. In the cerebellum, the neurochemical alterations were associated with Purkinje cell loss and increased GFAP immunoreactivity in the white matter. However, animals subjected to either stress or chemicals alone did not show any of these changes in comparison to vehicle-treated controls. Collectively, these results suggest that prolonged exposure to a combination of stress and the chemicals PB, DEET, and permethrin can produce significant damage to the cerebral cortex, hippocampus, and cerebellum, even in the absence of apparent BBB damage. As these areas of the brain are respectively important for the maintenance of motor and sensory functions, learning and memory, and gait and coordination of movements, such alterations could lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.


Journal/Gig Sanit. 78-80.


N-alcohols exert a dual action on neuronal nicotinic acetylcholine (ACh) receptors with short-chain alcohols exhibiting potentiating action and long-chain alcohols exhibiting inhibitory action. n-Butanol lies at the transition point from potentiation to inhibition. To elucidate the mechanism of dual action of alcohols, the effects of n-butanol on the human alpha4beta2 ACh receptors expressed in the HEK293 cell line were analyzed in detail by the whole-cell patch-clamp technique. Prolonged applications of n-butanol evoked small currents with an EC(50) value of 230 +/- 90 mM and a Hill coefficient of 1.8 +/- 0.4. This current was blocked by either the ACh channel blocker mecamylamine or the receptor blocker dihydro-beta-erythroidine, indicating that butanol activated receptors as a partial agonist. As expected from its partial agonist action, n-butanol also modulated ACh-induced currents in a concentration-dependent manner. Butanol at 300 mM potentiated currents induced by low concentrations of ACh (</=30 microM), while inhibiting the currents induced by high concentrations of ACh (100-3,000 microM). In addition, butanol at a low concentration (10 mM) suppressed the currents evoked by 10 to 3,000 microM ACh, a result consistent with a channel-blocking action. Most features of n-butanol effects were satisfactorily simulated by a model in which butanol acts as a partial agonist and as a channel blocker.


The present study examined whether post-traumatic stress disorder (PTSD) and comorbid substance use disorder (SUD) is associated with greater social and health morbidity than PTSD without SUD in a sample of female primary care patients. Participants were administered diagnostic interviews and assessed for work productivity, quality of interpersonal relationships, and degree of health functioning. No significant differences were found between the women with current PTSD and a comorbid lifetime substance use disorder (N = 56) and those with current PTSD and no lifetime substance use disorders (N = 60) in degree of work productivity, interpersonal functioning, and overall well-being and health, as well as number of lifetime medical illnesses. These findings suggest that the presence of comorbid SUD may not explain the level of social and health difficulties associated with the dual diagnosis of PTSD and SUD.


The epsilon-isozyme of protein kinase C (PKCepsilon) and the vanilloid receptor 1 (VR1) are both expressed in dorsal root ganglion (DRG) neurons and are reported to be predominantly and specifically involved in nociceptive function. Using phosphospecific antibody against the C-terminal hydrophobic site Ser729 of PKCepsilon as a marker of enzyme activation, the state-dependent activation of PKCepsilon, as well as the expression of VR1 in rat DRG neurons, was evaluated in different experimental pain models in vivo. Quantitative analysis showed that phosphorylation of PKCepsilon in DRG neurons was significantly up-regulated after carrageen- and Complete Freund’s Adjuvant-induced inflammation, while it was markedly down-regulated after chronic constriction injury. A double-labeling study showed that phosphorylation of PKCepsilon was expressed predominantly in VR1 immunoreactivity positive small diameter DRG neurons mediating the nociceptive information from peripheral tissue to spinal cord. The VR1 protein expression showed no significant changes after either inflammation or chronic constriction injury. These data indicate that functional activation of PKCepsilon has a close relationship with the production of inflammatory hyperalgesia and the sensitization of the nociceptors.
Inflammatory mediator-induced activation of PKCepsilon and subsequent sensitization of VR1 to noxious stimuli by PKCepsilon may be involved in nociceptor sensitization.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12694383

---------------------------------------------------------------

(2003) Developmental aspects of blood-brain barrier (BBB) and rat brain endothelial (RBE4) cells as in vitro model for studies on chlorpyrifos transport.

The mammalian central nervous system (CNS) is characterized by the blood-brain barrier (BBB), a restrictive barrier endowed with the maintenance of homeostatic control of an optimal milieu within the brain. Whereas in tissues other than the CNS, concentrations of various metabolites (amino acids, K+) can undergo frequent fluctuations, the CNS must keep rigorous control over the extracellular cerebral fluid composition, preventing the mirroring of transient fluctuations in blood, because abrupt changes in these metabolites can translate to aberrant CNS function. The BBB is a specialized structure accomplished by individual endothelial cells that are continuously linked by tight junctions. This brief review will address pertinent issues to development of the BBB. Particular emphasis will be directed at the role of astrocytes in the induction and maintenance of the restrictive properties of this barrier, and the utility of in vitro culture models in surveying transport kinetics, exemplified by recent studies with the pesticide, chlorpyrifos.

---------------------------------------------------------------


The effects of dietary restriction (DR) on the activities of liver superoxide dismutase (SOD), catalase (Cat), and glutathione peroxidase (GPX) and the level of lipid peroxidation (LP) in developing mice were investigated in this study. Male and female Kunmin mice were fed a standard rodent diet ad libitum (AL), 80% of AL food intake (20% DR), or 65% of AL food intake (35% DR) for 12 or 24 wk. Both 12 and 24 wk of DR resulted in retarded body weight gain in male and female mice. The activities of SOD, Cat, and GPX and the content of LP in DR male and female mice were not different (P > 0.05) from those in controls after 12 wk of DR. However, the SOD activity was increased at 24 wk in 20% DR (P < 0.05) and 35% DR (P < 0.01) male, but not in DR female, mice. The Cat activity was elevated at 24 wk in both DR male (P < 0.05 for 20% DR, P < 0.01 for 35% DR) and female (P < 0.01) mice with a greater increase in DR female (P < 0.05) than in DR male animals. GPX activity was also increased at 24 wk in DR male (P < 0.01) and female (P < 0.01) mice with a greater elevation in DR
females (P < 0.05) than in DR males. Furthermore, LP was decreased at 24 wk in both DR male (P < 0.01) and female (P < 0.01) animals with a greater reduction in DR females (P < 0.01) compared with DR males. These findings indicated that 24 wk, but not 12 wk, of DR led to differential effects on liver SOD, Cat, and GPX activities and LP content in male and female mice during development, suggesting sex-associated modulations of DR on antioxidant systems in developing animals.


The effects of caloric restriction (CR) on cognition and behavior in developing mice were investigated in this study. Male and female Kunmin mice were fed a standard rodent diet ad libitum (Control); 80% of control (20% CR) or 65% of control (35% CR) for 6 months. Body weight gain was significant reduced in CR mice relative to control. Learning and memory retention test in a Y maze demonstrated that CR increased learning but not retention in male mice, whereas CR did not affect learning or retention in females. Open field test revealed no difference in exploratory activity between CR and control mice. These findings suggest that CR produce sex-dependent effect on cognition, but not exploratory activity, in developing animals.


In this study we investigated the effects of deltamethrin on the expression of c-Fos and c-Jun in the cerebral cortex of rats. Immunohistochemical analysis demonstrated that the immunoreactivity for c-Fos was markedly increased in the cerebral cortex 5 h after deltamethrin treatment, and maintained at an increased level at 24 h, even though little immunoreactivity for c-Fos was seen in the same brain region of control rats. The immunostaining for c-Jun was also dramatically elevated in the same brain region, showing the same time course of c-Fos expression after deltamethrin treatment. Further, both MK-801, an N-methyl-D-aspartate (NMDA) receptor antagonist, and NBQX, an alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)/kainate (KA) receptor antagonist, attenuated deltamethrin-elicited prolonged expression of c-Fos and c-Jun. Since the persistent expression of c-Fos and c-Jun is unusual, and has been reported before in conditions involving neurodegeneration, our results are consistent with a model that deltamethrin induces neurodegeneration through a glutamate-dependent pathway.

In this study we investigated the induction of apoptotic cell death and its potential mechanisms in cultured cortical neurons in response to deltamethrin exposure. The cultured cortical neurons were treated at 7 days with deltamethrin at concentrations of 10, 100, and 1000 nM, respectively. MTT assay showed that higher concentrations of deltamethrin (100 and 1000 nM) decreased neuronal viability in a time- and dose-dependent way. TUNEL staining revealed that numerous apoptotic cells appeared in the treated cultures compared to controls at 24, 48, and 72 h after treatment of 100 nM deltamethrin. Western blot analysis demonstrated that p53 and Bax expression were dramatically increased at the same time points, whereas Bcl-2 expression was significantly reduced at all time points after deltamethrin treatment. Further, we found that nitric oxide synthase inhibitor N(G)-nitro-L-arginine prevented deltamethrin-induced neuronal apoptosis and altered expression of p53, Bax, and Bcl-2. These results suggest that nitric oxide synthase might mediate deltamethrin-elicited neuronal apoptosis through modulating the expression of apoptosis-related genes.


Isopentenyl diphosphate (IPP):dimethylallyl diphosphate (DMAPP) isomerase is a key enzyme in the biosynthesis of isoprenoids. The reaction involves protonation and deprotonation of the isoprenoid unit and proceeds through a carbocationic transition state. Analysis of the crystal structures (2 A) of complexes of Escherichia coli IPP.DMAPPs isomerase with a transition state analogue (N,N-dimethyl-2-amino-1-ethyl diphosphate) and a covalently attached irreversible inhibitor (3,4-epoxy-3-methyl-1-butyl diphosphate) indicates that Glu-116, Tyr-104, and Cys-67 are involved in the antarafacial addition/elimination of protons during isomerization. This work provides a new perspective about the mechanism of the reaction.
(2003) [Time series analysis for the evaluation of risk of death associated with environmental air pollution].
Wojtyniak, B, Rabczenko, D and Stokwiszewski, J Journal/Rocz Panstw Zakl Hig. 54 Suppl: 22.


OBJECTIVE: Previous studies showed that somatic symptoms can be acquired in response to chemical substances using an associative learning paradigm, but only when the substance was foul smelling and not when it smelled pleasant. In this study, we investigated whether warnings about environmental pollution would facilitate acquiring symptoms, regardless of the pleasantness of the smell. METHOD: One group received prior information framing the study in the context of the rapidly increasing chemical pollution of our environment. Another group received no prior information. Conditional odor stimuli (CS) were diluted ammonia (foul-smelling) and niaouli (neutral-positive smelling); the unconditional stimulus (UCS) was 10% CO2-enriched air. Each subject breathed one odor mixed with CO2 and a control odor mixed with air in 80-sec breathing trials. The type of odor mixed with CO2 was counterbalanced across participants. Next, the same breathing trials were administered without CO2. Breathing behavior was measured during each trial; subjective symptoms were assessed after each trial. RESULTS: Only participants who had been given warnings about environmental pollution reported more symptoms to the odor that had previously been associated with CO2, compared with the control odor. This was so for both the foul- and the pleasant-smelling odor. Symptom learning did not occur in the group that did not receive warnings. The elevated symptom level could not be accounted for by altered respiratory behavior, nor by experimental demand effects. CONCLUSIONS: Raising environmental awareness through warnings about chemical pollution facilitates learning of subjective health symptoms in response to chemical substances.

(2003) Are syndromes in environmental medicine variants of somatoform disorders?
To date, relatively little is known about the etiology, pathophysiology, diagnosis, therapy, prevention and prognosis of environment-related syndromes like multiple chemical sensitivity (MCS), idiopathic environmental intolerance (IEI), sick building syndrome (SBS), chronic fatigue syndrome (CFS), candida syndrome (CS) and burnout syndrome (BS). Part of the reason is that these syndromes have not been clearly defined and classified in scientific categories distinct from each other, and that they show clinical similarities to classified somatoform disorders. Furthermore, there are at least three possible explanations for the existence of these syndromes: (1) The syndromes may result from the interaction of environmental factors, individual susceptibility and psychological factors (i.e., how they are perceived and seen by the patient); (2) they may reflect socially and culturally accepted methods of expressing distress; and/or (3) they may be iatrogenic. Despite all the uncertainties in evaluation of environmental syndromes, physicians have the duty to take the affected person's problems seriously. A comprehensive systematic classification which better accounts for these complex clinical manifestations is long overdue. Until these syndromes are well defined, the terms used for them should definitely not be applied to connote a specific disease process.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=13679005


We have measured 29 pesticides in plasma samples collected at birth between 1998 and 2001 from 230 mother and newborn pairs enrolled in the Columbia Center for Children's Environmental Health prospective cohort study. Our prior research has shown widespread pesticide use during pregnancy among this urban minority cohort from New York City. We also measured eight pesticides in 48-hr personal air samples collected from the mothers during pregnancy. The following seven pesticides were detected in 48-83% of plasma samples (range, 1-270 pg/g): the organophosphates chlorpyrifos and diazinon, the carbamates bendiocarb and 2-isopropoxyphenol (metabolite of propoxur), and the fungicides dicloran, phthalimide (metabolite of folpet and captan), and tetrahydrophthalimide (metabolite of captan and captafol). Maternal and cord plasma levels were similar and, except for phthalimide, were highly correlated (p < 0.001). Chlorpyrifos, diazinon, and propoxur were detected in 100% of personal air samples (range, 0.7-6,010 ng/m(3)). Diazinon and propoxur levels were significantly higher in the personal air of women reporting use of an exterminator, can sprays, and or pest bombs during pregnancy compared with women reporting no pesticide use or use of lower toxicity methods only. A significant correlation was seen between personal
air level of chlorpyrifos, diazinon, and propoxur and levels of these insecticides or their metabolites in plasma samples (maternal and/or cord, p < 0.05). The fungicide ortho-phenylphenol was also detected in 100% of air samples but was not measured in plasma. The remaining 22 pesticides were detected in 0-45% of air or plasma samples. Chlorpyrifos, diazinon, propoxur, and bendiocarb levels in air and/or plasma decreased significantly between 1998 and 2001. Findings indicate that pesticide exposures are frequent but decreasing and that the pesticides are readily transferred to the developing fetus during pregnancy.

Ward, NC, Hodgson, JM, Croft, KD, Clarke, MW, Burke, V, Beilin, LJ and Puddey, IB

Background - Oxidative stress may contribute to the pathogenesis of hypertension and endothelial dysfunction via increased production of free radicals in the arterial wall. Objective - To investigate the effect of water-soluble antioxidants, vitamin C and polyphenols, on blood pressure (BP), endothelial function and oxidative stress in hypertensive individuals. Methods - 69 treated hypertensive individuals with a mean 24hr ambulatory systolic BP >=125 mmHg were involved in a randomised, double blind, placebo-controlled factorial trial. Following a 3-week washout, participants received either 500 mg/d vitamin C, 1000 mg/d grape-seed polyphenols, both vitamin C and polyphenols, or neither, for 6-weeks. At baseline and post-intervention, 24hr ambulatory BP, ultrasound assessed endothelium dependent and independent vasodilation of the brachial artery, and markers of oxidative damage, including plasma and urinary isoprostanes, oxidised low density lipoproteins and plasma tocopherols, were measured. Results - A significant interaction was observed, therefore results could not be analysed for main effects. In comparison to placebo, vitamin C lowered systolic BP (-1.8 +/- 0.8 mmHg, P=0.03), polyphenols did not significantly alter BP, but the combination of vitamin C and polyphenols significantly increased systolic (4.8 +/- 0.9 mmHg, P<0.0001), and diastolic (2.7 +/- 0.6 mmHg, P<0.0001) BP. Endothelium-dependent and independent vasodilation, and markers of oxidative damage were not significantly altered. Conclusion - The combination of vitamin C and polyphenols significantly increased BP, but the mechanism remains to be elucidated.

(2003) Antibodies to molds and satratoxin in individuals exposed in water-damaged buildings.
Vojdani, A, Thrasher, JD, Madison, RA, Gray, MR, Heuser, G and Campbell, AW
Journal/Arch Environ Health. 58: 421-32.
Immunoglobulin (Ig)A, IgM, and IgG antibodies against Penicillium notatum, Aspergillus niger, Stachybotrys chartarum, and satratoxin H were determined in the blood of 500 healthy blood donor controls, 500 random patients, and 500 patients with known exposure to molds. The patients were referred to the immunological testing laboratory for health reasons other than mold exposure, or for measurement of mold antibody levels. Levels of IgA, IgM, and IgG antibodies against molds were significantly greater in the patients (p < 0.001 for all measurements) than in the controls. However, in mold-exposed patients, levels of these antibodies against satratoxin differed significantly for IgG only (p < 0.001), but not for IgM or IgA. These differences in the levels of mold antibodies among the 3 groups were confirmed by calculation of z score and by Scheffe's significant difference tests. A general linear model was applied in the majority of cases, and 3 different subsets were formed, meaning that the healthy control groups were different from the random patients and from the mold-exposed patients. These findings indicated that mold exposure was more common in patients who were referred for immunological evaluation than it was in healthy blood donors. The detection of antibodies to molds and satratoxin H likely resulted from antigenic stimulation of the immune system and the reaction of serum with specially prepared mold antigens. These antigens, which had high protein content, were developed in this laboratory and used in the enzyme-linked immunosorbent assay (ELISA) procedure. The authors concluded that the antibodies studied are specific to mold antigens and mycotoxins, and therefore could be useful in epidemiological and other studies of humans exposed to molds and mycotoxins.


OBJECTIVES: The study examined acute neurobehavioral effects provoked by controlled exposure to 1-octanol and isopropanol among male volunteers. METHODS: In a 29-m3 exposure laboratory, 24 male students (mean age 25.8 years) were exposed to 1-octanol and isopropanol. Each substance was used in two concentrations (0.1 and 6.4 ppm for 1-octanol; 34.9 and 189.9 ppm for isopropanol). In a crossover design, each subject was exposed for 4 hours to the conditions. Twelve subjects reported enhanced chemical sensitivity; the other 12 were age-matched controls. At the onset and end of the exposures neurobehavioral tests were administered and symptoms were rated. RESULTS: At the end of the high and low isopropanol exposures the tiredness ratings were elevated, but no dose-dependence could be confirmed. For both substances and concentrations, the annoyance ratings increased during the exposure, but only for isopropanol did the increase show a dose-response relation. The subjects reported olfactory symptoms during the exposure to the high isopropanol and both 1-octanol concentrations. Isopropanol provoked no sensory
irritation, whereas high 1-octanol exposure slightly enhanced it. Only among the subjects with enhanced chemical sensitivity were both 1-octanol concentrations associated with a stronger increase in annoyance, and lower detection rates were observed in a divided attention task. CONCLUSIONS: Previous studies reporting no neurobehavioral effects for isopropanol (up to 400 ppm) were confirmed. The results obtained for 1-octanol lacked dose-dependency, and their evaluation, is difficult. The annoying odor of 1-octanol may mask sensory irritation and prevent subjects with enhanced chemical sensitivity from concentrating on performance in a demanding task.


van Hout, MS, Wekking, EM, Berg, IJ and Deelman, BG Journal/Psychother Psychosom. 72: 235-44.

BACKGROUND: Chronic toxic encephalopathy (CTE), which can result from long-term exposure to organic solvents, is characterized by problems of attention and memory, fatigue and affective symptoms. There is little experience with (neuro)psychological treatment in this patient group. We reviewed treatment outcome studies of CTE and comparable syndromes, namely, chronic whiplash-associated disorder (WAD) and chronic fatigue syndrome (CFS), with a view to providing recommendations for the psychological treatment of patients with CTE. METHODS: PubMed and PsychLIT were systematically searched and reference lists of retrieved articles were studied. The articles were classified according to study design and level of evidence. RESULTS: The studies of CFS provided high-level evidence for the effectiveness of cognitive-behavior therapy (CBT) in challenging dysfunctional cognitions regarding the effectiveness of rest and in stimulating graded activity. The studies of WAD were methodologically weaker, and most evaluated a combination of CBT and graded activity training. There was some evidence that changing fatigue- or pain-related behaviors may result in cognitive improvement. Two uncontrolled studies of CTE evaluated cognitive rehabilitation techniques but yielded inconsistent findings. CONCLUSIONS: CBT techniques focusing on changing illness attributions and on stimulating graded activity might be useful for patients with CTE, diminishing fatigue-related problems of concentration and memory. Future studies should evaluate whether cognitive deficits of CTE patients as a result of neurotoxic effects of exposure should be treated by cognitive rehabilitation.


Suboptimal performance during neuropsychological testing can seriously complicate assessment in behavioral neurotoxicology. We present data on the prevalence of suboptimal performance in a group of Dutch patients with suspected chronic toxic encephalopathy (CTE) after long-term occupational exposure to solvents. One hundred and forty-five subjects referred to one of two Dutch national assessment centers for CTE were administered the Amsterdam Short-Term Memory Test (ASTM) and the Test of Memory Malingering (TOMM), two tests specifically developed for the detection of suboptimal performance. For both tests, very cautious cut-off scores were chosen with a specificity of 99%. Results indicated that suboptimal performance appears to be a substantial problem in this group of patients with suspected CTE after long-term exposure to organic solvents. Only 54% of our subjects obtained normal scores on both tests of malingering, i.e. at or above cut-off score. The two tests seemed to measure the same concept in that nearly all the subjects with low TOMM scores also had low ASTM scores. However, a higher proportion of subjects scored below the cut-off on the ASTM than on the TOMM.


The neurotoxic organochlorine pesticides gamma-hexachlorocyclohexane, alpha-endosulfan and dieldrin induce in mammals a hyperexcitability syndrome accompanied by convulsions. They reduce the GABA-induced Cl(-) flux. The strychnine-sensitive glycine receptor also regulates Cl(-)-flux inhibitory responses. We studied the effects of these compounds on Cl(-) channels associated with glycine receptors in cultured cerebellar granule cells in comparison to the GABA(A) receptor. Both GABA (EC(50): 5 microM) and glycine (EC(50): 68 microM) increased (36)Cl(-) influx. This increase was antagonized by bicuculline and strychnine, respectively. Lindane inhibited with similar potency both GABA(A) (IC(50): 6.1 microM) and glycine (5.0 microM) receptors. alpha-Endosulfan and dieldrin inhibited the GABA(A) receptor (IC(50) values: 0.4 microM and 0.2 microM, respectively) more potently than the glycine receptor (IC(50) values: 3.5 microM and 3 microM, respectively). Picrotoxinin also inhibited the glycine receptor, although with low potency (IC(50)>100 microM). A 3D pharmacophore model, consisting of five hydrophobic regions and one hydrogen bond acceptor site in a specific three-dimensional arrangement, was developed for these compounds by computational modelling. We propose that the hydrogen bond acceptor moiety and the hydrophobic region were responsible for the affinity of these compounds at the GABA(A) receptor whereas only the hydrophobic region of the
molecules was responsible for their interaction with the glycine receptors. In summary, these compounds could produce neuronal hyperexcitability by blocking glycine receptors besides the GABA(A) receptor. We propose that two zones of the polychlorocycloalkane pesticide molecules (a lipophilic zone and a polar zone) differentially contribute to their binding to GABA(A) and glycine receptors.


Some ecologists propose in recent papers to replace the ideology of the maximum allowable concentrations (MAC) by a new biotic concept of regional environmental monitoring by the method of ecologically allowable levels (EAL). By comparing the basic provisions of MAC and EAL methodologies, by taking into account their advantages and disadvantages, the authors conclude that there is no alternative to the hygienic MAC concept. The principles of EAL substantiation have no well-grounded scientific-and-practical methodology. New concepts of the common control of environmental quality, the health status of man, animals, plants, and the microworld should be sought by using the existing regulations.


PURPOSE OF REVIEW: Alternative and complementary medicine approaches to allergic disorders are commonly used by patients. Not all have been subjected to experimental analysis to support or refute their validity in the armamentarium of a practitioner. This review covers some of the most common unproved alternative or complementary approaches to diagnosis and therapy that we see in use by patients. These include the use of specific IgG to foods accompanied by rotary diets, provocation-neutralization testing and therapy, applied kinesiology followed by acupressure or acupuncture, and changes in cell size upon in-vitro exposure of leukocytes to food extract (using automated assays going under various trade names) followed by elimination diets or rotary diets. RECENT FINDINGS: There continues to be a dearth of well performed studies investigating these approaches in the literature, but many testimonials have been posted on websites of practitioners using these methods attesting to their effectiveness. Several recent studies have refuted the use of applied kinesiology and provocation-neutralization in diagnosis. The placebo effect must not be overlooked as a potentially important factor in some approaches. SUMMARY: There have been no studies supporting the use of these techniques, and
several have refuted their utility. A beneficial placebo effect may be responsible for the perceived clinical effectiveness in many cases of food intolerance.

(2003) **Environmental sensitivity.**

The concept of environmental sensitivity is popular among a small group of physicians who believe that exposure to low levels of numerous environmental chemicals can cause a disease with numerous symptoms but no objective physical or laboratory abnormalities. The condition lacks a clear definition. Numerous theories that have been offered to explain the condition encompass immunotoxic, allergic, autoimmune, neurotoxic, cytotoxic, metabolic, behavioral, psychiatric, iatrogenic, and sociologic mechanisms. Environmental sensitivity has many features in common with other controversial syndromes, such as the chronic fatigue syndrome. Patients with environmental sensitivity frequently are subjected to unproven and unnecessary diagnostic tests and therapeutic modalities. In spite of the lack of physical illness and absence of pathology, patients often experience extreme disability, because their symptoms are triggered by common environmental exposures. The phenomenon of environmental sensitivity needs to be evaluated critically using scientifically sound methods. The practice of clinical ecology encompasses the practices of environmental sensitivity and its theories. Most methods of diagnosis and treatment have been disproved, and the concepts underlying these theories are not scientific. Alternative means of diagnosis and management are presented.

(2003) **[A new approach to diagnosing mutagenic and carcinogenic properties of environmental factors].**
Sycheva, LP, Zhurkov, VS and Rakhmanin Iu, A Journal/Gig Sanit. 87-91.

(2003) **Studies on the role of fungi in Sick Building Syndrome.**
Straus, DC, Cooley, JD, Wong, WC and Jumper, CA Journal/Arch Environ Health. 58: 475-8.

Sick Building Syndrome is a term used to describe symptoms in humans which result from problems with indoor air quality. Common complaints include dyspnea, flu-like symptoms, watering eyes, and allergic rhinitis. Although there is likely no single cause for Sick Building Syndrome, fungal contamination in buildings has increasingly been
associated with this spectrum of symptoms. The authors describe 2 case studies, and other experimentation, that have investigated the role of fungi in the occurrence of Sick Building Syndrome.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15259426

-----------------------------------------------

(2003) **ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures.**

Mammals detect temperature with specialized neurons in the peripheral nervous system. Four TRPV-class channels have been implicated in sensing heat, and one TRPM-class channel in sensing cold. The combined range of temperatures that activate these channels covers a majority of the relevant physiological spectrum sensed by most mammals, with a significant gap in the noxious cold range. Here, we describe the characterization of ANKTM1, a cold-activated channel with a lower activation temperature compared to the cold and menthol receptor, TRPM8. ANKTM1 is a distant family member of TRP channels with very little amino acid similarity to TRPM8. It is found in a subset of nociceptive sensory neurons where it is coexpressed with TRPV1/VR1 (the capsaicin/heat receptor) but not TRPM8. Consistent with the expression of ANKTM1, we identify noxious cold-sensitive sensory neurons that also respond to capsaicin but not to menthol.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12654248

-----------------------------------------------

(2003) **Idiopathic environmental intolerance: Part 2: A causation analysis applying Bradford Hill’s criteria to the psychogenic theory.**

Toxicogenic and psychogenic theories have been proposed to explain idiopathic environmental intolerance (IEI). Part 2 of this article is an evidence-based causality analysis of the psychogenic theory using an extended version of Bradford Hill’s criteria. The psychogenic theory meets all of the criteria directly or indirectly and is characterised by a progressive research programme including double-blind, placebo-controlled provocation challenge studies. We conclude that IEI is a belief characterised by an overvalued idea of toxic attribution of symptoms and disability, fulfilling criteria for a somatoform disorder and a functional somatic syndrome. A
neurobiological diathesis similar to anxiety, specifically panic disorder, is a neurobiologically plausible mechanism to explain trigger reactions to ambient doses of environmental agents, real or perceived. In addition, there is a cognitively mediated fear response mechanism characterised by vigilance for perceived exposures and bodily sensations that are subsequently amplified in the process of learned sensitivity. Implications for the assessment and treatment of patients are presented.


-------------------------------------------------------------------------------------------------------------------


Idiopathic environmental intolerance (IEI) is a descriptor for a phenomenon that has many names including environmental illness, multiple chemical sensitivity and chemical intolerance. Toxicogenic and psychogenic theories have been proposed to explain IEI. This paper presents a causality analysis of the toxicogenic theory using Bradford Hill's nine criteria (strength, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experimental intervention and analogy) and an additional criteria (reversibility) and reviews critically the scientific literature on the topic. The results of this analysis indicate that the toxicogenic theory fails all of these criteria. There is no convincing evidence to support the fundamental postulate that IEI has a toxic aetiology; the hypothesised biological processes and mechanisms are implausible.


-------------------------------------------------------------------------------------------------------------------

(2003) Steroid-naive adolescents with mild intermittent allergic asthma have airway hyperresponsiveness and elevated exhaled nitric oxide levels.

Although atopic asthma symptoms often seem to disappear around puberty, subjects in this age group may experience unexpected, often severe, asthma attacks. This may be related to persistence of untreated airway hyperresponsiveness/inflammation in a life period characterized by low perceptiveness of disease-related symptoms. This study was designed to evaluate the prevalence and the severity of bronchial hyperreactivity and the exhaled nitric oxide (FENO) levels in a group of steroid-naive asthmatic adolescents. Fifty-two patients with mild-intermittent asthma were studied, ages 12 to 16, sensitized to house dust mites; 22 age-matched controls, were also
studied. Asthma patients showed FEV1, FEF25-75%, and FVC values not significantly different from controls, (p > 0.05, each comparison). By contrast, although none of the control subjects showed bronchial hyperreactivity, increased airway responsiveness to methacholine (MCh) was demonstrated in the majority of the patients and found to be severe in 36.5% (MCh PD20 > or = 400 microg or accumulative dose < or = 1220 microg) and moderate in 32.7% (MCh PD20 400-1400 microg or accumulative dose 1220-4620 microg). In addition, FENO concentrations were significantly higher in asthmatics, as compared with controls (20.4 +/- 5.3 ppb and 4.4 +/- 0.7 ppb, respectively; p < 0.01) and 83% of the patients had FENO levels higher than 8.9 ppb (i.e., > 2 standard deviations of the mean in control subjects). A positive, statistically significant correlation was found between FEF25-75% values and MCh PD20 (r = 0.358; p < 0.01) or MCh accumulative dose (r = 0.355; p < 0.05). No correlations were demonstrated between MCh responsiveness and FVC or FEV1 values or FENO levels and between FENO levels and pulmonary function parameters (p > 0.05). The high incidence of bronchial hyperresponsiveness to MCh and of airway inflammation (as demonstrated by the elevated FENO levels) in adolescents with mild asthma suggests the need for more accurate evaluation and, possibly, for early intervention with antiinflammatory drugs in a significant proportion of patients in this age group.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12807174

Souery, D, Oswald, P, Linkowski, P and Mendlewicz, J Journal/Ann Med. 35: 191-6.

Each year, one million people die of suicide. Among the different identified risk factors, genetic factors seem to be part of a multidimensional behavior, including psychiatric, psychosocial, biological factors and physical illness. Family studies have provided evidence for familial transmission in suicide, confirmed in twin and adoption studies. At a molecular level, serotonin seems to be one of the key neurotransmitters implicated in suicidal behavior. Therefore, genes coding for proteins involved in serotonergic neurotransmission have been extensively studied in case-control association studies on suicide. Major findings concern Tryptophan hydroxylase (TPH) gene, particularly in violent suicidal behavior. Though they may seem contradictory, studies on Serotonin transporter (5-HTT), Monoamine oxidase (MAOA), Serotonin 2A and 2C receptors (5-HT2A and 5-HT2C) and Tyrosine hydroxylase (TH) genes are promising. In spite of those observations having some limitations, it appears that genetic factors are a serious risk factor, besides environmental aspects of suicidal behavior.

The pathophysiology of chronic fatigue syndrome (CFS) remains unclear; however, both biological and psychological factors have been implicated in establishing or maintaining this condition. People with CFS report significant and disabling cognitive difficulties such as impaired concentration that in some cases are exacerbated by exposure to chemical triggers. The aim of this study was to determine if neuropsychological deficits in CFS are triggered by exposure to chemicals, or perceptions about the properties of these substances. Participants were 36 people with a primary diagnosis of CFS, defined according to Centers for Disease Control (CDC) criteria. A randomized, double-blind, placebo-controlled, crossover design was used, with objective assessment of neuropsychological function and participant rating of substance type, before and after exposure to placebo or chemical trigger. Results showed decrements in neuropsychological tests scores on three out of four outcome measures when participants rated the substance they had been exposed to as "chemical." No change in performance was found based on actual substance type. These results suggest that cognitive attributions about exposure substances in people with CFS may be associated with worse performance on neuropsychological tasks. In addition, these findings suggest that psychological interventions aimed at modifying substance-related cognitions may reduce some symptoms of CFS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12763708

---------------------------------------------------------------


In this retrospective analysis the authors compared brain scintigrams, performed using triple-head single-photon emission computed tomography (tripleSPECT), of subjects who were judged clinically impaired from exposure to toxins during the Desert Storm Desert Shield military action, and of subjects exposed to mycotoxins, with those of normal controls. The scintigrams for both exposed groups exhibited similar patterns of abnormalities, which were consistent with neurotoxic impairment. The authors conclude that further study is needed to determine whether mycotoxin exposure may be a cause of abnormalities seen in tripleSPECT images.

---------------------------------------------------------------
Correlations between exhaled nitric oxide levels, blood eosinophilia, and airway obstruction reversibility in childhood asthma are detectable only in atopic individuals.


The aim of this study was to compare in atopic and nonatopic asthmatic children correlations between two inflammation parameters, i.e., blood eosinophilia and exhaled nitric oxide (FE(NO)), and pulmonary function values, at baseline and after beta(2)-adrenergic bronchodilators. Ninety-two steroid-naive asthmatic children were evaluated: 26 were skin prick test- and RAST-negative (nonatopic subjects), whereas 66 were atopic, 15 being sensitized only to house dust mites (monosensitized) and 51 to mites and to at least one other class of allergens (polysensitized). Baseline spirometric values (FEV(1) and FEF(25-75%)) were similar in atopic and nonatopic groups (P > 0.1, each comparison). However, when compared to nonatopic subjects, atopic children showed a significantly higher degree of blood eosinophilia (3.0% and 6.7% white blood cell count, respectively; P = 0.0001) and higher FE(NO) levels (6.8 ppb and 16.0 ppb, respectively; P = 0.0001). While a positive correlation between FE(NO) levels and blood eosinophilia was observed in atopic children (r = 0.25, P = 0.041), no correlations between these two inflammation parameters and baseline pulmonary function values were demonstrated in any of the asthmatic groups. Inhalation of a beta(2)-agonist drug induced in the two asthmatic populations similar improvements in FEV(1) and FEF(25-75%) and no changes in FE(NO) levels or blood eosinophilia. However, only in atopic children positive correlations were found between percent variation in FEV(1) (delta%FEV(1)) and FE(NO) levels (r = 0.35, P = 0.006) or blood eosinophilia (r = 0.26, P = 0.04). Within the atopic group, no differences were found between mono- and polysensitized individuals in all parameters evaluated. Thus only in atopic children did parameters of inflammation correlate with airway obstruction reversibility.


Age-related seasonal patterns of emergency department visits for acute asthma in an urban environment.


STUDY OBJECTIVE: Asthma morbidity is greater in younger patients. The reasons are not fully understood, although identifying demographic patterns of seasonality may help determine causes and potential prevention. The objective of this study is to determine the relationship between age and seasonal asthma periodicity in patients presenting to the emergency department (ED). METHODS: We conducted a retrospective study of ED visits from 1991 to 2000 in 11 municipal hospitals in New York City, with 911 receiving facilities. There were 673,141 patients who presented to...
the ED during the study period and had a primary diagnosis of acute asthma.
RESULTS: Distinct seasonal patterns were observed, with the highest number of visits
occurring in the fall and the fewest in the summer. Seasonal fluctuations of ED visits
were highest in children aged 13 years or younger (coefficient of variation [CV] 37.8%;
95% confidence interval [CI] 37.5% to 38.1%), with a peak in CV occurring at
approximately age 7 years (CV 43.3%; 95% CI 43.0% to 43.6%). Less variability was
noted with increasing age, and the population aged 30 years and older appeared to be
the least susceptible to seasonal influences (CV 11.7%; 95% CI 11.3% to 12.1%).
Although the total number of asthma visits decreased by more than 30% from 1991 to
2000, the CVs for each year remained within a relatively narrow range of 24.2% to
30.5%. CONCLUSION: In an urban population, seasonal variability of asthma episodes
requiring ED visits are closely linked to age, which may be important in understanding
the causes of asthma and developing disease-management strategies for the
prevention of asthma episodes.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14520329

Questionnaire.
Schneider, CD, Meek, PM and Bell, IR Journal/BMC Med Educ. 3: 5.

BACKGROUND: Complementary/alternative medicine and integrative medicine (CAM
IM) are increasingly used in the U.S. We set out to develop and validate a brief
questionnaire measuring health care provider and medical student attitudes regarding
these approaches to healthcare. METHODS: IMAQ is a 29-item, 7-point Likert scale
rated instrument, developed from focus groups consisting of faculty, fellows, visiting
residents, and medical students at a university based integrative medicine program.
Respondents included 111 (of 574 contacted) internal medicine physicians on an
academic medical center CME list and 85 healthcare providers (mostly physicians)
attending an American Holistic Medical Association Annual Conference (296
attending). Cohorts were selected for expected differences in attitudes toward CAM/IM.
RESULTS: Factor analysis demonstrated that a 2 factor solution best explained the
variance in responses (38%). Factor 1 ("openness to new ideas and paradigms")
explained 26% of variance with loadings ranging from 0.79 to 0.3, with factor 2 ("value
of both introspection and relationship to patient") contributing an additional 12% of the
explained variance with loadings ranging from 0.69 to 0.42. Both factors demonstrated
adequate reliability. Factor 1 had a Cronbach's alpha of 0.91, while factor 2 was 0.72.
As expected, AHMA conference attendees scored higher (F = 120.00, p < 0.001) than
the internists on the IMAQ, supporting the construct validity. Although 63% of the
AHMA subjects, and only 32% of the internists were female, analysis revealed that
gender did not explain the score differences (F = 2.6, p > 0.05). CONCLUSIONS:
Analysis of the IMAQ provided evidence of its reliability and validity in measuring
attitudes toward CAM/IM, specifically openness to new ideas and paradigms, and the
value of relationship to self and patient. Initial findings support use of the IMAQ in measuring attitudes of students and practitioners towards CAM/IM interventions as a first step in understanding willingness to use these approaches to healing. It is our desire that this preliminary instrument will continue to be refined as the field of CAM/IM matures.

(2003) Do effects on blood pressure contribute to improved clinical outcomes with metformin?

Hyperinsulinaemia and hypertension commonly coexist, and a large body of evidence points to a common pathogenesis based on the presence of underlying insulin resistance (the "insulin hypothesis" of hypertension). Metformin improves insulin sensitivity in liver and muscle as its primary antihyperglycaemic mechanism of action, and intensive glycaemic management with metformin significantly reduced the risk of macrovascular diabetic complications in the UK Prospective Diabetes Study. The clinical outcome benefits in the metformin group included a significant reduction in the risk of stroke (-41% vs +14% with sulphonylurea or insulin treatment, p=0.032), which is well known to be highly sensitive to changes in blood pressure. Furthermore, a placebo-controlled study has shown that metformin significantly improved endothelial function, a key regulator of vascular tone and blood pressure, in type 2 diabetic patients. However, clinical studies have shown that metformin treatment is not associated with clinically relevant reductions in blood pressure in man. These apparently conflicting observations are difficult to reconcile. Either the beneficial vascular actions of metformin involve physiological systems not involved in the control of blood pressure, or counter-regulatory mechanisms prevent beneficial effects of metformin on the vasculature being translated into a clinically meaningful antihypertensive effect. Further research will be required to resolve this paradox.


http://www.sciencedirect.com/science/article/B6T4S-49MX2KJ-5/2
4a1b319eb6052b0b175e1a7129050102
Salameh, PR, Baldi, I, Brochard, P, Raherison, C, Abi Saleh, B and Salamon, R

In Lebanon, childhood asthma is an important disease and pesticides are commonly used. The objective of this study was to evaluate whether exposure to pesticides has chronic effects on the respiratory health of Lebanese children. A cross-sectional study was performed on children from a randomly selected sample of Lebanese public schools. Exposure to pesticides was evaluated by a standardised questionnaire and a residential exposure score, and respiratory symptoms were assessed by using the American Thoracic Society standardised questionnaire. A chronic respiratory disease was reported in 407 (12.4%) out of 3,291 children. The baseline difference in mean age was small but statistically significant. Any exposure to pesticides, including residential, para-occupational and domestic, was associated with respiratory disease and chronic respiratory symptoms (chronic phlegm, chronic wheezing, ever wheezing), except for chronic cough. Exposure to pesticides was associated with chronic respiratory symptoms and disease among Lebanese children.

(2003) Total and allergen-specific IgE levels in serum reflect blood eosinophilia and fractional exhaled nitric oxide concentrations but not pulmonary functions in allergic asthmatic children sensitized to house dust mites.

Although elevated levels of serum immunoglobulin E (IgE) are considered the hallmark of atopic diseases, their clinical value in evaluating subjects with allergic disorders is under debate. To evaluate possible relationships between serum IgE levels and a variety of clinical parameters, 83 mild asthmatic children [10.98-year-old (2.95)], sensitized to house dust mites (HDM) Dermatophagoides pteronyssinus (Dp) or D. farinae (Df), were enrolled. As compared with normal control reference values detected in our laboratory, children with allergic asthma had higher blood eosinophil counts (expressed both as percentage and as absolute number) and higher fractional exhaled nitric oxide (FeNO) levels but similar values in pulmonary function parameters. In the allergic asthmatic population, serum levels of total, Dp-specific or Df-specific IgE correlated positively with eosinophil counts (Rho > or = 0.30, p < 0.01, each correlation) and FeNO levels (Rho > or = 0.33, p < 0.01, each correlation) but not with pulmonary function parameters (p > 0.1, each correlation). Finally, significant correlations, although moderate, were found in the allergic asthmatic population between eosinophil counts and FeNO levels (Rho > or = 0.42, p < 0.001, each correlation). Thus, in atopic children sensitized to HDM with mild intermittent asthma, IgE levels in blood appear to reflect systemic (blood eosinophils) and organ-specific
(FeNO) markers of allergic inflammation but not pulmonary volumes or the degree of airflow limitation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14675476

(2003) High levels of airborne ultrafine and fine particulate matter in indoor ice arenas.

The high prevalence of airway dysfunction among ice arena athletes may be related to rink air exposure; in particular, high concentrations of ultrafine and fine particulate matter (0.02-1.0 micro m diameter, PM(1)) from ice resurfacing machines may enhance airway inflammation and hyperreactivity. The purpose of this study was to identify levels of PM(1) emitted from ice resurfacing machines used in indoor ice arenas, and to compare [PM(1)] pre- and post-resurfacing to each other and to outdoor [PM(1)]. Multiple one Hz measurements were recorded on 28 different days as 15-s mean of PM(1).cm(-3) for 2 min at 1-1.5 m "above ice" in 10 rinks pre- and post-resurfacing, with measured airborne PM(1) outside each rink to be used individual rink references. Rink PM(1).cm(-3) was approximately 30 times greater than PM(1).cm(-3) outside the respective rinks (p <.05). Rink values were 104.2 +/- 59.3 x 10(3) PM(1).cm(-3) during prime usage, compared to outdoor values of 3.8 +/- 2.5 x 10(3) PM(1).cm(-3). Ice resurfacing increased PM(1).cm(-3) 4-fold (p <.05). No difference in PM(1) emissions between gasoline and propane powered resurfacing machines was identified. The rate of PM(1) dissipation after resurfacing was highly variable between rinks and probably dependent upon rink ventilation and resurfacing machine engine efficiency. Gas-powered edging increased PM(1).cm(-3) 18-fold and 158-fold versus pre-edging rink and outdoor values, respectively. We conclude that the primary source of airborne indoor rink PM(1) is internal combustion ice-resurfacing machines and that this poor air quality may be causal to the unique and high prevalence of airway dysfunction in ice arena athletes.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14595929
The attributive death rates due to ambient air pollution were estimated in the urban areas of Byelarus. Estimation used the data of daily atmospheric contamination monitoring made by the Main Hydrometeorology Committee of Byelarus in 15 towns from 1990 to 1999. To establish a dose-response relationship, the results of the well-known investigations by Dockery were used, which covering prospective cohort studies in 6 towns of the USA, have demonstrated a statistically significant correlation between atmospheric pollution and mortality rates. In Byelarus, about 7.5 thousand premature deaths or 6% of the total annual death rates may be induced by atmospheric pollution. Possible factors that influence the accuracy of estimates are discussed in the paper.

Capsaicinoids, found in less-than-lethal self-defense weapons, have been associated with respiratory failure and death in exposed animals and people. The studies described herein provide evidence for acute respiratory inflammation and damage to epithelial cells in experimental animals, and provide precise molecular mechanisms that mediate these effects using human bronchiolar and alveolar epithelial cells. Inhalation exposure of rats to pepper sprays (capsaicinoids) produced acute inflammation and damage to nasal, tracheal, bronchiolar, and alveolar cells in a dose-related manner. In vitro cytotoxicity assays demonstrated that cultured human lung cells (BEAS-2B and A549) were more susceptible to necrotic cell death than liver (HepG2) cells. Transcription of the human vanilloid receptor type-1, VR1 or TRPV1, was demonstrated by RT-PCR in all of these cells, and the relative transcript levels were correlated to cellular susceptibility. TRPV1 receptor activation was presumably responsible for cellular cytotoxicity, but prototypical functional antagonists of this receptor were cytotoxic themselves, and did not ameliorate capsaicinoid-induced damage. Conversely, the TRPV1 antagonist capsazepine, as well as calcium chelation by EGTA ablated cytokine (IL-6) production after capsaicin exposure. To address these seemingly contradictory results, recombinant human TRPV1 was cloned and overexpressed in BEAS-2B cells. These cells exhibited dramatically increased cellular susceptibility to capsaicinoids, measured using IL-6 production and cytotoxicity, and an apoptotic mechanism of cell death. Surprisingly, the cytotoxic effects of capsaicin in TRPV1 overexpressing cells were also not inhibited by TRPV1 antagonists or by treatments that modified extracellular calcium. Thus, capsaicin interacted with TRPV1 expressed by BEAS-2B and other airway epithelial cells to cause the
calcium-dependent production of cytokines and, conversely, calcium-independent cell death. These results have demonstrated that capsaicinoids contained in pepper spray products produce airway inflammation and cause respiratory epithelial cell death. The mechanisms of these cellular responses to capsaicinoids appear to proceed via distinct cellular pathways, but both pathways are initiated by TRPV1.


Capsaicin is a common dietary constituent and a popular homeopathic treatment for chronic pain. Exposure to capsaicin has been shown to cause various dose-dependent acute physiological responses including the sensation of burning and pain, respiratory depression, and death. In this study, the P450-dependent metabolism of capsaicin by recombinant P450 enzymes and hepatic and lung microsomes from various species, including humans, was determined. A combination of LC/MS, LC/MS/MS, and LC/NMR was used to identify several metabolites of capsaicin that were generated by aromatic (M5 and M7) and alkyl hydroxylation (M2 and M3), O-demethylation (M6), N- (M9) and alkyl dehydrogenation (M1 and M4), and an additional ring oxygenation of M9 (M8). Dehydrogenation of capsaicin was a novel metabolic pathway and produced unique macrocyclic, diene, and imide metabolites. Metabolism of capsaicin by microsomes was inhibited by the nonselective P450 inhibitor 1-aminobenzotriazole (1-ABT). Metabolism was catalyzed by CYP1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4. Addition of GSH (2 mM) to microsomal incubations stimulated the metabolism of capsaicin and trapped several reactive electrophilic intermediates as their GSH adducts. These results suggested that reactive intermediates, which inactivated certain P450 enzymes, were produced during catalytic turnover. Comparison of the rate and types of metabolites produced from capsaicin and its analogue, nonivamide, demonstrated similar pathways in the P450-dependent metabolism of these two capsaicinoids. However, production of the dehydrogenated (M4), macrocyclic (M1), and omega-1-hydroxylated (M3) metabolites was not observed for nonivamide. These differences may be reflective of the mechanism of formation of these metabolites of capsaicin. The role of metabolism in the cytotoxicity of capsaicin and nonivamide was also assessed in cultured lung and liver cells. Lung cells were markedly more sensitive to cytotoxicity by capsaicin and nonivamide. Cytotoxicity was enhanced 5 and 40% for both compounds by 1-ABT in BEAS-2B and HepG2, respectively. These data suggested that metabolism of capsaicinoids by P450 in cells represented a detoxification mechanism (in contrast to bioactivation).

The improvements of the force fields and the more accurate treatment of long-range interactions are providing more reliable molecular dynamics simulations of nucleic acids. The abilities of certain nucleic acid force fields to represent the structural and conformational properties of nucleic acids in solution are compared. The force fields are AMBER 4.1, BMS, CHARMM22, and CHARMM27; the comparison of the latter two is the primary focus of this paper. The performance of each force field is evaluated first on its ability to reproduce the B-DNA decamer d(CGATTAATCG)(2) in solution with simulations in which the long-range electrostatics were treated by the particle mesh Ewald method; the crystal structure determined by Quintana et al. (1992) is used as the starting point for all simulations. A detailed analysis of the structural and solvation properties shows how well the different force fields can reproduce sequence-specific features. The results are compared with data from experimental and previous theoretical studies.


The authors studied 100 patients who had been exposed to toxic molds in their homes. The predominant molds identified were Alternaria, Cladosporium, Aspergillus, Penicillium, Stachybotrys, Curvularia, Basidiomycetes, Myxomycetes, smuts, Epicoccus, Fusarium, Bipolaris, and Rhizopus. A variety of tests were performed on all, or on subgroups of, these patients. Sensitivities and exposures were confirmed in all patients by intradermal skin testing for individual molds (44-98% positive), and by measurement of serum antibodies. Abnormalities in T and B cells, and subsets, were found in more than 80% of the patients. The findings of trichothecene toxin and breakdown products in the urine, serum antibodies to molds, and positive intradermal skin tests confirmed mycotoxin exposure. Respiratory signs (e.g., rhinorrhea, sinus tenderness, wheezing) were found in 64% of all patients, and physical signs and symptoms of neurological dysfunction (e.g., inability to stand on the toes or to walk a straight line with eyes closed, as well as short-term memory loss) were identified in 70% of all patients. Objective abnormal autonomic nervous system tests were positive in all 100 patients tested. Brain scans, conducted using triple-head single photon emission computed tomography, were abnormal in 26 (86%) of 30 (subgroup of the 100) patients tested. Objective neuropsychological evaluations of 46 of the patients who exhibited symptoms of neurological impairment showed typical abnormalities in short-term memory, executive function/judgment, concentration, and hand/eye coordination.
(2003) [Effect of plant protective chemicals on the environment and human health].
Prokhorov, NI and Drozdova, TV Journal/Gig Sanit. 8-11.

The developed and promoted package of ecological and hygienic measures and the specific programme introduced by the State Sanitary-and-Epidemiological Surveillance Committee have yielded positive results in sanitizing the Yakhroma flood land, approaches to rationally managing the medical and sanitary situation. The implemented measures are a preparatory stage of introduction of the assessment of a health risk in hygienic monitoring.


In these past decades an important increase in the prevalence of allergic respiratory diseases has been documented in most countries of the world with large differences being reported within different areas, particularly in industrialized countries. Persistent environmental exposure to particulate air pollution from motor vehicles has been suggested to be an important factor contributing to the observed increased prevalence of allergic diseases. Data from various investigators in different parts of the world have shown an important association between environmental levels of motor vehicle exhaust emissions and increased symptoms of asthma and rhinitis. In addition, recent human and animal laboratory-based studies have shown that particulate toxic pollutants, and especially diesel exhaust particles, can enhance allergic inflammation and induce the development of allergic immune responses. This article reviews the current state of knowledge on the role of diesel exhaust particles in the susceptibility to allergy. It scrutinizes the epidemiological evidence that supports the causative link between particulate air pollution from motor vehicles and the increasing prevalence in allergic conditions and the immunologic mechanisms by which diesel exhaust particles enhance the susceptibility to allergy.

(2003) [Epidemiologic study Salus domestica: evaluation of health damage in a sample of women living near the Malpensa 2000 airport].
The opening of the new Malpensa 2000 Airport worried people living in the neighbouring towns about possible effects of acoustic and air pollution on health status. For this reason, Varese Health Unit set up a study involving housewives and General Practitioners. This study has been carried out in 3 Areas: A Area, bordering the airport, B Area, at intermediate distance, and C Area, at long distance. On the whole, 932 housewives (18 to 64 years old) and 92 General Practitioners, were involved. The questionnaire, distributed to housewives between May 1st and November 30th 2000, was filled out in the doctor's surgery who furthermore added clinical data. Chi-square statistics were calculated to test the association between living area and personal data, behavioural and environmental characteristics, and reported disorders. To describe possible interrelationships between living Area and the answers supplied by housewives and General Practitioners the multiple correspondence multivariate analysis technique was applied. The housewives living next to the airport (A area) frequently report insomnia, nocturnal waking, anxiety and difficulty in hearing words. The multivariate analysis has shown a relationship between recently increasing noise noted by the housewives, and the area where they live, as well as a noticeable coherence between the answers given by the housewives and those given by the General Practitioners, who reported higher frequencies of cephalgy, allergies, anxiety neurosis, medical consultation, benzodiazepine's and sleeping disorder's prescriptions in A Area compared to C Area. The airport's presence seems to be associated with the onset of subjective disorders in neighbouring population. Some of these disorders, in particular neuropsychological ones, are clinically confirmed by General Practitioners, and are consistent with different noise exposure levels.


As surgeons, otolaryngologists tend to most be interested in operative procedures and leave the hospital environment to the care of administrators and the nursing staff. Given the dangers that are present, it would seem prudent to spend some time considering the agents that used in patient care and in operating suites, to minimize the risk to patients and co-workers.


DESCRIPTION (provided by applicant): Parkinson's disease (PD) results from loss of dopamine (DA) neurons in substantia nigra (SN). The cause of this cell death is unknown, although there is considerable evidence that oxidative stress plays a
significant role. Our research group has considerable experience with several models of PD in which oxidative stress is induced in dopaminergic cells by exposure to 6-hydroxydopamine (6-OHDA) or to DA itself. Both 6-OHDA and DA can cause the selective death of dopaminergic cells that can be blocked both by several drugs, including those that block uptake of 6-OHDA by the cells and that increase cellular antioxidant defenses. Particularly interesting is the capacity of trophic factors such as glial cell line-derived neurotrophic factor (GDNF) to attenuate the neurotoxic effects of oxidative stress. Over the past two years, we have developed an in vitro model of cell death/cell survival using the dopaminergic cell line, MN9D. Using these cells, we have shown that 6-OHDA causes cell death that is accompanied by several measurable cellular responses, that GDNF attenuates some of those responses, and that these protective effects can in turn be blocked by inhibitors of PI3 kinase or MEK. We now propose to further develop a model system to screen chemical libraries for compounds with neuroprotective activity that can be adapted to high throughput screening (HTS). We will focus on two specific aims. First, using Hoechst reagent to detect cell death and altered nuclear morphology, we will optimize our cellular model with respect to susceptibility to 6-OHDA-induced toxicity. To do so we will identify subclones of MN9D cells that exhibit a high degree of sensitivity to dopaminergic toxins. As necessary, we will also transfected the cells to further enhance their sensitivity to oxidative stress related to dopaminergic toxins. After using 6-OHDA to select sensitive subclones, we will examine additional oxidative stressors, for example DA itself and/or MPP+. Second, we will establish the optimal conditions for evaluating these cells within an HTS assay. We then will optimize the assay conditions to enhance cell attachment and thereby obtain cells amenable to robotic manipulations requiring multiple wash steps. Finally, we will identify simple fluorescent readouts of cell death for use with an automated fluorescent plate reader. We believe that approach has the potential to generate a robust, reproducible method to identify novel compounds by HTS with therapeutic potential for the treatment of PD.


Inner-city, minority populations are high-risk groups for adverse birth outcomes and also are more likely to be exposed to environmental contaminants, including environmental tobacco smoke (ETS), polycyclic aromatic hydrocarbons (PAHs), and pesticides. In a sample of 263 nonsmoking African-American and Dominican women, we evaluated the effects on birth outcomes of prenatal exposure to airborne PAHs monitored during pregnancy by personal air sampling, along with ETS estimated by plasma cotinine, and an organophosphate pesticide (OP) estimated by plasma chlorpyrifos (CPF). Plasma CPF was used as a covariate because it was the most
often detected in plasma and was highly correlated with other pesticides frequently detected in plasma. Among African Americans, high prenatal exposure to PAHs was associated with lower birth weight (p = 0.003) and smaller head circumference (p = 0.01) after adjusting for potential confounders. CPF was associated with decreased birth weight and birth length overall (p = 0.01 and p = 0.003, respectively) and with lower birth weight among African Americans (p = 0.04) and reduced birth length in Dominicans (p < 0.001), and was therefore included as a covariate in the model with PAH. After controlling for CPF, relationships between PAHs and birth outcomes were essentially unchanged. In this analysis, PAHs and CPF appear to be significant independent determinants of birth outcomes. Further analyses of pesticides will be carried out. Possible explanations of the failure to find a significant effect of PAHs in the Hispanic subsample are discussed. This study provides evidence that environmental pollutants at levels currently encountered in New York City adversely affect fetal development.


To improve the potency of 2-pralidoxime (2-PAM) for treating organophosphate poisoning, we dimerized 2-PAM and its analogs according to Wilson's pioneering work and the 3D structure of human acetylcholinesterase (hAChE) inactivated by isoflurophate. 1,7-Heptylene-bis-N,N'-syn-2-pyridiniumaldoxime, the most potent of the alkylene-linked dimeric reactivators, was readily synthesized using bistriflate and is 100 times more potent than 2-PAM in reactivating hAChE poisoned by isoflurophate. Experimental and computational studies confirm that 2-PAM in its biologically active form adopts the syn-I configuration. Further, they suggest that the improved performance of dimeric oximes is conferred by two-site binding with one oxime pointing toward the diisopropyl ester at the catalytic site of hAChE and the other anchored at the peripheral site. This type of binding may induce a conformational change in the acyl pocket loop which modulates the catalytic site via a domino effect.


The elevated nitric oxide/peroxynitrite and the neural sensitization theories of multiple chemical sensitivity (MCS) are extended here to propose a central mechanism for the exquisite sensitivity to organic solvents apparently induced by previous chemical
exposure in MCS. This mechanism is centered on the activation of N-methyl-D-aspartate (NMDA) receptors by organic solvents producing elevated nitric oxide and peroxynitrite, leading in turn to increased stimulating of and hypersensitivity of NMDA receptors. In this way, organic solvent exposure may produce progressive sensitivity to organic solvents. Pesticides such as organophosphates and carbamates may act via muscarinic stimulation to produce a similar biochemical and sensitivity response. Accessory mechanisms of sensitivity may involve both increased blood-brain barrier permeability, induced by peroxynitrite, and cytochrome P450 inhibition by nitric oxide. The NMDA hyperactivity/hypersensitivity and excessive nitric oxide/peroxynitrite view of MCS provides answers to many of the most puzzling aspects of MCS while building on previous studies and views of this condition.


Pall, ML Journal/Arch Environ Health. 58: 605.


OBJECTIVES: This study explored the subjective reactions and psychological test performance of smell-intolerant subjects during consecutive challenges to chemicals with contrasting neurotoxic properties. METHODS: Women with symptoms compatible with multiple chemical sensitivity (N=10) and healthy referents (N=20) were individually challenged in an exposure chamber. All the subjects attended two separate 2-hour sessions of exposure to n-butyl acetate and toluene, in counterbalanced sequence. After an initial phase without exposure, air concentrations were increased in steps ranging from 3.6 to 57 mg/m3 for n-butyl acetate and from 11 to 180 mg/m3 for toluene. The response measures comprised ratings of annoyance and smell intensity and also neurobehavioral test performance. RESULTS: Both groups showed an increase in annoyance ratings and a decrease in test performance in the initial unexposed chamber phase and also in the first phase of the chemical exposure, these results indicating slight immediate expectancy or "suggestion" effects. During the six chamber phases, the ratings of mucous membrane irritation and fatigue showed a steeper increase in the group with multiple chemical sensitivity than among the referents, while the ratings of smell intensity and smell annoyance were similar in the two groups. A reduction in test performance was observed during the chamber phases,
particularly in the group with multiple chemical sensitivity. No relation was found between the ratings or performance and chemical substance. CONCLUSIONS: Stronger immediate expectancy or "suggestion" reactions than normal did not characterize the group with multiple chemical sensitivity. This group showed a stronger than normal gradual build-up of fatigue, mucous membrane irritation, and reduced performance during chemical exposure. The results offer the most support to an irritative basis for multiple chemical sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12630435

(2003) [Methodological approaches in validation of rehabilitation technologies of occupational and environmental diseases].

(2003) [The environmental and population health of Dagestan].

(2003) [Multiple chemical sensitivity. Environment victim or imaginary patient?].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14524065

(2003) [Appraisal of damages associated with atmospheric air pollution in the summer of 2002 to the health status of the Moscow population].
Diet can play an important role in the precipitation of headaches in children and adolescents with migraine. The diet factor in pediatric migraine is frequently neglected in favor of preventive drug therapy. The list of foods, beverages, and additives that trigger migraine includes cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer. Underage drinking is a significant potential cause of recurrent headache in today's adolescent patients. Tyramine, phenylethylamine, histamine, nitrites, and sulfites are involved in the mechanism of food intolerance headache. Immunoglobulin E-mediated food allergy is an infrequent cause. Dietary triggers affect phases of the migraine process by influencing release of serotonin and norepinephrine, causing vasoconstriction or vasodilatation, or by direct stimulation of trigeminal ganglia, brainstem, and cortical neuronal pathways. Treatment begins with a headache and diet diary and the selective avoidance of foods presumed to trigger attacks. A universal migraine diet with simultaneous elimination of all potential food triggers is generally not advised in practice. A well-balanced diet is encouraged, with avoidance of fasting or skipped meals. Long-term prophylactic drug therapy is appropriate only after exclusion of headache-precipitating trigger factors, including dietary factors.

A reconnaissance study was undertaken to determine potential contaminant exposures to children through soil from elementary school playgrounds. Soil samples were collected from areas along the Texas-Mexico border, inland areas (soils from elementary school yards in cities/towns within the state of Texas), and three National Parks (one on the border, one in Tennessee, and one in Washington). The present study focused on organochlorine (OC) pesticides as the potential contaminants of concern because of their historical (and possibly current) use, and their importance as persistent organic pollutants (POPs). DDE and heptachlor were the most frequently detected OCs (69 and 63%, respectively), although heptachlor concentrations in soil never exceeded 5 ppb. Relatively higher concentrations of DDE were observed in agricultural areas along the border (50-60 ppb in soils from McAllen, Palmview, and San Benito) than in other soils. However, a school yard in Lubbock, TX had the highest OC concentration observed (70 ppb dieldrin). These results may be due to historical agriculture activity prior to the banning of OC pesticides such as DDT in the early 1970s, as well as the more recent use of DDT in Central and South America for malaria control.


OBJECTIVE: Poisoning with organophosphate pesticides can cause sensory and motor neuropathy with permanent paralysis. Paralysis at the site of dermal exposure has not been reported. CASE REPORT: A 61-year-old carpenter sprayed a nest of termites with an insecticide containing chlorpyrifos without protective equipment and with direct contact of pesticide solution to hands, lower arms, feet, and lower legs, as well as inhalation of vapors from spraying. After 30 min he became ill with nausea, abdominal cramping, arm and leg weakness, bilateral shoulder pain, chest pain, and numbness in the left hand and arm. At a hospital, he was treated with atropine 1 mg IV and pralidoxime CI 2 g IV There was 0/5 strength in the hands and wrists and 3/5 elsewhere, a left peritoneal palsy, and urinary retention. He was transferred to a tertiary care hospital where paralysis persisted. Electromyogram studies documented widespread peripheral neuropathy. With continued progression of neuropathy, pralidoxime was repeated on the third day. By day 12, motor strength improved except for the hands and left lower leg. Right interosseous muscle strength was 1/5 and left was 0/5. Right-hand grip was 2/5, and left-hand grip was 0/5. He was transferred to a rehabilitation center. He never regained use of his hands and was disabled from employment as a carpenter. There was a disturbed gait, with inability to clear his left foot with walking. Urinary retention persisted and required self-catherization. CONCLUSION: Dermal exposure of the hands and feet to chlorpyrifos was associated with atrophy and permanent paralysis of exposed areas. The importance of protective equipment is emphasized.


Exposure to sinusoidal (power-frequency) magnetic fields during prenatal development is implicated in adulthood behavioral impairments. However, the effects of prenatal exposure to weak-intensity, nonsinusoidal complex magnetic fields (CMFs), an increasingly common feature of the modern environment, have not been rigorously
examined. In the present study, male and female Wistar-strain rats were exposed continually during prenatal development to one of three extremely low-frequency CMFs or a sham condition. As adults, rats were trained in an acquisition/reversal radial maze task. All rats exposed to the prenatal CMFs increased their commission of reference memory errors, but differences in working memory and motivation to complete the maze task were specific to the type of prenatal CMF. These results provide the first evidence that prenatal exposures to specific shapes of CMFs impair complex learning behaviors into adulthood.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12471631

(2003) Behavioral effects of combined perinatal L-NAME and 0.5 Hz magnetic field treatments.

The behavioral effects of the nitric oxide synthase inhibitor N-nitro-L-arginine methyl ester (L-NAME), when perinatally (2 d prenatal-14 d postnatal) co-administered with extremely low frequency magnetic fields, were examined in weanling and adult rats. Litters of rat pups and their dams were exposed continuously to biphasic pulsed fields presented once every 2 s. The magnetic fields were amplitude modulated in successively increasing and decreasing steps (each 30 min) between 0 and 1.8 microT or between 0 to 13 nanoT (reference field) during 4-h periods (6 periods per day). These two treatments were subdivided into dams that received tap water and dams that received 1.0 g/L L-NAME in tap water. The behavioral sequelae to these treatments for 242 progeny from 41 litters were followed from weaning (1 wk after termination of treatment) into adulthood. Compared to exposures to water and nanoT magnetic fields, perinatal exposures to the microT magnetic fields or to L-NAME in the maternal water supply were associated with increased activity levels when the rats were tested as weanling, but decreased activity levels when the rats were tested as adults. However, the activity of rats that received the combination of L-NAME and microT magnetic fields did not differ significantly from the activity of the rats that had received water and the nanoT fields. Long-term (adulthood) effects of these perinatal treatments on associative learning, as inferred by learned fear to contextual stimuli, were not evident. These results indicate that L-NAME and this particular pattern of magnetic field antagonized one another when co-administered during the perinatal period.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12691004

McEwen, BS Journal/Biological Psychiatry. 54: 200-207.

http://www.sciencedirect.com/science/article/B6T4S-48GVXHH-5/2
e90047f50c7aec8c88a6c1695ea603d2


(2003) [Mathematical simulation of dynamic systems used in the study of the impact of environmental air pollution on morbidity in children].
Matorova, NI, Efimova, NV and Baturin, VA Journal/Gig Sanit. 75-7.

(2003) Structural bioinformatics and QSAR analysis applied to the acetylcholinesterase and bispyridinium aldoximes.

The methods of bioinformatics, molecular modelling, and quantitative structure-activity relationships (QSARs) using regression and artificial neural network (ANN) analyses were applied to develop safer aldoxime antidotes against poisoning by organophosphorus (OP) agents with high, mean, and low aging rates. We start here from a molecular modelling of the mouse AChE at an atomistic level. Aim is to predict qualitatively the structural requirements of an aldoxime that shows an unique reactivating activity against the three classes of OPs. An antidotal action should occur by a three-site mechanism: the aldoxime groups of the first pyridinium ring should point towards the catalytic site, and the second pyridinium ring and its substituents should be anchored at the peripheral and anionic subsites. Based on this model, it is predicted that a suitable substituent is based on an arginine-like moiety. Then, an ANN-based QSAR analysis using a training set of aldoximes with known structure and activities was applied. Its input layer consisted of seven nodes: the group-membership descriptors that parameterize the type of the OP, the logarithms of the distribution coefficients at pH 7.4 and their squared term, the lowest unoccupied molecular orbital (LUMO) energies, the scaled molar refractions of the substituents, and their squared term. It was shown that the qualitative prediction made by molecular modelling can be quantified by an ANN prediction.
**Joint symptoms and diseases associated with moisture damage in a health center.**

Rheumatic diseases do not usually cluster in time and space. It has been proposed that environmental exposures may initiate autoimmune responses. We describe a cluster of rheumatic diseases among a group of health center employees who began to complain of symptoms typically related to moldy houses, including mucocutaneous symptoms, nausea and fatigue, within a year of moving into a new building. Dampness was found in the insulation space of the concrete floor below ground level. Microbes indicating mold damage and actinobacteria were found in the flooring material and in the outer wall insulation. The case histories of the personnel involved were examined. All 34 subjects working at the health center had at least some rheumatic complaints. Two fell ill with a typical rheumatoid factor (RF)-positive rheumatoid arthritis (RA), and 10 had arthritis that did not conform to any definite arthritic syndrome (three met the classification criteria for RA). Prior to moving into the problem building one subject had suffered reactive arthritis, which had then recurred. Another employee had undiagnosed ankylosing spondylitis and later developed psoriatic arthritis, and another developed undifferentiated vasculitis. A total of 16 subjects developed joint pains, 11 of these after beginning work at the health center. Three subjects developed Raynaud's symptom. Fourteen cases had elevated levels of circulating immune complexes in 1998, 17 in 1999, but there were only three cases in 2001, when the health center had been closed for 18 months. The high incidence of joint problems among these employees suggests a common triggering factor for most of the cases. As some of the symptoms had tended to subside while the health center was closed, the underlying causes are probably related to the building itself and possibly to the abnormal microbial growth in its structures.

**Altered MGMT in Acquired Drug Resistance.**
Liu, L Journal/Crisp Data Base National Institutes of Health.

One of the mechanisms responsible for the therapeutic failure of alkylating agents is the DNA repair protein, O6-alkylguanine-DNA alkyltransferase (AGT), encoded by the MGMT gene. AGT removes the alkyl group from O6-alkylguanine in a fast and single step reaction, thereby preventing the formation of DNA cross-links by chloroethylating agents such as BCNU. Currently, a strategy involving the inactivation of AGT by O6-benzylguanine (BG) followed by BCNU treatment has shown evidence of significantly increased antitumor effect of BCNU. Ongoing clinical trials are evaluating its efficacy in tumor chemotherapy. However, repeated administration of BG and BCNU
will raise the possibility that BG resistant cells develop, subsequently, resulting in the failure of chemotherapy. In our recent studies, we selected two MMR deficient colon cancer cells for resistance to BG and BCNU and found two different mutations at amino acid 165 of AGT, to form K165E and K165N mutant AGT in these two cell lines. The cells harboring the K165 mutations have dramatically decreased AGT activity but remarkably increased resistance to BG+BCNU. Thus, we hypothesize that MMR deficiency leads to a high mutation frequency in DNA repair gene such as AGT gene and that two K165 mutant AGTs predominantly confer acquired resistance either to the combination BG+BCNU and BG+TMZ or alkylating agents alone. To test this hypothesis, it is necessary to distinguish acquired resistance caused by mutated AG from other resistance factors. This is of concern because the two BG-resistant AGTs were identified in cell lines with MMR defects. Once cells lose MMR, their sensitivity to various chemotherapeutic agents is decreased directly by impairing the ability to recognize or process DNA damage and indirectly by increasing the mutation rate throughout the genome. Therefore, it is possible that not only does mutation in AGT confer drug resistance, but other mechanisms of drug resistance as well. Thus, these specific objectives are proposed: to define whether K165 mutant AGTs are the major factor of acquired resistance to BG and BCNU, despite low AGT activity; to define whether colon cancer tumors with MMR deficiency are more likely to acquire resistance to BG+BCNU through mutations in MGMT than MMR wt tumors; and to determine whether BG-resistant AGT could be selected in the xenograft setting after mice carrying the tumor received multiple treatments with BG and BCNU. The long-term goal is to define the conditions in which MGMT mutations are observed in human tumors after clinical use of BG and BCNU. Overall, this project promises to provide novel information on the induction of BG-resistant AGT in drug treated MMR defective tumors and the impact of the altered AGT-resistance to BG+BCNU.

(2003) Differential roles of spinal protein kinases C and a in development of primary heat and mechanical hypersensitivity induced by subcutaneous bee venom chemical injury in the rat.
Li, KC and Chen, J Journal/Neurosignals. 12: 292-301.

It has been demonstrated that subcutaneous injection of bee venom (BV) can produce different types of pain and hypersensitivity including persistent spontaneous nociception (PSN), primary heat and mechanical hypersensitivity (hyperalgesia) and mirror-image heat (MIH) hypersensitivity in an individual animal, and the changes of spinal neurons are likely to be responsible for the production of these pain-related behaviors. In this study, we examined the roles of spinal protein kinase C (PKC) and protein kinase A (PKA) in the BV-induced different types of pain and hypersensitivity in conscious rats. We found that: (1). BV-induced primary heat hypersensitivity could be blocked by intrathecal pre- or posttreatment with a PKC inhibitor, chelerythrine chloride (CH), while a PKA inhibitor, N-(2-[P-bromocinnamylamino]ethyl)-5-isoquinolinesulphonamide hydrochloride (H89),
had no effect. (2). BV-induced primary mechanical hypersensitivity could be blocked by pre- or posttreatment with H89, whereas CH had no effect. (3). Both pre- and posttreatment with H89 produced suppressive effects on both induction and maintenance of the BV-induced PSN and MIH hypersensitivity. Based on the present findings, we proposed that spinal PKC might be activated during the central processes of primary heat hypersensitivity, while spinal PKA is likely to be involved in primary mechanical hypersensitivity induced by subcutaneous BV chemical injury. Taken together with our previous report however, spinal PKC and PKA are likely to be simultaneously involved in the central processes of both PSN and MIH hypersensitivity.

---------------------------------------------------------------

(2003) Chlorpyrifos exposure of developing zebrafish: effects on survival and long-term effects on response latency and spatial discrimination.

Chlorpyrifos (CPF) is a widely used insecticide, which has been shown to interfere with neurobehavioral development. Rat models have been key in demonstrating that prenatal CPF exposure causes choice accuracy deficits and motor alterations, which persist into adulthood. Complementary nonmammalian models can be useful in determining the molecular mechanisms underlying the persisting behavioral effects of developmental CPF exposure. Zebrafish with their clear chorion and extensive developmental information base provide an excellent model for assessment of molecular processes of toxicant impacted neurodevelopment. To facilitate the use of the zebrafish model and to compare it to the more typical rodent models, the behavioral phenotype of CPF toxicity in zebrafish must be well characterized. Our laboratory has developed methods for assessing spatial discrimination learning in zebrafish, which can differentiate response latency from choice accuracy in a three chambered fish tank. Low and high doses of CPF (10 and 100 ng/ml on days 1-5 postfertilization) both had significant persisting effects on both spatial discrimination and response latency over 18 weeks of testing. The high, but not the low dose, significantly accelerated mortality rates of the fish during the study from 20-38 weeks of age. Developmental exposure to either 10 or 100 ng/ml of CPF caused significant spatial discrimination impairments in zebrafish when they were adults. The impairment caused by 10 ng/ml was seen during early but not later testing, while the impairment caused by 100 ng/ml became more pronounced with continued testing. The higher dose caused a more pervasive impairment. The 10 and 100 ng/ml doses had opposite effects on response latency. The low 10 ng/ml dose significantly slowed response latency, while the high 100 ng/ml dose significant increased response latency. Both of these effects diminished with continued testing. CPF exposure during early development caused clear behavioral impairments, which lasted throughout adulthood in zebrafish. The molecular mechanisms by which early developmental CPF exposure produces these behavioral impairments expressed in adulthood can now be studied in the zebrafish model.
Electromagnetic sensibility, the ability to perceive electric and electromagnetic exposure, and electromagnetic hypersensitivity (EHS), developing health symptoms due to exposure to environmental electromagnetic fields, need to be distinguished. Increased electromagnetically sensibility is a necessary, however, not a sufficient condition for electromagnetic hypersensitivity. At an extended sample of the general population of 708 adults, including 349 men and 359 women aged between 17 and 60 years, electromagnetically sensibility was investigated and characterized by perception threshold and its standard deviation. By analyzing the probability distributions of the perception threshold of electric 50 Hz currents, evidence could be found for the existence of a subgroup of people with significantly increased electromagnetically sensibility (hypersensibility) who as a group could be differentiated from the general population. The presented data show that the variation of the electromagnetically sensibility among the general population is significantly larger than has yet been estimated by nonionizing radiation protection bodies, but much smaller than claimed by hypersensitivity self-aid groups. These quantitative results should contribute to a less emotional discussion of this problem. The investigation method presented, is capable of exclusion diagnostics for persons suffering from the hypersensitivity syndrome.

Multiple chemical sensitivity (MCS) is a syndrome in which multiple symptoms occur with low-level chemical exposure; whether it is an organic disease initiated by environmental exposure or a psychological disorder is still controversial. We report a 38-year-old male worker with chronic toluene exposure who developed symptoms such as palpitation, insomnia, dizziness with headache, memory impairment, euphoria while working, and depression during the weekend. Upon cessation of exposure, follow-up neurobehavioural tests, including the cognitive ability screening instrument and the mini-mental state examination, gradually improved and eventually became normal. Although no further toluene exposure was noted, non-specific symptoms reappeared whenever the subject smelled automotive exhaust fumes or paint, or visited a petrol station, followed by anxiety with sleep disturbance. During hospitalization for a toluene provocation test, there was no difference between pre-challenge and post-challenge PaCO(2), PaO(2), SaO(2) or pulmonary function tests, except some elevation of pulse
rate. The clinical manifestations suggested that MCS was more relevant to psychophysiological than pathophysiological factors.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14581647


A majority of occupants of a newly renovated historic courthouse in Calgary, Alberta, Canada, reported multiple (3 or more) health-related symptoms, and several reported more than 10 persistent symptoms. Most required at least 1 day outside of the building to recover from their symptoms. Molds that produce mycotoxins, such as Stachybotrys chartarum and Emericella nidulans, were identified in the building, along with fungal organisms of the genera Aspergillus, Penicillium, Streptomyces, Cladosporium, Chaetomium, Rhizopus/Mucor, Alternaria, Ulocladium, and Basidiomycetes. Renovations to this historic had building failed to provide adequate thermal and vapor barriers, thus allowing moist indoor air to migrate into the building enclosure, causing condensation to develop. Mold grew on the condensation and was dispersed throughout the courthouse, including on furniture and files. The courthouse was closed and a new facility was modified with low-offgassing materials, better ventilation and air filtration, and strict building maintenance to accommodate those occupants of the older building who had developed multiple chemical sensitivities.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15143857


Primary acquired cold urticaria (ACU) is the most common type of cold urticaria characterized by rapid onset of pruritic hives, swelling, and possible severe systemic reactions including hypotension and shock after cold exposure. Primary ACU is diagnosed by history of such symptoms, a positive immediate cold-contact stimulation test, and negative laboratory evaluation for underlying systemic disorders. Clinicians should be aware that patients with ACU may be susceptible to life-threatening systemic reactions especially during aquatic activities and that proper patient education is extremely important. This article reviews the clinical presentation, pathogenesis, diagnosis, and management of primary ACU.
An association between multiple sclerosis (MS) and exposure to organic solvents has been discussed. Organic solvents are metabolised by enzyme systems like glutathione Transferase M1 (GSTM1) and CYP2D6, which express polymorphisms in the general population. GSTM1 null genotype has been associated with solvent-induced chronic toxic encephalopathy. Our aim was to see if a defect in one of these enzyme systems could explain the association between MS and exposure to organic solvents. In our study, 50 patients with MS were investigated, including 24 who had been significantly exposed to organic solvents and 26 who were not exposed. Polymerase chain reaction-based methods were used for genotyping GSTM1 and CYP2D6 polymorphisms in leukocyte DNA. No differences in genetic predisposition were found between MS patients exposed and those not exposed to organic solvents regarding GSTM1 null or CYP2D6 poor metaboliser genotypes. The possible association between multiple sclerosis and solvents may not, as for chronic toxic encephalopathy, be explained by defects in these systems.


OBJECTIVES: We sought to identify factors associated with wheezing symptoms in children found to have bronchial hyperresponsiveness (BHR) at 10 years of age. METHODS: Children were seen at birth, 1, 2, 4 and 10 years of age in an entire population birth cohort study (n = 1456). At each stage information was collected prospectively on genetic and environmental risk factors for BHR. Skin prick testing was performed at 4 and 10 years of age. Spirometry and methacholine bronchial challenge were conducted at 10 years of age when BHR was considered present if PC(20) FEV(1) was < 4.0 mg/mL. In children with BHR at 10 years of age, factors independently associated with current wheeze were determined by logistic regression. RESULTS: BHR was identified in 169 10-year-olds at bronchial challenge, 55.6% of whom manifested current wheeze. In children with BHR, current wheezers had higher Log(10) total IgE and greater BHR than those who had never wheezed. Symptomatic BHR was independently associated with atopic sensitization (P <.001) and maternal asthma (P =.011) at 10 years of age. If only factors present in the first 4 years of life were considered, parental smoking at 4 years of age (P =.021), maternal asthma (P =.017), and atopic sensitization at 4 years of age (P =.004) were independently associated with symptomatic BHR at 10 years of age. CONCLUSIONS:
Symptomatic BHR is associated with greater degrees of BHR and higher total IgE. Heredity, atopy, and environmental exposure might influence symptom expression in children with BHR.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12897736

(2003) [Formaldehyde exposure and multiple chemical sensitivity].

Multiple chemical sensitivity (MCS) is characterized by various somatic symptoms which cannot be explained organically and by sensitivity to extremely low concentrations of chemicals including formaldehyde. In the absence of a widely accepted definition of MCS, contradictory etiological hypotheses and therapeutic suggestions are discussed. Formaldehyde is a flammable, colorless and readily polymerized gas at ambient temperature. It is present in the environment as a result of natural processes and from man-made sources, including motor vehicle exhaust, residues, emissions, or wastes produced during the manufacture of formaldehyde, and cigarette smoke. Formaldehyde exposure is considered to be one of the causes of MCS. This review describes the current knowledge about MCS and preventive measures of the administration.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12813865

Koch, CJ Journal/Crisp Data Base National Institutes of Health.
DESCRIPTION (provided by applicant): Redox regulation is a term describing modification of function by a change in the state of oxidation vs. reduction of critical control molecules, usually proteins. When cells are subjected to reactive oxygen species in a process described as 'oxidative stress', pathways susceptible to redox regulation may be altered. Defining the mechanism of such alteration is often difficult because oxidative stress can additionally cause damage to multiple cellular targets, including membrane, organelles and chromatin, often leading to mitotic or apoptotic death. Our proposed experiments will allow a separation of damage to the redox-regulated proteins from that of damage to targets of cytotoxicity. Our hypothesis is that alterations in the redox status of DNA repair proteins may impair DNA damage repair. In order to cause the mild and specific oxidation of protein thiols we employ the disulfide of mercaptoethanol, hydroxy-ethylidisulfide (HEDS). Normal cells are able to prevent thiol-disulfide exchange of their protein and non-protein thiols with HEDS via reducing equivalents produced by the pentose cycle, whose key regulatory enzyme is glucose-6-phosphate-dehydrogenase (G6PD). To prevent this, we investigated a CHO
cell line without G6PD activity (E89). Reversibility of observed effects was established by transfecting the G6PD gene back into the E89 mutant. With this model system, we will demonstrate that radiation sensitization, inhibition of DNA repair and inhibition of Ku binding to DNA ends are all caused by incubation of E89 cells with non-toxic concentrations of HEDS. These effects are not seen in parental cells or A1A transfectants. Just as 'p53' may be the 'guardian of the genome' we suggest that G6PD is the 'protector of proteins'. This Application will test this interesting concept using combined biochemical and genetic approaches. Specific Aim 1 will determine the kinetic relationships between HEDS mediated radiosensitization and biochemical modulation. Multiple genetic and biochemical tests will determine the specific sensitivity of Ku to oxidative modification by HEDS treatment. Specific Aim 2 will determine the (bio)chemical mechanism of HEDS oxidation of cellular protein thiols. Specific Aim 3 will investigate other aspects of DNA repair and DNA structural organization to determine their sensitivity to redox regulation.

(2003) Brain but not lung functions impaired after a chlorine incident.
Kilburn, KH Journal/Ind Health. 41: 299-305.

A workplace bleach exposure incident was studied in 13 women to determine whether chlorine caused neurobehavioral and pulmonary functional effects. We compared neurophysiological and neuropsychological measurements in 13 chlorine-exposed women, 4.5 years after exposure, and 41 unexposed women. Reaction times, balance, blink reflex latency, color discrimination and several psychological tests were measured. Pulmonary function was assessed by spirometry. A profile of mood states and frequencies of 35 symptoms were obtained. Chlorine exposed women performed statistically significantly below unexposed women for simple and choice reaction times, balance with eyes open and eyes closed, color discrimination, grip strength, Culture Fair, digit symbol substitution, vocabulary, trail making B and pegboard. Profile of mood states scores and frequency symptoms were elevated. Respiratory symptoms were elevated but pulmonary volumes and flows were not reduced. Chlorine bleach exposure was associated with impaired neurobehavioral functions and elevated POMS scores and symptom frequencies. Alternatives to chlorine should be used.

Kilburn, KH Journal/Arch Environ Health. 58: 746-55.

Chlorine and potassium cresylate spilled from a train wreck forced evacuation of nearly 1000 people in and near the town of Alberton, Montana, in 1996. Because respiratory and other symptoms persisted in this population, neurobehavioral and pulmonary
functions were evaluated in a cohort of exposed vs. unexposed individuals. Ninety-seven subjects were tested 7 wk after exposure. Three years later, 36 of the original subjects were retested, along with 21 new patients exposed in the same incident. These 57 were compared with 22 unexposed individuals. Twenty-six neurobehavioral functions were tested, and spirometry was performed on each subject. At 7 wk postexposure, patients showed significant differences in 5 neurobehavioral functions (i.e., balance, simple reaction time, abnormal visual quadrants, vocabulary, and information), compared with the unexposed individuals recruited in 1999. Patients' Profile of Mood States scores and frequencies of 35 symptoms were also elevated, compared with the unexposed group. At 3 yr postexposure, patients exhibited differences in 7 additional neurobehavioral functions (i.e., choice reaction time, balance with eyes open, color errors, visual fields, Culture Fair, and verbal recall). Respiratory symptoms were increased, but pulmonary functions did not change. Exposure to chlorine and potassium cresylate produced neurobehavioral impairments that have been observed to increase across 3 yr. Spills in heavily populated areas could injure thousands, overwhelming medical facilities.


Recently, patients who have been exposed indoors to mixed molds, spores, and mycotoxins have reported asthma, airway irritation and bleeding, dizziness, and impaired memory and concentration, all of which suggest the presence of pulmonary and neurobehavioral problems. The author evaluated whether such patients had measurable pulmonary and neurobehavioral impairments by comparing consecutive cases in a series vs. a referent group. Sixty-five consecutive outpatients exposed to mold in their respective homes in Arizona, California, and Texas were compared with 202 community subjects who had no known mold or chemical exposures. Balance, choice reaction time, color discrimination, blink reflex, visual fields, grip, hearing, problem-solving, verbal recall, perceptual motor speed, and memory were measured. Medical histories, mood states, and symptom frequencies were recorded with checklists, and spirometry was used to measure various pulmonary volumes and flows. Neurobehavioral comparisons were made after individual measurements were adjusted for age, educational attainment, and sex. Significant differences between groups were assessed by analysis of variance; a p value of less than 0.05 was used for all statistical tests. The mold-exposed group exhibited decreased function for balance, reaction time, blink-reflex latency, color discrimination, visual fields, and grip, compared with referents. The exposed group's scores were reduced for the following tests: digit-symbol substitution, peg placement, trail making, verbal recall, and picture completion. Twenty-one of 26 functions tested were abnormal. Airway obstructions were found, and vital capacities were reduced. Mood state scores and symptom frequencies were elevated. The author concluded that indoor mold exposures were
associated with neurobehavioral and pulmonary impairments that likely resulted from the presence of mycotoxins, such as trichothecenes.

(2003) **Why is chemical brain injury ignored? Pondering causes and risks.**

(2003) **Paraoxonase 1 promoter and coding region polymorphisms in Parkinson’s disease.**

(2003) **The role of nitric oxide in locomotor regulation in mice and its interaction with nitrous oxide.**


(2003) **Lessons from peppers and peppermint: the molecular logic of thermosensation.**

Sensory neurons report a wide range of temperatures, from noxious heat to noxious cold. Natural products that elicit psychophysical sensations of hot or cold, such as capsaicin or menthol, were instrumental in the discovery of thermal detectors belonging to the transient receptor potential (TRP) family of cation channels. Studies are now beginning to reveal how these channels contribute to thermosensation and how chemical signaling pathways, such as those activated by tissue injury, alter thermal sensitivity through TRP channel modulation. Analysis of TRP channel expression
among sensory neurons is also providing insight into how thermal stimuli are encoded by the peripheral nervous system.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12965298

Jarvis, BB Journal/Arch Environ Health. 58: 479-83.

Mycotoxins are fungal metabolites that pose a health risk to exposed animals and humans. In recent years, concern has mounted regarding human exposure to mycotoxins via inhalation of mold spores produced in damp buildings and homes. Although mycotoxins can be detected in such buildings, reliable means for measuring an occupant’s level of exposure to most mycotoxins are lacking. The author briefly reviews the chemical methods currently available for mycotoxin analysis, outlining accepted practices and discussing the limitations of these measurements.

(2003) [Occupational factors in parents and morbidity in their children].
Iusupova, NZ and Khakimova, RF Journal/Gig Sanit. 31-2.

Nonspecific resistance and the incidence of allergic diseases were studied in children living in areas with varying ambient air pollution, whose parents were exposed before conception to deleterious occupational factors at chemical and petrochemical enterprises. Nonspecific resistance was found to reduce drastically in children of female workers of chemical and petrochemical enterprises. In the children of female workers of the above enterprises, the incidence of allergic diseases was significantly higher (p < 0.01) than that in the control group. The findings suggest that environmental factors (ambient air pollution, occupational harms in parents) exert a substantial influence on a rise in the incidence of allergic diseases in children.


The number of reports on the effects induced by electromagnetic radiation (EMR) from cellular telephones in various cellular systems is still increasing. Until now, no satisfactory mechanism has been proposed to explain the biological effects of this
radiation except a role suggested for mast cells. Merkel cells may also play a role in the mechanisms of biological effects of EMR. This study was undertaken to investigate the influence of EMR from a cellular telephone (900 MHz) on Merkel cells in rats. A group of rats was exposed to a cellular telephone in speech position for 30 min. Another group of rats was sham-exposed under the same environmental conditions for 30 min. Exposure led to significantly higher exocytotic activity in Merkel cells compared with the sham exposure group. This finding may indicate the possible role of Merkel cells in the pathophysiology of the effects of EMR.


(2003) "Where does the damp come from?" Investigations into the indoor environment and respiratory health in Boston public housing.

The self-reported prevalence of asthma increased by 75% from 1980 to 1994, a trend found to be significant and evident in every region of the country. The increase has been most marked in children 0-14 years of age, and there is evidence that, as with lead poisoning, inner-city and urban populations are most at risk. Attention has turned to the role of indoor environment risk factors, especially in homes and schools. Such factors include moisture and mold growth, pest infestation, dust mites, the building envelope, heating systems, inadequate ventilation, NO2, and environmental tobacco smoke. The Healthy Public Housing Initiative (HPHI) is a Boston-based community-centered research and intervention project designed to engage Boston Housing Authority residents in a collaborative process to improve respiratory health, quality of life, building conditions, and building maintenance in public housing. This article summarizes the significant research findings from four pilot studies in housing developments that lay the foundation for the larger HPHI asthma-related environmental intervention study. The research design for the pilot projects is informed by principles of community-collaborative research. The strengths of this model of research to our work are also discussed.


Whether persons with multiple chemical sensitivity syndrome (MCS) have immunological abnormalities is unknown. To assess the reliability of selected immunological tests that have been hypothesized to be associated with MCS, replicate blood samples from 19 healthy volunteers, 15 persons diagnosed with MCS, and 11 persons diagnosed with autoimmune disease were analyzed in five laboratories for expression of four T-cell surface activation markers (CD25, CD26, CD38, and HLA-DR) and in four laboratories for autoantibodies (to smooth muscle, thyroid antigens, and myelin). For T-cell activation markers, the intralaboratory reproducibility was very good, with 90% of the replicates analyzed in the same laboratory differing by < or = 3%. Interlaboratory differences were statistically significant for all T-cell subsets except CD4+ cells, ranging from minor to eightfold for CD25+ subsets. Within laboratories, the date of analysis was significantly associated with the values for all cellular activation markers. Although reproducibility of autoantibodies could not be precisely assessed due to the rarity of abnormal results, there were inconsistencies across laboratories. The effect of shipping on all measurements, while sometimes statistically significant, was very small. These results support the reliability of fresh and shipped samples for detecting large (but perhaps not small) differences between groups of donors in the T-cell subsets tested. When comparing markers that are not well standardized, it may be important to distribute samples from different study groups evenly over time.


The main objective of this paper is to review the chemical and genetic methods used in authentication of ginseng, especially the recent advances in microsatellite genotyping and its application to the authentication of other traditional Chinese medicines (TCM). The standardization and modernization of TCM hinge on the authentication of their botanical identities. Analysis of well-characterized marker compounds is now the most popular method for identifying the herbal materials and quality control of TCM, eg, ginsenoside profiling for authentication of Panax species. However, in many herbal species the chemical composition of the plant changes with the external environment and processing conditions, which lowers the reliability of these authentication methods. In the light of the advances in molecular biotechnology in the past few decades, genetic tools are now considered to provide more standardized and reliable methods for authentication of herbal materials at the DNA level. These genetic tools include random amplified polymorphic DNA (RAPD), DNA fingerprinting using multi-loci probes, restriction fragment length polymorphism (RFLP), amplified fragment length polymorphism (AFLP), and microsatellite marker technology. The practicality of these methods varies in terms of their sensitivity, reliability, reproducibility, and running cost.
Using ginseng as an example, we reviewed the advantages and limitations of these molecular techniques in TCM authentication. We have developed a set of microsatellite markers from American ginseng that are able to differentiate Panax ginseng and Panax quinquetolius with the resolution down to farm level, ie, confirmation of its botanical identity and origin. Compared with other molecular techniques, microsatellite marker technology is more robust, accurate, reproducible, reliable, and sensitive. This is essential for large-scale TCM authentication centers.


A standardized questionnaire has not been established for screening or diagnostic assessment of patients with multiple chemical sensitivity (MCS) in Japan. In the US, Miller and Prihoda (1999a,b) developed a questionnaire that could be used internationally, the Quick Environment Exposure Sensitivity Inventory (QEESI), to assist researchers and clinicians in evaluating patients and populations for chemical sensitivity. The Japanese version of QEESI was subsequently translated by Ishikawa and Miyata (1999). The present study was performed to investigate the reliability and validity of QEESI (Japanese version) for research purposes and for evaluation of patients with MCS in Japan. A total of 498 subjects were recruited from the general population of Miyagi prefecture, Japan. The factor structure in QEESI was analyzed with 40 items on four subscales except for the items in 'Masking' using principal components analysis with Promax rotation. The results showed that 30 items on three subscales, 'Chemical Inhalant Intolerances,' 'Symptom Severity,' and 'Life Impact' except for 'Other Intolerances' were consistent with those reported for the US population by Miller and Prihoda (1999a). Cronbach's alpha reliability coefficient ranged between 0.87 and 0.94 indicating high internal consistency in the 30 items on three subscales. Next, we compared the mean scores on three subscales of QEESI in two groups: 131 self-reported MCS group who were new outpatients at the Environmental Medical Center in Kitasato Institute Hospital, and 131 members of the general population (controls) who were matched for both gender and age with the self-reported MCS group. Mean scores on each subscale for the self-reported MCS group were significantly greater than those for controls (P <0.001). Mean scores on all of the 30 items on three subscales for the self-reported MCS group were also significantly greater than for the controls (P <0.001). These findings indicated that the 30 items on three subscales in QEESI can be used for surveys and for diagnostic assessment of patients with MCS as well as for comparative studies between patients in Japan and in other countries.

Hockings, GI, Grice, JE, Ward, WK, Walters, MM, Jensen, GR and Jackson, RV
Journal/Biological Psychiatry. 33: 585-593.

http://www.sciencedirect.com/science/article/B6T4S-484N9S1-18K/2
d8f2e5e4d246a83613d2a23af4ff747

(2003) New environmental illnesses: what are their characteristics?

(2003) [Multiple chemical sensitivity. Is the patient suffering as a result of environmental pollutants or psychological problems?].

Multiple chemical sensitivity (MCS) poses a medical challenge. Proposed etiologies are as numerous as they are contradictory, direct and indirect costs are high, and patient suffering considerable. In the absence of objective diagnostic criteria, estimation of its prevalence is difficult. Nevertheless, establishment of the diagnosis is frequently strikingly uncritical. We support an holistic approach that gives consideration both to psychological and physical aspects, as well as taking account of the high level of comorbidity, and we warn against "over-diagnosis". Therapeutical approaches should consider carefully the risk of avoidance and social withdrawal.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14526571

Controversy surrounds the origin of symptoms attributed to environmental pollutants or widely used chemicals, and the authors believed that a psychiatric evaluation could advance understanding of this contentious condition. They assessed psychiatric morbidity, somatization, and self-attentiveness in patients seen in their Environmental Clinic. Two hundred ninety-five consecutive patients underwent SCID-I and -II interviews and were investigated with self-rating scales for self-attentiveness and somatization. The authors found a high prevalence of mental disorders (66% had a current SCID diagnosis, and 75% had a lifetime SCID diagnosis) and a low level of self-attentiveness, which was not necessarily associated with psychiatric disease. Among patients visiting an Environmental Clinic, mental disorders were common and needed to be diagnosed and treated by standard interventions. Patients who did not meet diagnostic criteria for a psychiatric disorder had relatively low somatization scores and low private self-attentiveness. These "externalizers" could benefit from an intervention that teaches them to focus on their internal and emotional lives. In these patients, the authors consider low self-attentiveness a major feature that may act as a pathogenic factor for environmental illness.


Fcp1 is an essential protein serine phosphatase that dephosphorylates the C-terminal domain (CTD) of RNA polymerase II. By testing the effects of serial N- and C-terminal deletions of the 723-amino acid Schizosaccharomyces pombe Fcp1, we defined a minimal phosphatase domain spanning amino acids 156-580. We employed site-directed mutagenesis (introducing 24 mutations at 14 conserved positions) to locate candidate catalytic residues. We found that alanine substitutions for Arg(223), Asp(258), Lys(280), Asp(297), and Asp(298) abrogated the phosphatase activity with either p-nitrophenyl phosphate or CTD-PO(4) as substrates. Structure-activity relationships were determined by introducing conservative substitutions at each essential position. Our results, together with previous mutational studies, highlight a constellation of seven amino acids (Asp(170), Asp(172), Arg(223), Asp(258), Lys(280), Asp(297), and Asp(298)) that are conserved in all Fcp1 orthologs and likely comprise the active site. Five of these residues (Asp(170), Asp(172), Lys(280), Asp(297), and Asp(298)) are conserved at the active site of T4 polynucleotide 3'-phosphatase, suggesting that Fcp1 and T4 phosphatase are structurally and mechanistically related members of the DXD phosphotransferase superfamily.

This paper deals with the assumption that young adults with self-reported multiple chemical sensitivity (SMCS) show a heightened sensitivity of autonomic functions during experimental solvent exposure. Male SMCS-subjects were selected (out of n=274) on the base of a German questionnaire on chemical and environmental sensitivity (CGES). Two independent experiments were carried out, each with 12 SMCS-subjects and 12 age-matched control-subjects. In experiment I two concentrations of the solvents ethyl benzene (10 and 98 ppm) and 2-butanone (10 and 189 ppm) were used. Experiment II investigated 2-propanol (35 and 190 ppm) and 1-octanol (0.1 and 6.4 ppm). The low concentrations correspond nearly to the olfactory thresholds while the high concentrations correspond to the German occupational threshold limit values (MAC). The exposure duration under each condition was 4h. The sequence of the four exposure conditions was random including intervals of at least 2 days without exposure. During the exposure physiological changes of breathing rate and heart rate were recorded. Two 30 min intervals with a sedentary position of the subjects at the beginning and end of exposure were chosen for analyses. Neither in experiment I nor in experiment II significant specific reactions to the type or level of the exposures were found. The autonomic functions in both experiments revealed alterations within the exposure sessions. The heart rate in experiment II and the breathing rate in both experiments decreased significantly during the analyzed 30 min intervals. Furthermore, in both experiments the heart rates decreased significantly from beginning to end of exposure. Only in experiment I the mean breathing rate of SMCS-subjects was generally higher compared to the control-subjects. Regarding the assumption of a heightened sensitivity of SMCS-subjects the two experiments yielded controversial results. Thus, the hypothesis of stronger responses of autonomic functions of SMCS-subjects provoked by various exposure scenarios remains open.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12606290


BACKGROUND: Reported cases of ALS in young veterans of the 1991 Gulf War have suggested excess incidence. OBJECTIVE: To compare observed and expected
incidence of ALS in Gulf War veterans diagnosed before age 45 years (young veterans). METHODS: Cases of ALS diagnosed from 1991 through 1998 were collected from military registries and a publicity campaign in late 1998. Diagnoses were established from neurologists' medical records using El Escorial criteria. Expected incidence was estimated from the age distribution of the Gulf War veteran population, weighted by age-specific death rates of the US population. Secular changes in nationwide ALS rates were assessed using calculations of the age-specific US population death rates from vital statistics data of 1979 to 1998. RESULTS: During 8 postwar years, 20 ALS cases were confirmed in approximately 690,000 Gulf War veterans, and 17 were diagnosed before age 45 years. All developed bulbar and spinal involvement, and 11 have died. In young veterans, the expected incidence increased from 0.93 cases/year in 1991 to 1.57 cases/year in 1998, but the observed incidence increased from 1 to 5 cases/year. The observed incidence was 0.94 (95% CI, 0.26 to 2.41) times that expected in the baseline period from 1991 to 1994 (4 vs 4.25 cases; p = 0.6); it increased to 2.27 (95% CI, 1.27 to 3.88) times that expected during the 4-year period from 1995 to 1998 (13 vs 5.72 cases; p = 0.006); and it peaked at 3.19 (95% CI, 1.03 to 7.43) times that expected in 1998 (5 vs 1.57 cases; p = 0.02). The magnitude of the excess of ALS cases over the expected incidence increased during the 8-year period (Poisson trend test, p = 0.05), and the increase was not explained by a change in the interval from onset to diagnosis or by a change in the US population death rate of ALS in those aged <45 years. CONCLUSIONS: The observed incidence of ALS in young Gulf War veterans exceeded the expected, suggesting a war-related environmental trigger.

(2003) [Patients with "environmental illnesses". Umpteen thousand euros unnecessarily wasted?].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14584435

(2003) [Amalgam, exhaust gases, atomic power--or psychological factors. What is behind environmental anxiety in Germans?].

(2003) Role of cross-allergies to latex in clinical routine of anesthesia.

STUDY OBJECTIVE: To determine the applicability and reliability of a screening questionnaire to detect patients at high-risk of latex allergy; to assess the importance of other allergies such as profilin allergies (pollinosis) for presence of latex sensitization; and to determine the clinical effectiveness of preemptive avoidance of latex exposure in high-risk patients. DESIGN: Prospective, clinical trial. SETTING: Operative theater of a university hospital. PATIENTS: 95 adult patients. INTERVENTIONS: Patients were preoperatively screened and classified for present latex allergy (high-risk and low-risk group) according to a specially designed screening questionnaire. Anesthesia and surgery in the high-risk group were performed strictly avoiding latex-containing materials. The low-risk group (other allergies including pollinosis) received routine treatment, without latex-avoidance. Effects of latex avoidance or exposure were evaluated by measuring specific IgE titers perioperatively. MEASUREMENTS AND MAIN RESULTS: According to the questionnaire, 45 patients at high risk were defined. Validity of classification of high-risk patients is supported by significantly higher total IgE and latex and grass profilin specific IgE compared to the low-risk group. There were no significant differences in other profilin-specific IgEs. In one case of severe anaphylactic reaction a drop of latex-specific IgE during surgery could be observed. CONCLUSION: The questionnaire allowed the identification of most patients at high risk for latex allergy. In isolated pollinosis no changes in any specific IgE levels were detectable. Strict avoidance of perioperative latex exposure in high-risk patients increases safety during anesthesia and surgery.


Testing for food and chemical sensitivities usually becomes necessary as part of the evaluation of otolaryngology patients who have chronic illness. The more complex the patient, and the more recalcitrant the problem is to treatment, the more likely it is that allergies, and especially food or chemical sensitivities, are involved in the pathogenesis of the illness. Failure to consider all major allergen contacts, including foods and chemicals, can lead to inadequate therapy. Similarly, failure to understand total allergic and oxidant load and the effects of chemical toxicity can lead to inappropriate or ineffective treatment. Clinically, food allergies occur in two different types: immediate, anaphylactic, fixed reactions and delayed, chronic, cyclic reactions. Different test methods have been developed for the two types. Fixed food allergies can be safely and efficiently detected by in vitro specific IgE or histamine release tests. Cyclic food allergies are best detected by either oral food challenges or by the IPDFT test. Choosing the best test for a particular patient requires a clear understanding of the two food allergy types and how their clinical presentations differ. Other tests for food allergies are compared and contrasted with these primary tests. Chemical sensitivity
also occurs in two different clinical types: allergic, and toxic. True allergy to chemical haptens, either type I, IgE-mediated, or type IV, delayed hypersensitivity, occurs with significant frequency but is often unsuspected. Chemical toxicity can be caused by the aftereffects of an acute exposure or as a result of chronic, low-level exposure, but is even more frequently unsuspected and will not be diagnosed without a high index of suspicion. Both types of chemical sensitivity need to be addressed in any patients who have either a high allergen or chemical exposure load [105]. Either in vitro or in vivo tests can be used for chemical allergy detection; the advantages of each are outlined. Chemical toxicity screening tests are available and useful but do not detect all possible toxicants. Definitive toxic chemical tests usually require specialized laboratory facilities and expert consultation, for which possible sources are specified. The most important point in testing for food or chemical sensitivity is to be aware that food or chemical sensitivity can be contributing to a specific patient's clinical problems. Only then can appropriate investigations be undertaken to understand and then, perhaps, to intervene successfully in that illness.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14743781


http://www.sciencedirect.com/science/article/B6T4S-49JVH73-B/2051ab0d3e84ac50678121a3e2626de13

(2003) Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity.

Multiple chemical sensitivity (MCS) is a condition in which persons experience negative health effects in multiple organ systems from exposure to low levels of common chemicals. Although symptoms experienced from particular chemicals vary across persons, they are generally stable within persons. The sensitivities often spread over time, first to related chemicals and then to other classes of chemicals. This study examined self-reported perceived treatment efficacy of 101 treatments used by 917 persons with self-reported MCS. Treatments examined included environmental medicine techniques, holistic therapies, individual nutritional supplements, detoxification techniques, body therapies, Eastern-origin techniques, newer therapies,
prescription items, and others. The three most highly rated treatments were creating a chemical-free living space, chemical avoidance, and prayer. Both creating a chemical-free living space and chemical avoidance were rated by 95% of respondents as helpful. Results for most therapies were mixed. Participants had consulted a mean of 12 health care providers and spent over one-third of their annual income on health care costs. We discuss this drain on personal resources and describe respondents' attitudes toward the possibility of healing from MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12948890

(2003) Multiple chemical sensitivity in male painters; a controlled provocation study.

The purpose of the present study was to examine whether male painters reporting multiple chemical sensitivity (MCS) differ from their matched controls (male painters without such sensitivity) during controlled chamber challenges to singular and mixtures of odorous chemicals with respect to: (1) Subjective rating of symptoms (i.e., symptoms related to central nervous system (CNS) and symptoms related to irritation) and sensations of smell elicited by low-level chemical exposures. (2) Changes in serum prolactin and cortisol levels, changes in nasal cavity and eye redness as a result of the various exposures. Moreover, background assessments were made regarding mental well-being, sense of coherence (SOC) as well as state of anxiety and depression in both groups. The MCS and control group consisted of 14 and 15 male painters respectively. Regarding background assessments of mental well-being, anxiety, depression and SOC, statistically significant differences were obtained between painters with MCS and their controls. During the controlled chamber challenges, neither difference regarding sensations of smell nor development of CNS related symptoms were seen between MCS and control group. In contrast, subjective rating of symptoms related to irritation (i.e., eyes, nose, throat, skin, and breathing difficulties) was significant higher in subjects with MCS. No differences between the groups as a result of the different exposures were seen concerning nasal cavity, eye redness and serum cortisol levels. However, a trend (P = 0.056) between the groups was measured regarding a decline of serum prolactin levels in the MCS group. This is a relatively small study with a limited number of volunteers; and no definitive conclusions can be drawn concerning the above findings. But it is the first controlled challenge study that incorporates similarly exposed groups (painters) recruited from a community rather than from a clinical population.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14626900
It has long been recognized that the symptom complex of fibromyalgia can be seen with hypothyroidism. Hypothyroidism may been categorized, like diabetes, into type I (hormone deficient) and type II (hormone resistant). Most cases of fibromyalgia fall into the latter category. The syndrome is reversible with treatment, and is usually of late onset. It is likely more often acquired than due to mutated receptors. Now that there is evidence to support the hypothesis that fibromyalgia may be due to thyroid hormone resistance, four major questions appear addressable. First, can a simple biomarker be found to help diagnose it? Second, what other syndromes similar to Fibromyalgia may share a thyroid-resistant nature? Third, in non-genetic cases, how is resistance acquired? Fourth, what other methods of treatment become available through this new understanding? Preliminary evidence suggests that serum hyaluronic acid is a simple, inexpensive, sensitive, and specific test that identifies fibromyalgia. Overlapping symptom complexes suggest that chronic fatigue syndrome, Gulf war syndrome, premenstrual syndrome, post traumatic stress disorder, breast implant silicone sensitivity syndrome, bipolar affective disorder, systemic candidiasis, myofascial pain syndrome, and idiopathic environmental intolerance are similar enough to fibromyalgia to merit investigation for possible thyroid resistance. Acquired resistance may be due most often to a recently recognized chronic consumptive coagulopathy, which itself may be most often associated with chronic infections with mycoplasmids and related microbes or parasites. Other precipitants of thyroid resistance may use this or other paths as well. In addition to experimentally proven treatment with supraphysiologic doses of thyroid hormone, the thyroid-resistant disorders might be treatable with anti-hypercoagulant, anti-infective, insulin-sensitizing, and hyaluronolytic strategies.

Methyl parathion is an organophosphorus (OP) insecticide with insecticidal properties derived from acetylcholinesterase (AChE) inhibition; this same property is also the root of its toxicity in humans. Poisoning with methyl parathion leads to cholinergic overstimulation with signs of toxicity including sweating, dizziness, vomiting, diarrhea, convulsions, cardiac arrest, respiratory arrest, and, in extreme cases, death. Reports of methyl parathion intoxication, usually seen only in field pesticide applicators, have increased throughout the United States as a result of unauthorized application of methyl parathion inside homes. The health concerns of the use of methyl parathion have resulted in cancellation of its use in most food crops in the United States. This
review examines the well-documented neurotoxicity of methyl parathion as well as effects on other organ systems.


The environment plays a crucial role in determining the development and expression of allergic disorders. Epidemiologic studies allow us to understand risk factors for allergic disease, which may lead to interventional studies to provide the evidence base for our clinical advice. Articles published in The Journal of Allergy and Clinical Immunology last year highlighted the relevance of mold exposure and environmental tobacco smoke as risk factors for the development of asthma and the expression of symptoms. The role of fitted carpets as a reservoir for house dust allergens was also challenged by data arising from this work. Occupational allergy is an important clinical and socioeconomic problem. A large body of work on latex allergy has been reported in the past year, demonstrating the impact of containment strategies on exposure to latex and the incidence of sensitization to latex. Other articles have explored the range of latex allergens to which patients are sensitized and the HLA associations of latex allergy. Two models of isocyanate sensitization were reported, providing some insight into possible mechanisms of isocyanate asthma and some clues for understanding nonallergic asthma. Environmental and occupational disorders are highly relevant to our readership, and the new Editorial Board hopes to encourage submission and publication of relevant articles in this area.

Freeman, K Journal/Environ Health Perspect. 111: A591.


A 70-year-old man developed a slowly progressive cerebellar syndrome after having been exposed to carbon disulfide (CS2) in a viscose rayon plant for 27 years. Ataxia, dysmetria, dysarthria and adiadochokinesia appeared 7 years after retirement from work (at age 54), and were later accompanied by cognitive deterioration, dysmnesia, spatio-temporal disorientation, emotional lability, and paranoid-obsessive disturbances.
Brain computed tomography (CT) and magnetic resonance imaging (MRI) showed advanced global cerebellar atrophy, and a picture of less severe cerebrocortical atrophy. The case illustrates the possibility of chronic toxic encephalopathy among patients with previous long-term exposure to CS2. In such instances, cerebellar damage may develop as an exceptional, delayed manifestation of neurotoxicity: brain imaging techniques can significantly contribute to the diagnosis and follow-up, in addition to occupational anamnesis and neuropsychiatric evaluation. The patient presented also serves as a remainder that neurodegenerative disorders of apparently unknown origin sometimes derive from occupational toxic exposures suffered in the past. The clinical manifestations may appear several years after retirement from work, when the effects of toxic damage combine with age-related neuronal loss to overcome the brain functional reserve.

(2003) Effect of glutamate carboxypeptidase II and reduced folate carrier polymorphisms on folate and total homocysteine concentrations in dialysis patients.

This study was designed to examine the effect of two single nucleotide polymorphisms in the reduced folate carrier 1 (RFC1 80G>A) and the glutamate carboxypeptidase 2 (GCP2 1561C>T) gene on total homocysteine (tHcy) plasma level and folate status in 120 chronic dialysis patients. Red blood cell folate concentration was higher in patients with the GCP2 CT or TT genotype (ANOVA, P = 0.04). Among patient groups with different RFC1 genotypes, red blood cell folate level was not significantly different. A multivariate analysis confirmed that the GCP2 1561C>T genotype (P = 0.011) had a significant influence on the red blood cell folate concentration. Overall, serum folate, creatinine, and the GCP2 polymorphism explained nearly 50% of the variance of red blood cell folate. A linear multivariate regression analysis showed that red blood cell folate (P < 0.001), creatinine (P < 0.001), and the 5,10-methylenetetrahydrofolate reductase (MTHFR) 677T allele (P = 0.013) are independent predictors of tHcy plasma level explaining 49% of the variance of tHcy plasma concentration. GCP2 1561C>T and RFC1 80G>A showed no effect on tHcy and folate plasma level. In conclusion, GCP2 1561C>T, but not RFC1 80G>A, is a predictor of red blood cell folate level in chronic dialysis patients. Both polymorphisms have no major effect on tHcy plasma concentration in end-stage renal disease patients.

(2003) Role of hippocampal M1 and M4 muscarinic receptor subtypes in memory consolidation in the rat.

Muscarinic receptors in the hippocampus are relevant to learning and memory, but the role of each subtype is poorly understood. Muscarinic toxins (MTs) from Dendroaspis snakes venom are selective for muscarinic receptor subtypes. MT2, a selective agonist for M(1) receptors, given into the hippocampus immediately after training, improved memory consolidation of an inhibitory avoidance task in rats, whereas the antagonist pirenzepine was amnestic, supporting a facilitatory role of M(1) receptors. Instead, MT3, a selective antagonist at M(4) receptors, caused amnesia. Neither M(1) nor M(4) receptor appeared involved in habituation to a new environment. Thus, our results suggest that memory consolidation of an inhibitory avoidance task in the rat involves the participation of both M(1) and M(4) hippocampal receptors, with a positive modulatory role.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12479962


This paper is about industrial chemicals, the manner in which their toxicity is assessed and the use of such assessments in regulatory decision-making. It begins with general points concerning toxicological data availability and hazard identification, then moves on to risk assessment and occupational exposure limits, and finally looks briefly at three specific toxicological issues, asthma, chronic toxic encephalopathy, and "low toxicity" dust effects on the lung, where the science is far from resolved. The overall purpose of the paper is to raise, or perhaps to act as a reminder of a number of issues of particular relevance to industrial chemicals and the occupational setting, and hopefully to prompt further thinking and perhaps some new initiatives directed at the areas in question.

OBJECTIVE: Posttraumatic psychological stress may be associated with increases in somatic illness, including asthma, but the impact of the psychological sequelae of the September 11, 2001 terrorist attacks on physical illness has not been well documented. The authors assessed the relationship between the psychological sequelae of the attacks and asthma symptom severity and the utilization of urgent health care services for asthma since September 11. MATERIALS AND METHODS: The authors performed a random digit dial telephone survey of adults in the New York City (NYC) metropolitan area 6 to 9 months after September 11, 2001. Two thousand seven hundred fifty-five demographically representative adults including 364 asthmatics were recruited. The authors assessed self-reported asthma symptom severity, emergency room (ER) visits, and unscheduled physician office visits for asthma since September 11. RESULTS: After adjustment for asthma measures before September 11, demographics, and event exposure in multivariate models posttraumatic stress disorder (PTSD) were a significant predictor of self-reported moderate-to-severe asthma symptoms (OR = 3.4; CI = 1.2-9.4), seeking care for asthma at an ER since September 11 (OR = 6.6; CI = 1.6-28.0), and unscheduled physician visits for asthma since September 11 (OR = 3.6; CI = 1.1-11.5). The number of PTSD symptoms was also significantly related to moderate-to-severe asthma symptoms and unscheduled physician visits since September 11. Neither a panic attack on September 11 nor depression since September 11 was an independent predictor of asthma severity or utilization in multivariate models after September 11. CONCLUSIONS: PTSD related to the September 11 terrorist attacks contributed to symptom severity and the utilization of urgent health care services among asthmatics in the NYC metropolitan area.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14645777

El-Masry, EM and Abou-Donia, MB Journal/Life Sci. 73: 981-91.

It has been reported that functional expression of the multidrug resistance protein P-glycoprotein (P-gp) in E. coli is useful for screening P-gp substrates and inhibitors. In the present study, we have constructed by nitrosoguanidine and UV mutagenesis 28 leaky mutants of E. coli UT5600. These mutants are significantly susceptible to the toxic effect of known P-gp substrates and lipophilic cancer drugs. Mouse mdr1 was functionally expressed in the most permeable E. coli mutant (UTP17). Expression of P-gp in this mutant confers cross-resistance to mitomycin C, tegafur, daunorubicin, rhodamine 6G, tetraphenylphosphonium bromide and ciprofloxacin. To examine the reversal of P-gp expressed in this heterologous system, UTP17 cells expressing mouse mdr1 or lac permease as negative control were treated with various concentrations of mitomycin C with or without ascorbic acid. We found that ascorbic acid abrogated P-gp mediated multidrug resistance, suggesting that ascorbic acid
might be used in combination with anticancer drugs to reduce emergence of multidrug resistance. We also demonstrated that tomato lectin antagonized the inhibitory action of ascorbic acid. This study provide a heterologous system for mdr1 expression in E. coli leaky mutant that can be used as a system for the screening of P-gp inducers and inhibitors, since it is quick and simple.

(2003) Wheat gliadin promotes the interleukin-4-induced IgE production by normal human peripheral mononuclear cells through a redox-dependent mechanism.

Increased levels of serum IgE have been described in gliadin-intolerant patients; however, biological mechanisms implicated in this immunoglobulin production remained unknown. In this study, we demonstrated that in vitro crude gliadins and gliadin lysates (Glilys) promoted the IL-4-induced IgE production by human peripheral blood mononuclear cells (PBMC), indicating that the biological process related to gliadin intolerance and/or allergy may lead to IgE production in vivo. It was found that crude gliadin and Glilys potentiated, after 13 days of culture in a dose-dependent manner, IL-4-induced IgE production and, to a lesser extent, the IgG production, while they did not affect IgA or IgM productions. This promoting effect of gliadin and Glilys on the IL-4-induced activation of normal human PBMC was also observed on the early release (2 days) of the soluble fraction of CD23, suggesting its possible involvement in IgE potentiation. The promoting effect of crude gliadin and Glilys appeared to be indirect because they did not modify purified B-lymphocytes IgE production after IL-4 and anti-CD40 monoclonal antibody stimulation. In addition, as revealed by luminol-dependent chemiluminescence, we demonstrated that crude gliadin and Glilys promoted a substantial production of free radicals by normal human PBMC, treated or not with IL-4. This redox imbalance associated with an increased IgE production led us to evaluate the effect of pharmacological antioxidants (N-acetyl-cysteine (NAC) and Cu Zn-superoxide dismutase (SOD1)) on IgE production by human PBMC. The NAC and the intracellularly delivered SOD1 were found to suppress the IL-4+-crude gliadin or Glilys-induced IgE production by normal human PBMC. Taken together, these data indicated that gliadin specifically enhanced IL-4-induced IgE production by normal human PBMC, probably by the regulation of redox pathways, and that this 'pro-allergenic' effect could be counteracted by natural antioxidants: thiols and/or vectorized SOD1.

Islet-cell antigen 512 (IA-2) and phogrin (IA-2beta) are atypical members of the receptor protein tyrosine phosphatase (PTP) family that are characterized by a lack of activity against conventional PTP substrates. The physiological role(s) of these proteins remain poorly defined, although recent studies indicate that IA-2 may be involved in granule trafficking and exocytosis. To further understand their function, we have embarked upon developing low-molecular-mass inhibitors of IA-2 and IA-2beta. Previously, we have shown that a general PTP inhibitor, 2-(oxalylamino)benzoic acid (OBA), can be developed into highly selective and potent inhibitors of PTP1B. However, since wild-type IA-2 and IA-2beta lack conventional PTP activity, a novel strategy was designed whereby catalytically active species were generated by 'back-mutating' key non-consensus catalytic region residues to those of PTP1B. These mutants were then used as tools with which to test the potency and selectivity of OBA and a variety of its derivatives. Catalytically competent IA-2 and IA-2beta species were generated by 'back-mutation' of only three key residues (equivalent to Tyr(46), Asp(181) and Ala(217) using the human PTP1B numbering) to those of PTP1B. Importantly, enzyme kinetic analyses indicated that the overall fold of both mutant and wild-type IA-2 and IA-2beta was similar to that of classic PTPs. In particular, one derivative of OBA, namely 7-(1,1-dioxo-1 H -benzo[d]isothiazol-3-yloxymethyl)-2-(oxalylamino)-4,7-dihydro-5 H -thieno[2,3- c]pyran-3-carboxylic acid ('Compound 6' shown in the main paper), which inhibited IA-2beta((S762Y/Y898P/D933A)) (IA-2beta in which Ser(762) has been mutated to tyrosine, Tyr(898) to proline, and Asp(933) to alanine) with a K(i) value of approximately 8 microM, appeared ideal for future lead optimization. Thus molecular modelling of this classical, competitive inhibitor in the catalytic site of wild-type IA-2beta identified two residues (Ser(762) and Asp(933)) that offer the possibility for unique interaction with an appropriately modified 'Compound 6'. Such a compound has the potential to be a highly selective and potent active-site inhibitor of wild-type IA-2beta.

Donnay, A Journal/Environ Health Perspect. 111: A511-2; author reply A512.

(2003) [Use of the Bayes classification for the assessment of individual risk].
Dimitriev, DA, Dimitriev, AD and Vorontsova, GM Journal/Gig Sanit. 64-6.
Damodaran, TV, Jones, KH, Patel, AG and Abou-Donia, MB Journal/Biochem Pharmacol.  65: 2041-7.

We carried out a time-course study on the effects of a single intramuscular (i.m.) dose (0.5x LD(50)) of sarin (O-isopropyl methylphosphonofluoridate), also known as nerve agent GB, on the mRNA expression of acetylcholinesterase (AChE) in the brain of male Sprague-Dawley rats. Sarin inactivates the enzyme AChE which is responsible for the breakdown of the neurotransmitter acetylcholine (ACh), leading to its accumulation at ACh receptors and overstimulation of the cholinergic system. Rats were treated with 50 microg/kg of sarin (0.5x LD(50)) in 1 mL saline/kg and terminated at the following time points: 1 and 2 hr and 1, 3, and 7 days post-treatment. Control rats were treated with normal saline. Total RNA was extracted, and northern blots were hybridized with cDNA probes for AChE and 28S RNA (control). Poly-A RNA from both treated and control cortex was used for reverse transcription-polymerase chain reaction (RT-PCR)-based verification of the data from the northern blots. The results obtained indicate that a single (i.m.) dose of sarin (0.5x LD(50)) produced differential induction and persistence of AChE mRNA levels in different regions of the brain. Immediate induction of AChE transcripts was noted in the brainstem (126+/−6%), cortex (149+/−4%), midbrain (153+/−5%), and cerebellum (234+/−2%) at 1 hr. The AChE expression level, however, increased over time and remained elevated after a decline at 1 day in the previously shown more susceptible brainstem. The transcript levels remained elevated at a later time point (3 days) in the midbrain, after a dramatic decline at day 1 (110+/−2%). In the cortex, transcript levels came down to control values by day 1. The cerebellum also showed a decline of the elevated levels observed at 2 hr (275+/−2%) to control values by day 1. RT-PCR analysis of the AChE transcript at 30 min in the cortex showed an induction to 213+/−3% of the control level, confirming the expression pattern obtained by the northern blot data. The immediate induction followed by the complex pattern of the AChE mRNA time-course in the CNS may indicate that the activation of both cholinergic-related and unrelated functions of the gene plays an important role in the pathological manifestations of sarin-induced neurotoxicity.

(2003) Polymorphisms of paraoxonase (PON1) and their significance in clinical toxicology of organophosphates.
Paraoxonase (PON1) is an HDL-associated enzyme capable of hydrolyzing multiple substrates, including several organophosphorous insecticides and nerve agents, oxidized lipids, and a number of drugs or pro-drugs. Several polymorphisms in the paraoxonase (PON1) gene have been described, which have been shown to affect either the catalytic efficiency of hydrolysis or the expression level of PON1. This review discusses the relevance of these polymorphisms for modulating sensitivity to organophosphorous compounds. Animal studies characterizing the PON1 polymorphisms have demonstrated the relevance of PON1 in modulating OP toxicity and have indicated the importance of an individual's PON1 status (i.e., genotype and phenotype taken together) rather than genotyping alone. Nevertheless, direct confirmation in humans of the relevance of PON1 status in conferring susceptibility to OP toxicity is still elusive. Recent studies examining the involvement of PON1 status in determining OP susceptibility of Gulf War veterans, sheep dippers, and individuals poisoned with chemical warfare agents represent a step in the right direction, but more studies are needed, with better documentation of both the level of exposure and the consequences of exposure.

Ciccone, DS and Natelson, BH Journal/Psychosom Med. 65: 268-75.

OBJECTIVE: Evidence of comorbidity among unexplained illness syndromes raises the possibility that all are variants of a single functional disorder, leading some to suggest that separate case definitions for chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivity (MCS) may be unnecessary. Our objective was to determine whether discrete diagnostic labels provide useful information about physical functioning, symptom severity, and risk of psychiatric illness. METHODS: The sample consisted of 163 consecutive female referrals with CFS enrolled at a tertiary clinic. Each participant was retrospectively assigned to one of four groups: CFS only, CFS FM, CFS/MCS, and CFS/FM/MCS. At enrollment, participants gave their history, underwent a physical examination and a standardized psychiatric interview (Diagnostic Interview Schedule), and answered self-report questionnaires. RESULTS: Additional unexplained syndromes were prevalent: 37% met criteria for FM, and 33% met criteria for MCS. With the exception of FM-related pain and disability, there were few differences between the CFS only and CFS with comorbid illness groups. Patients with additional illness were more likely to have major depression and a higher risk of psychiatric morbidity compared with patients in the CFS only group (p <.01). Rates of lifetime depression increased from 27.4% in the CFS only group to 52.3% in the CFS FM group, 45.2% in the CFS/MCS group, and 69.2% in the CFS/FM/MCS group. CONCLUSIONS: The prevalence of comorbid illness in the present CFS sample and the failure to find widespread differences in symptom severity can be seen as support for the single syndrome hypothesis. On the other hand, the existence of discrete syndromes could not be ruled out because of reliable differences between CFS and
CFS/FM. Increasing comorbidity was associated with a corresponding increase in risk of major depression.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12651994

(2003) **Women living with environmental illness.**

We used a case study approach to explore the experiences of 4 women who live with environmental illness (EI). From the unstructured interviews we found a variety of themes that pointed to the complexity of EI and its severe impact on the lives of these women, their families, and their significant others. The methodology was guided by an ecofeminist approach, which enabled a critical analysis of the data to move beyond the personal to the broader sociopolitical forces shaping society. We identified the following themes from the women's stories: indirect exposure to incitants through people with whom these women come in close physical contact; the phenomenon of burden of proof, meaning that these women are forced to explain and legitimize their illness on a continuous basis; taking refuge from a hostile environment in social isolation to a more controlled environment, not as a matter of choice, but because of the severity of the illness; and, finally, a change in value system was integral to the entire process of living with EI.

(2003) **[Hygienic regulation of environmental air pollution with consideration of epidemiological data].**
Chiburaev, VI, Privalova, LI, Katsnel'son, BA, Kuz'min, SV, Nikonov, BI, Gurvich, VB, Voronin, SA, Kosheleva, AA and Malykh, OL Journal/Gig Sanit. 53-5.

The authors hold that the maximum allowable concentrations (MAC) established in Russia for some ambient air pollutants can adversely affect human health and that they are worthy of reconsideration. This opinion is based on the published results of epidemiological studies of Western investigators and on the authors' own data obtained from the analysis by the time series method for a relationship of daily variations of dust or gaseous ambient air pollution to the so-called acute mortality or for that of the variations to respiratory symptoms and to the values of the maximum expiratory flow rate in preschool with or without respiratory abnormalities in their history; from the cross analysis of an association of the characteristics of atmospheric contamination in 13 urban areas with the prevalence of chronic respiratory diseases in junior schoolchildren, which was established by a special questionnaire. Particular emphasis should be laid on the reconsideration of not only established values, but mainly on the principles in laying down MAC for dust particles. The Western practice in
measuring and evaluating risks separately for fractions of particles of varying sizes should be assessed for its use in Russian conditions; however, the authors' experience argues for this practice.


Reversible phosphorylation is recognized to be a major mechanism for the control of intracellular events in eukaryotic cells. From a human fetal brain cDNA library, we isolated a cDNA clone encoding a novel dual specificity protein phosphatase, which showed 88% identity with previously reported mouse LMW-DSP3 at the amino acid level. The deduced protein had a single dual-specificity phosphatase catalytic domain, and lacked a cdc25 homology domain. LMW-DSP3 was expressed in the heart, lung, liver, and pancreas, and the expression level in the pancreas was highest. The LMW-DSP3 gene was located in human chromosome 2q32, and consisted of five exons spanning 21kb of human genomic DNA. LMW-DSP3 fused to GST showed phosphatase activity towards p-nitrophenyl phosphate which was optimal at pH 7.0 and 40 degrees C, and the activity was enhanced by Ca(2+) and Mn(2+). The phosphatase activity of LMW-DSP3 was inhibited by orthovanate. LMW-DSP3 showed phosphatase activity toward oligopeptides containing pSer/Thr and pTyr, indicating that LMW-DSP3 is a protein phosphatase with dual substrate specificity.


OBJECTIVE: To review the available literature on the subject of fungi (molds) and their potential impact on health and to segregate information that has scientific validity from information that is yet unproved and controversial. DATA SOURCES: This review represents a synthesis of the available literature in this area with the authors' collective experience with many patients presenting with complaints of mold-related illness. STUDY SELECTION: Pertinent scientific investigation on toxic mold issues and previously published reviews on this and related subjects that met the educational objectives were critically reviewed. RESULTS: Indoor mold growth is variable, and its discovery in a building does not necessarily mean occupants have been exposed. Human response to fungal antigens may induce IgE or IgG antibodies that connote prior exposure but not necessarily a symptomatic state. Mold-related disease has been discussed in the framework of noncontroversial and controversial disorders.
CONCLUSIONS: When mold-related symptoms occur, they are likely the result of transient irritation, allergy, or infection. Building-related illness due to mycotoxicosis has never been proved in the medical literature. Prompt remediation of water-damaged material and infrastructure repair should be the primary response to fungal contamination in buildings.


Besides Tullio’s phenomenon, resulting from anatomic changes in the labyrinth, a hypersensitivity to acoustic stimuli of the saccular structures appears to be the underlying cause of the vestibular responses detected in some patients. In order to evaluate the incidence of vestibular symptoms triggered by acute exposure to auditory stress (disco music), 40 subjects aged between 18 and 26 years, with no audiological and vestibular disorders, were submitted to otoneurologic tests. Subjects were exposed to disco music [intensity 128 dB (C)], for 3 hours. Tests have been carried out before and immediately after exposure. Canalar and macular functions have been evaluated using vestibular investigation techniques and vestibular evoked myogenic potentials. When compared to baseline data, post-exposure test results did not reveal any canalar damage. Pre- and post-exposure recordings of the vestibular-oculomotor reflex threshold have shown no significant changes. Conversely, post-stimulus recordings have shown a significant increase in the amplitude of the vestibular evoked myogenic potential response, thus indicating a possible irritative involvement of the macular receptor. This result suggests a direct action upon the receptor by acoustic stimulation which could, therefore, be the underlying cause of vestibular symptoms reported by patients following exposure to sufficiently intense acoustic stimuli. Prior to this study, a questionnaire concerning the relationship between habitual disco visiting and audio-vestibular symptoms has been completed by 310 students at the University of Catanzaro. This survey revealed a significant incidence of vestibular symptoms due to acoustic stress (Tullio’s phenomenon) which led us to hypothesise that balance disorders due to auditory stress are much more frequent than commonly held, particularly since, in many cases, diagnoses is unknown or not easy due to the difficult procedures by which these conditions are diagnosed.

(2003) On the definition of complementary, alternative, and integrative medicine: societal mega-stereotypes vs. the patients’ perspectives.
Much confusion exists regarding the definitions of complementary, alternative, and integrative medicine. Whereas 'complementary and alternative medicine' (CAM) is used to describe a variable set of diagnostic and therapeutic modalities considered as non-conventional, 'integrative medicine' is commonly used to describe the combination of allopathy and CAM. CAM, however, is nothing more than a categorical label that subsumes numerous therapeutic modalities generally sharing few commonalities. Creating a unique category out of such diversity has lead to misunderstanding and skepticism. From the physician's stand-point, this can generate numerous stereotypes, prejudices, and misconceptions that may compromise the therapeutic relationship, impede compliance, and lead to treatment failure. To help avoid this dangerous pitfall, we propose a distinctly new operational definition for CAM; one that shifts the focus from the traditional, population-based approach to a definition that focuses on the individual. This paper outlines various definitions of CAM and discusses their relative strengths and weaknesses for the 21st century practice of medicine. It is our conclusion that individual patients, rather than society, should be the frame of reference and defining source for what constitutes integrative medicine and CAM.

(2003) [From industrial hygiene and toxicology to environmental hygiene and toxicology: problems and prospects].

BACKGROUND: Low-dose exposures to mixtures of substances have received increasing interest and they involve many different occupational and environmental situations. The presence in the population (working and general) of groups of susceptible individuals is an important public health issue that poses new challenges to science and society. OBJECTIVES: To discuss the evolution from traditional occupational hygiene and toxicology to the new environmental (general and occupational) hygiene and toxicology. RESULTS: Environmental hygiene and toxicology have remarkably improved analytical tools available to solve most of the analytical issues posed by the present exposure scenario. Biomarkers of low-dose exposure, early effects and individual susceptibility are being intensively investigated. CONCLUSIONS: The challenge in this field for the coming years appears to be not the analytical but the medical and ethical implications.

In this review we summarize the findings of a two-phase study of the prevalence, symptomatology, and etiology of multiple chemical sensitivities (MCS). We also explore possible triggers, the potential linkage between MCS and other disorders, and the lifestyle alterations produced by MCS. The first phase of the study consisted of a random sampling of 1,582 individuals from the Atlanta, Georgia, metropolitan area to determine the reported prevalence of a hypersensitivity to common chemicals. In this phase, 12.6% of the sample reported a hypersensitivity. Further questioning of individuals with a hypersensitivity indicated that 13.5% (1.8% of the entire sample) reported losing their jobs because of their hypersensitivity. The second phase was a follow-up questioning of the respondents who initially reported hypersensitivity. In this phase, we found that individuals with hypersensitivity experience a variety of symptoms and triggers. A significant percentage (27.5%) reported that their hypersensitivity was initiated by an exposure to pesticides, whereas an equal percentage (27.5%) attributed it to solvents. Only 1.4% had a history of prior emotional problems, but 37.7% developed these problems after the physical symptoms emerged. This suggests that MCS has a physiologic and not a psychologic etiology.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12948889

Campbell, AW, Thrasher, JD, Madison, RA, Vojdani, A, Gray, MR and Johnson, A

Adverse health effects of fungal bioaerosols on occupants of water-damaged homes and other buildings have been reported. Recently, it has been suggested that mold exposure causes neurological injury. The authors investigated neurological antibodies and neurophysiological abnormalities in patients exposed to molds at home who developed symptoms of peripheral neuropathy (i.e., numbness, tingling, tremors, and muscle weakness in the extremities). Serum samples were collected and analyzed with the enzyme-linked immunosorbent assay (ELISA) technique for antibodies to myelin basic protein, myelin-associated glycoprotein, ganglioside GM1, sulfatide, myelin oligodendrocyte glycoprotein, alpha-B-crystallin, chondroitin sulfate, tubulin, and neurofilament. Antibodies to molds and mycotoxins were also determined with ELISA, as reported previously. Neurophysiologic evaluations for latency, amplitude, and velocity were performed on 4 motor nerves (median, ulnar, peroneal, and tibial), and for latency and amplitude on 3 sensory nerves (median, ulnar, and sural). Patients with documented, measured exposure to molds had elevated titers of antibodies (immunoglobulin [Ig]A, IgM, and IgG) to neural-specific antigens. Nerve conduction studies revealed 4 patient groupings: (1) mixed sensory-motor polyneuropathy (n = 55, abnormal), (2) motor neuropathy (n = 17, abnormal), (3) sensory neuropathy (n = 27, abnormal), and (4) those with symptoms but no neurophysiological abnormalities (n = 20, normal controls). All groups showed significantly increased autoantibody titers for
all isotypes (IgA, IgM, and IgG) of antibodies to neural antigens when compared with
500 healthy controls. Groups 1 through 3 also exhibited abnormal neurophysiologic
findings. The authors concluded that exposure to molds in water-damaged buildings
increased the risk for development of neural autoantibodies, peripheral neuropathy,
and neurophysiologic abnormalities in exposed individuals.

(2003) Redox regulation of heat shock protein expression in aging and
neurodegenerative disorders associated with oxidative stress: a nutritional
approach.
Calabrese, V, Scapagnini, G, Colombrita, C, Ravagna, A, Pennisi, G, Giuffrida Stella,
AM, Galli, F and Butterfield, DA Journal/Amino Acids. 25: 437-44.

Oxidative stress has been implicated in mechanisms leading to neuronal cell injury in
various pathological states of the brain. Alzheimer's disease (AD) is a progressive
disorder with cognitive and memory decline, speech loss, personality changes and
synapse loss. Many approaches have been undertaken to understand AD, but the
heterogeneity of the etiologic factors makes it difficult to define the clinically most
important factor determining the onset and progression of the disease. However,
increasing evidence indicates that factors such as oxidative stress and disturbed
protein metabolism and their interaction in a vicious cycle are central to AD
pathogenesis. Brains of AD patients undergo many changes, such as disruption of
protein synthesis and degradation, classically associated with the heat shock
response, which is one form of stress response. Heat shock proteins are proteins
serving as molecular chaperones involved in the protection of cells from various forms
of stress. Recently, the involvement of the heme oxygenase (HO) pathway in
anti-degenerative mechanisms operating in AD has received considerable attention, as
it has been demonstrated that the expression of HO is closely related to that of amyloid
precursor protein (APP). HO induction occurs together with the induction of other HSPs
during various physiopathological conditions. The vasoactive molecule carbon
monoxide and the potent antioxidant bilirubin, products of HO-catalyzed reaction,
represent a protective system potentially active against brain oxidative injury. Given the
broad cytoprotective properties of the heat shock response there is now strong interest
in discovering and developing pharmacological agents capable of inducing the heat
shock response. Increasing interest has been focused on identifying dietary compounds
that can inhibit, retard or reverse the multi-stage pathophysiological events underlying
AD pathology. Alzheimer's disease, in fact, involves a chronic inflammatory response
associated with both brain injury and beta-amyloid associated pathology. All of the
above evidence suggests that stimulation of various repair pathways by mild stress has
significant effects on delaying the onset of various age-associated alterations in cells,
tissues and organisms. Spice and herbs contain phenolic substances with potent
antioxidative and chemopreventive properties, and it is generally assumed that the
phenol moiety is responsible for the antioxidant activity. In particular, curcumin, a
powerful antioxidant derived from the curry spice turmeric, has emerged as a strong
inducer of the heat shock response. In light of this finding, curcumin supplementation has been recently considered as an alternative, nutritional approach to reduce oxidative damage and amyloid pathology associated with AD. Here we review the importance of the heme oxygenase pathway in brain stress tolerance and its significance as an antidegenerative mechanism potentially important in AD pathogenesis. These findings have offered new perspectives in medicine and pharmacology, as molecules inducing this defense mechanism appear to be possible candidates for novel cytoprotective strategies. In particular, manipulation of endogenous cellular defense mechanisms such as the heat shock response, through nutritional antioxidants or pharmacological compounds, represents an innovative approach to therapeutic intervention in diseases causing tissue damage, such as neurodegeneration. Consistent with this notion, maintenance or recovery of the activity of vitagenes, such as the HO gene, conceivably may delay the aging process and decrease the occurrence of age-related neurodegenerative diseases.


Oxidative stress has been implicated in mechanisms leading to neuronal cell injury in various pathological states of the brain. Alzheimer's disease (AD) is a progressive disorder with cognitive and memory decline, speech loss, personality changes and synapse loss. Many approaches have been undertaken to understand AD, but the heterogeneity of the etiologic factors makes it difficult to define the clinically most important factor determining the onset and progression of the disease. However, increasing evidence indicates that factors such as oxidative stress and disturbed protein metabolism and their interaction in a vicious cycle are central to AD pathogenesis. Brains of AD patients undergo many changes, such as disruption of protein synthesis and degradation, classically associated with the heat shock response, which is one form of stress response. Heat-shock proteins are proteins serving as molecular chaperones involved in the protection of cells from various forms of stress. Recently, the involvement of the heme oxygenase (HO) pathway in anti-degenerative mechanisms operating in AD has received considerable attention, as it has been demonstrated that the expression of HO is closely related to that of amyloid precursor protein (APP). HO induction, which occurs together with the induction of other HSPs during various physiopathological conditions, by generating the vasoactive molecule carbon monoxide and the potent antioxidant bilirubin, represents a protective system potentially active against brain oxidative injury. Given the broad cytoprotective properties of the heat shock response there is now strong interest in discovering and developing pharmacological agents capable of inducing the heat shock response. Recently, increasing interest has been focused on identifying dietary compounds that can inhibit, retard or reverse the multi-stage pathophysiological events underlying AD pathology. Alzheimer's disease, in fact, involves a chronic inflammatory response.
associated with both brain injury and beta-amyloid associated pathology. Spice and herbs contain phenolic substances with potent antioxidative and chemopreventive properties, and it is generally assumed that the phenol moiety is responsible for the antioxidant activity. In particular, curcumin, a powerful antioxidant derived from the curry spice turmeric, has emerged as a strong inducer of the heat shock response. In light of this finding, curcumin supplementation has been recently considered as an alternative, nutritional approach to reduce oxidative damage and amyloid pathology associated with AD. Here we review the importance of the heme oxygenase pathway in brain stress tolerance and its significance as antidegenerative mechanism operating in AD pathogenesis. We also discuss the role that exogenous antioxidant supplementation, conceivably, could play in AD in combating oxidative damage and compensating for the decreased level of endogenous antioxidants. Conceivably, dietary supplementation with vitamin E or with polyphenolic agents, such as curcumin and its derivatives, can forestall the development of AD, consistent with a major "metabolic" component to this disorder. Such an outcome would provide optimism that the signs and symptoms of this devastating brain disorder of aging may be largely delayed and/or modulated.

(2003) Rapid recovery from acoustic trauma: chicken soup, potato knish, or drug interaction?

OBJECTIVES: To describe the phenomenology and consider possible mechanisms mediating rapid and unexpected recovery from acoustic trauma after ingestion of a food substance (potato knish). STUDY DESIGN: Single subject with repeated test measures. SETTING: Regional Veteran's Administration Medical Center, tertiary care medical center. METHODS: Pure-tone audiometry and distortion product otoacoustic emissions (DPOAEs) performed at 6 days, 21 days, and 1 year postexposure. RESULTS: Medical treatment with corticosteroids and a diuretic alone failed to improve auditory function and related symptoms (tinnitus and aural fullness) over a 2-week period. Rapid recovery of auditory function (dramatic improvement in pure tone thresholds; reappearance of DPOAEs) and abatement of related symptoms directly followed physiologic reactions from ingesting a food substance. CONCLUSIONS: Rapid recovery from acoustic trauma was temporally correlated with urodynamic and cardiovascular reactions from ingesting food containing sulfite preservative, a substance to which the individual was allergic. Factors that may have contributed to recovery of function include massive diuresis, increased heart rate, release of biochemical mediators, mediator-induced vasodilation, and changes in vascular or cell membrane permeability. Establishing relationships that lead to recovery of function from acoustic trauma may facilitate research and aid in the development of new treatment options for this condition.

1. The aim of the present study was to examine the effects of long-term nitric oxide (NO) blockade on contractions of the rat ileum induced by muscarinic agonists. 2. Male Wistar rats received the NO synthesis inhibitor NG-nitro-l-arginine methyl ester (l-NAME; 20 mg/rat per day) in drinking water for 7, 15, 30 and 60 days. Concentration-responses curves to methacholine and carbachol were obtained and pEC50 values were calculated. Saturation binding assays were performed in membranes prepared from rat ileum after 60 days of l-NAME treatment and the dissociation constant (KD) and maximal number of binding sites (Bmax) were determined by Scatchard analysis. 3. The NO synthase activity of the ileum was markedly reduced in all l-NAME-treated groups. At 60 days after l-NAME treatment, a significant increase in the potency of methacholine (fourfold) and carbachol (threelfold) was observed. In binding studies, we found a significant increase in Bmax for [3H]-quinuclidinyl benzilate of approximately 57% in the l-NAME treated group without any significant change in KD values. The contractile response to methacholine was not modified by the soluble guanylate cyclase inhibitor 1H-[1,2,4]oxadiazolo-[4,3-a]quinoxalin-1-one (3 micro mol/L). No morphological alterations in the rat ileum were observed in l-NAME-treated rats. 4. Our findings suggest that treatment with l-NAME for 60 days induces a marked increase in the potency of methacholine and carbachol, as well as an increase in receptor number in the rat ileum.


OBJECTIVE: Organophosphates are used as pesticides, herbicides, and chemical warfare agents. Treatment of organophosphate poisoning is with intravenous atropine and pralidoxime in addition to supportive care. This study determined the efficacy of oral agents in preventing death from organophosphate poisoning. METHODS: The organophosphate paraaxon (8 mg/kg) was used in a murine model with lethality at four and 24 hours as an end point. For oral treatment, 15 male Balbc mice were given either atropine sulfate (4 mg/kg), or a combination of atropine sulfate (4 mg/kg) with pralidoxime (100 mg/kg), by oral gavage. A control group of 22 mice received water by oral gavage. Chi-square analysis was used to compare results in the different groups. RESULTS: Of the control group, six of 22 survived to four hours after paraaxon
exposure. Of the exposed animals treated with oral atropine, eight of 15 survived to four hours. Of the exposed animals treated with a combination of atropine and pralidoxime, 13 of 15 survived to four hours. All animals surviving to four hours survived to 24 hours. The increased survival of animals in the atropine group relative to the control group was not significant (p = 0.09). Survival was significant in the group treated with atropine and pralidoxime relative to atropine alone (p = 0.02) and to the control group (p = 0.0002). All treated mice surviving at four hours were alive at 24 hours. CONCLUSIONS: Both oral atropine and a combination of oral atropine and pralidoxime improved survival, and combination therapy achieved statistical significance. Generalization of this result to other organophosphate pesticides, other doses of paraoxon, and other species cannot be made without further investigations.


The importance of the isoform CYP2E1 of the human cytochrome P-450 superfamily of enzymes for occupational and environmental medicine is derived from its unique substrate spectrum that includes a number of highly important high-production chemicals, such as aliphatic and aromatic hydrocarbons, solvents and industrial monomers (i.a. alkanes, alkenes, aromatic and halogenated hydrocarbons). Many polymorphic genes, such as CYP2E1, show considerable differences in allelic distribution between different human populations. The polymorphic nature of the human CYP2E1 gene is significant for inter-individual differences in toxicity of its substrates. Since the substrate spectrum of CYP2E1 includes many compounds of basic relevance to industrial toxicology, a rationale for metabolic interactions of different CYP2E1 substrates is provided. In-depth research into the inter-individual phenotypic differences of human CYP2E1 enzyme activities was enabled by the recognition that the 6-hydroxylation of the drug chlorzoxazone is mediated by CYP2E1. Studies on CYP2E1 phenotyping have pointed to inter-individual variations in enzyme activities. There are consistent ethnic differences in CYP2E1 enzyme expression, mostly demonstrated between European and Japanese populations, which point to a major impact of genetic factors. The most frequently studied genetic polymorphisms are the restriction fragment length polymorphisms PstI/ Rsal (mutant allele: CYP2E1*5B) located in the 5'-flanking region of the gene, as well as the DraI polymorphism (mutant allele: CYP2E1*6) located in intron 6. These polymorphisms are partly related, as they form the common allele designated CYP2E1*5A. Striking inter-ethnic differences between Europeans and Asians appear with respect to the frequencies of the CYP2E1*5A allele (only approximately 5% of Europeans are heterozygous, but 37% of Asians are, whilst 6% of Asians are homozygous). Available studies indicate a wide variation in human CYP2E1 expression, which are very likely based on complex gene-environment interactions. Major inter-ethnic differences are
apparent on the genotyping and the phenotyping levels. Selected cases are presented where inter-ethnic variations of CYP2E1 may provide likely explanations for unexplained findings concerning industrial chemicals that are CYP2E1 substrates. Possible consequences of differential inter-individual and inter-ethnic susceptibilities are related to individual expressions of clinical symptoms of chemical toxicity, to results of biological monitoring of exposed workers, and to the interpretation of results of epidemiological or molecular-epidemiological studies.

(2003) Are specific hydrolases bioscavengers for defense against organophosphorus nerve agents?

(2003) Threonine deprivation rapidly activates the system A amino acid transporter in primary cultures of rat neurons from the essential amino acid sensor in the anterior piriform cortex.

Omnivores show recognition of essential (indispensable) amino acid deficiency by changing their feeding behavior within 20 min, yet the cellular mechanisms of amino acid sensation in eukaryotes are poorly understood. The anterior piriform cortex (APC) of the brain in rats or its analog in birds likely houses the in vivo amino acid chemosensor. Because amino acid transporters adapt rapidly to essential amino acid deficiency in several cell models, we hypothesized that activation of electrogenic amino acid transport in APC neurons might contribute to the function of the amino acid sensor. We evaluated transport systems in primary cultures of neurons from the APC, hippocampus and cerebellum, or glia, incubated in complete or threonine-devoid (deficient) medium. After 10 min in deficient medium, uptake of threonine or a system A-selective substrate, methyl amino-isobutyric acid, was increased 60% in APC neurons only (P < 0.05). These results demonstrated upregulation of system A, an electrogenic amino acid-sodium symporter. This depletion-induced activation required sodium, intact intracellular trafficking, and phosphorylation of signal transduction-related kinases. Efflux studies showed that other transporter types were functional in the APC; they appeared to be altered dynamically in threonine-deficient cells in response to rapid increases in system A activity. The present data provided support for the chemical sensitivity of the APC and its role as the brain area housing the indispensable amino acid chemosensor. They also showed a region-specific, phosphorylation-dependent activation of the system A transporter in the brain in response to threonine deficiency.
(2003) **Chemical sensitivity in symptomatic Cambodia veterans.**  
Bischoff, EW, Soetekouw, PM, De Vries, M, Scheepers, PT, Bleijenberg, G and van der Meer, JW  
Journal/Arch Environ Health.  58:  740-5.

Following their participation in a United Nations peacekeeping operation in Cambodia (1992-1993), Dutch veterans complained of symptoms similar to those reported by Gulf War veterans. The authors conducted a matched case-control study to evaluate 76 symptomatic and 32 matched asymptomatic Cambodia veterans on the basis of data collected by postal questionnaire. The number of symptomatic veterans who reported having used insect repellants that contained N,N-diethyl-meta-toluamide (DEET) during the mission in Cambodia was significantly higher, compared with asymptomatic veterans. The percentage of veterans who reported feeling ill following brief exposures to chemicals such as paint or pesticides was equal in both groups, but the percentage was low compared with the results of other studies of Multiple Chemical Sensitivity Syndrome. The current study was limited by self-report and time delay (potential recall bias) between deployment to Cambodia and the time of survey. Nevertheless, the study results did not support the hypothesis that symptoms in the total group of Cambodia veterans could be related to Multiple Chemical Sensitivity Syndrome.


(2003) **Gas discharge visualization evaluation of ultramolecular doses of homeopathic medicines under blinded, controlled conditions.**  
Bell, IR, Lewis, DA, 2nd, Brooks, AJ, Lewis, SE and Schwartz, GE  

OBJECTIVES: To determine the feasibility of using a computerized biophysical method, gas discharge visualization (GDV), to differentiate ultramolecular doses of homeopathic remedies from solvent controls and from each other. DESIGN: Blinded, randomized assessment of four split samples each of 30c potencies of three homeopathic remedies from different kingdoms, for example, Natrum muriaticum (mineral), Pulsatilla (plant), and Lachesis (animal), dissolved in a 20% alcohol-water solvent versus two different control solutions (that is, solvent with untreated lactose sucrose pellets and unsuccussed solvent alone). PROCEDURES: GDV measurements, involving application of a brief electrical impulse at four different voltage levels, were performed over 10 successive images on each of 10 drops from each bottle (total 400 images per test solution per voltage). The dependent variables were the quantified image characteristics of the liquid drops (form coefficient, area, and brightness) from the resultant burst of electron-ion emission and optical radiation in the
visual and ultraviolet ranges. RESULTS: The procedure generated measurable images at the two highest voltage levels. At 17 kV, the remedies exhibited overall lower image parameter values compared with solvents (significant for Pulsatilla and Lachesis), as well as differences from solvents in fluctuations over repeated images (exposures to the same voltage). At 24 kV, other patterns emerged, with individual remedies showing higher or lower image parameters compared with other remedies and the solvent controls. CONCLUSIONS: GDV technology may provide an electromagnetic probe into the properties of homeopathic remedies as distinguished from solvent controls. However, the present findings also highlight the need for additional research to evaluate factors that may affect reproducibility of results.


OBJECTIVES: To identify areas that classical homeopathic practitioners would want to see evaluated in a patient self-report questionnaire sensitive to change during constitutional treatment. DESIGN: Open-ended, written practitioner questionnaire, analyzed using inductive content analysis. SETTINGS/LOCATION: Two classical homeopathic meetings held in the western United States. SUBJECTS: Homeopathic practitioners attending the above professional meetings and volunteering to complete the questionnaire in response to announcements prior to sessions. DATA COLLECTION METHODS: Practitioners completed a demographic questionnaire and answered an open-ended question inquiring for changes about which to ask people undergoing classical homeopathic constitutional treatment. RESULTS: The categories that the 38 homeopaths identified included changes in: (1) emotions; (2) mentation; (3) specific physical functioning; (4) general physical changes; (5) perception of self; (6) relationships; (7) spirituality; (8) lifestyle; (9) energy; (10) dream content and tone; (11) well-being; (12) perceptions by others; (13) life relationships; (14) a sense of freedom or feeling less "stuck"; (15) sleep; (16) coping; (17) ability to adapt; (18) creativity; and (19) recall of past experiences. Sixteen percent (16%) of participants added more in-depth description of the nature of changes across categories (i.e., a rhythmical process of innovation and flux). CONCLUSIONS: The findings are consistent with the systemic orientation of classical homeopathic philosophy to evaluate and treat the patient as a whole. Taken together, the results support the need for development of new, multidimensional outcome measures for clinical research in homeopathy beyond the disease-specific and health-related quality-of-life scales available from conventional medical research.
Barnes, RJ Journal/Crisp Data Base National Institutes of Health.
DESCRIPTION (provided by applicant): The goal of the proposed research is to couple a compact tunable ultraviolet (UV) laser system with a compact jet-REMPI time-of-flight mass spectrometer in order to provide a fieldable system for real-time concentration measurements of vapors from volatile hazardous species over contaminated sites. By allowing rapid vapor phase measurements in a matter of seconds, this technique provides real-time continuous monitoring of hazardous waste site remediation progress, and facilitates rapid mapping of waste distribution within a site, without the need for lengthy excavation and analysis of multiple soil samples. In addition, the time-varying exposure of neighboring communities to hazardous air pollutants out-gassing from the site can be monitored as out-gassing rates within the site change due to environmental conditions and waste plume migration. The jet-REMPI technique has already proven a powerful technique for measuring a variety of hazardous air pollutants with excellent sensitivity and chemical specificity in the laboratory. By coupling molecular mass measurement with optical spectroscopy, the technique can provide accurate measurements even in complex mixtures of multiple pollutants such as those found in real-world sites. The Phase I targets of his project will take this promising technology from the laboratory and yield a device that can make meaningful field measurements.


(2003)  [Ill due to amalgam? 10 rules for managing the symptomatic patient].

Over the past two decades, mercury released by amalgam fillings has been held responsible for a number of mental and somatic health complaints. However, a systematic relation between increased mercury levels and the severity of the reported symptoms has never been demonstrated in any of the present well-controlled multidisciplinary studies. These studies, however, have found a high prevalence of mental disorders, especially somatization syndromes, among patients with self-diagnosed "amalgam illness". Additionally, our own studies indicate that amalgam anxiety is often merely one aspect of a general environmental anxiety. Overall, the present findings suggest a psychological etiology for amalgam-related complaints. Our psychosomatic model of "amalgam illness" integrates external factors, individual predispositions and specific processes of perception, awareness, evaluation and
attribution. Practical management strategies for primary care physicians can be derived from this model.

-----------------------------------------------------------------------------------------------


Endosulfan and malathion are organochlorine and organophosphate insecticides, respectively. The toxicity of both the insecticides are well known on non-target organisms. Both endosulfan and malathion are reported to suppress humoral as well as cellular immune responses. We investigated the possible effect of both these insecticides on lipid peroxidation, nitrite production and TNF-alpha generation in rat peritoneal macrophages under in vitro conditions. Rat peritoneal cells were collected and cultured with or without insecticides and relevant stimulants for lipid peroxidation, generation of nitric oxide and TNF-alpha. FeSO(4) was used as an inducer for lipid peroxidation and LPS was used to induce nitric oxide synthase and release of TNF-alpha. Lipid peroxidation was assayed by estimating MDA; nitric oxide was determined by estimating nitrite and TNF-alpha by using an assay kit in culture supernatants. Both endosulfan and malathion had no effect on lipid peroxidation. Endosulfan did not have any influence on nitrite production, but suppressed the LPS-induced TNF-alpha generation. Malathion, however, showed a direct suppression on nitrite production and suppression of LPS-induced TNF-alpha generation. This study suggests that functional aberrations of macrophages may contribute significantly to the immunomodulation reported for these insecticides.

-----------------------------------------------------------------------------------------------


-----------------------------------------------------------------------------------------------

BACKGROUND: A subset of drug-intolerant patients show a marked propensity to react to several chemically unrelated antibacterial drugs. This condition is termed multiple drug allergy syndrome (MDAS). The pathogenesis of MDAS is still unclear. A possible mechanism is that a nonspecific patient-related factor leading to direct histamine release from mast cells and basophils is involved. We investigated whether a patient-related facilitating factor such as the clinically unapparent presence of circulating histamine-releasing factors may represent a nonspecific mechanism underlying drug-induced histamine release in patients with MDAS. METHODS: 38 otherwise healthy adults with a history of acute urticaria following the ingestion of antibacterial drugs [18 subjects with MDAS (patients) and 20 monosensitive subjects (drug-allergic controls) on the basis of both clinical history and single-blind peroral challenges with alternative substances] and 20 subjects without a history of drug allergy (normal controls) underwent an autologous serum skin test (ASST). IgE specific for beta-lactams was measured in sera from 25 subjects (11 patients and 14 drug-allergic controls) with a history of amoxicillin intolerance. Sera from 13 patients and 5 drug-allergic controls (all positive on ASST) were used in the in vitro histamine release assay using basophils from 3 normal donors. RESULTS: 17 of 18 patients (94%) versus 8 of 20 drug-allergic controls (40%) showed an unequivocal wheal-and-flare reaction on ASST (p < 0.05). Skin reactions were generally more intense in the patient group. In one MDAS patient, the ASST was not assessable due to dermographism. No normal control was positive on ASST. Sera from 3 of 13 patients (23%) versus 0 of 6 drug-allergic controls (not significant) induced significant histamine release from basophils of normal donors. IgE specific for beta-lactams was detected in sera from 1 of 11 patients (9%) versus 5 of 14 drug-allergic controls (36%) (not significant). CONCLUSION: Most patients with MDAS and more than one third of subjects with a history of hypersensitivity to a single antibacterial drug were characterized by the presence of circulating histamine-releasing factors. Such factors might play a role in drug-induced adverse reactions observed in these patients.


Injection of the glutamate agonist N-methyl-D-aspartate (NMDA) into the vitreous body of rats resulted in severe degeneration of neurons in the retina, with a loss of 81% of ganglion cells and 43% of non-ganglion cells. The cocktail EM-X is a novel antioxidant drink derived from ferment of unpolished rice, papaya and sea-weeds with effective
microorganisms (EM-X). In animals treated with an intraperitoneal injection of EM-X, the loss of ganglion cells was reduced to 55% and that of non-ganglion cells to 34% when compared to untreated NMDA-injected retinas. Cell degeneration resulting from NMDA excitotoxicity, is thought to be mediated via oxidative stress mechanisms. The neuroprotective effect of the EM-X in this system is therefore likely to be due, at least in part, to its flavonoids, saponins, vitamin E and ascorbic content.


Sickness absenteeism caused by musculoskeletal disorders (MSDs) is a persistent and costly occupational health challenge. In a prospective controlled trial, we compared the effects on sickness absenteeism of a more proactive role for insurance case managers as well as workplace ergonomic interventions with that of traditional case management. Patients with physician-diagnosed MSDs were randomized either to the intervention group or the reference group offered the traditional case management routines. Participants filled out a comprehensive questionnaire at the initiation of the study and after 6 months. In addition, administrative data were collected at 0.6, and 12 months after the initiation of the project. For the entire 12-month period, the total mean number of sick days for the intervention group was 144.9 (SEM 11.8) days/person as compared to 197.9 (14.0) days in the reference group (P < 0.01). Compared with the reference group, employees in the intervention group significantly more often received a complete rehabilitation investigation (84% versus 27%). The time for doing this was reduced by half (59.4 (5.2) days versus 126.8 (19.2), P < .01). The odds ratio for returning to work in the intervention group was 2.5 (95% confidence interval 1.2-5.1) as compared with the reference group. The direct cost savings were USD 1195 per case, yielding a direct benefit-to-cost ratio of 6.8. It is suggested that the management of MSDs should to a greater degree focus on early return to work and building on functional capacity and employee ability. Allowing the case managers a more active role as well as involving an ergonomist in workplace adaptation meetings might also be beneficial.

The phenomenon of building-related diseases is attracting much research interest in recent years because of the extent to which it affects people with compromised immune systems, especially children. In this study, we reported the neurological findings in children who attended our Center because of chronic exposure to toxic molds. Clinical neurological and neurobehavioral questionnaires were administered with the cooperation of the children's parents. The children then underwent a series of neurophysiological tests including electroencephalogram (EEG), brainstem evoked potential (BAEP), visual evoked potential (VEP), and somatosensory evoked potential (SSEP). The results showed high levels of abnormalities in the analysis of the subjective responses derived from the questionnaires. The EEG examination was abnormal in seven out of ten of the patients compared to the controls with only one in ten with episodes of bihemispheric sharp activity. In all the patients, there was frontotemporal theta wave activity that seemed to indicate diffuse changes characteristic of metabolic encephalopathies. Also, there was highly marked 1 to 3 Hz delta activity that was asymmetrical in the right hemisphere of the brain in three out of ten patients. The waveforms of BAEP showed abnormalities in 90% of the patients with both 15' and 31' check sizes compared to none in the controls. There were significant delays in waveform V in a majority of the patients representing dysfunctional cognitive process and conductive hearing loss in both ears. VEP showed clear abnormalities in four in ten of the patients with P100 amplitudes and latencies decreased bilaterally. In all the patients, there was slowing of conduction in the right tibial at an average of 36.9 ms and there was significant decrease in amplitude of response at the proximal stimulation site. Sensory latencies obtained in the median, ulnar, and sural nerves bilaterally showed abnormalities in five out of ten compared to none in the controls. The median, ulnar, and sural sensory potentials were abnormal in six out of ten patients. There was prolongation of the median distal sensory latencies bilaterally at an average of 4.55 ms on the right and an average of 6.10 ms on the left as compared to the ulnars of 2.55 ms bilaterally. There was no abnormality in the controls. These findings represent evidence of diffuse polyneuropathy to which three patients demonstrated borderline slow motor conduction at an average of 41.1 ms. Overall, the objective neurophysiological measurements (EEG, BAEP, VEP, and SSEP) were abnormal, indicating significant neurological deficits in all the patients. Our findings revealed the extent to which toxic molds can affect the neurological and behavioral status of children. Further work should be encouraged in this regard.


Tasks concerning environmental medicine are a significant aspect of the expert work done by the medical review board of the social health insurance fund. Thus far there are no commonly accepted theories and/or criteria with regard to the cause of environmental incompatibilities, nor are there generally accepted criteria/standards for
clinical diagnostic procedures and therapy. Problems arise from the fact that the field of environmental medicine not only offers scientifically accepted and verified diagnostic and therapeutic methods, but also numerous unconventional procedures without verified validity. The decision of the scientific expert has to be based on the legal principles of social legislation and jurisdiction. His/her opinion must be competent, objective and independent. Further research is urgently needed to improve the scientific data pool. With it, well-grounded methods and standards can be offered.


ras genes are known critical DNA targets for chemical carcinogens. Exocrine pancreatic cancer (EPC) is the human tumor with the highest prevalence of K-ras mutations at diagnosis. We analyzed the relationship between past occupational exposure to dyes, metals, polycyclic aromatic hydrocarbons (PAHs) and other agents and mutations in codon 12 of the K-ras gene in 107 incident cases of EPC. Information on occupational and life-style factors was obtained from personal interviews conducted during hospital stay. Occupational exposures were examined using industrial hygienists (IH) assessment and the Finnish job-exposure matrix (Finjem). Specific occupational exposures among K-ras mutated EPC cases (n = 83) were compared to those of K-ras wild-type EPC cases (n = 24) (case-case analysis). Multivariate-adjusted odds ratios (OR) and their corresponding 95% confidence limits were estimated by unconditional logistic regression. Cases with K-ras mutations were significantly more likely than wild-type cases to have been exposed to dyes and organic pigments (OR 4.8; p<0.05). There was some indication of weaker associations between K-ras mutations and occupational exposure to lead, PAHs, benzo[a]pyrene, gasoline, nickel, inhalatory exposure to chromium and sedentary work. The association with chromium compounds was stronger for G to T transversions, a finding compatible with experimental studies on mutation spectra for chromium. Results lend moderate support to the hypothesis of indirect relationships between occupational exposure to dyes and organic pigments and the activation of the K-ras gene in the etiopathogenesis of human exocrine pancreatic cancer.

P-Glycoprotein (P-gp) is a transmembrane protein, playing significant roles in the process of drug discovery and development and in pest resistance to pesticides. P-gp affects absorption, disposition, and elimination of different compounds and is mainly expressed in intestines, liver, kidneys, heart, colon, and placenta. The expression of P-gp in the blood-brain barrier (BBB) has been associated with the restricted access of many compounds to the central nervous system. Generated knockout mice by disruption of mdr 1a gene, encoding for P-gp, showed that this protein was expressed in the BBB. The absence or the low levels of P-gp elevated drug concentrations in tissues and decreased drug elimination. P-gp is responsible for resistance of cells to agents, particularly the anticancer drugs, by removing these drugs from cells. Increased expression of P-gp is implicated in decreased HIV drug availability at certain intracellular sites. The role of P-gp in affecting efficacy and toxicity of environmental toxicants such as pesticides and heavy metals has not been adequately investigated. Studies showed that P-gp contributes to resistance to pesticides in certain pest species, and to decrease toxicity by removing compounds from cells in mammals. Placental drug-transporting P-gp plays a significant role in limiting the transport of toxicants such as potential teratogens to the fetus. Several in vitro or in vivo assays, including using P-gp knockout or naturally deficient mice, were described for testing P-gp modulators. The role of P-gp following concurrent exposure to more multiple compounds needs further research. P-gp modulators should be carefully used, since some modulators that reverse P-gp efflux action in vitro may lead to alterations of tissue function and increase toxicity of xenobiotics in normal tissues. Recent reports from the pharmaceutical studies on the significance of P-gp as transporters in altering the efficacy and toxicity clearly highlight the need for further research in interaction with environmental toxicants.

(2003) Combined exposure to DEET (N,N-diethyl-m-toluamide) and permethrin: pharmacokinetics and toxicological effects.

Permethrin and DEET are concurrently used for pests control inside homes, in public places, and in military shelters. Combined exposure to these compounds produced greater biochemical, behavioral, and metabolic alterations in animals compared to each individual compound. Concurrent application of DEET and permethrin induced urinary excretion of 3-nitrotyrosine and 8-hydroxy-2'-deoxyguanosine, markers of DNA damage and oxidative stress in rats, increased the release of rat brain mitochondrial cytochrome c, disrupted the blood-brain barrier (BBB) in rats, decreased m2 muscarinic acetylcholine receptor ligand binding density in rat brain, increased urinary excretion of 6 beta-hydroxycortisol, a marker CYP3A4 induction, altered sensorimotor and locomotor activities in rats, and changed in vivo and in vitro metabolism and pharmacokinetic profiles of the individual compound. These findings show that more research is needed to examine adverse effects of the combined use of DEET and
permethrin on other biochemical/physiological system(s) and to predict mechanistic pathways for these effects, particularly mechanism of action at cellular and molecular levels and alterations of genes transcription.

------------------------------------------------------------------------------------------------------------------------

(2003) Testicular germ-cell apoptosis in stressed rats following combined exposure to pyridostigmine bromide, N,N-diethyl m-toluamide (DEET), and permethrin.

This study reports and characterizes the testicular apoptosis following daily exposure of male Sprague-Dawley rats to subchronic combined doses of pyridostigmine bromide (PB, 1.3 mg/kg/d in water, oral), a drug used for treatment of myasthenia gravis and prophylactic treatment against nerve agents during the Persian Gulf War; the insect repellent N,N-diethyl m-toluamide (DEET, 40 mg/kg/d in ethanol, dermal); and the insecticide permethrin (0.13 mg/kg in ethanol, dermal), with and without stress for 28 d. Combined exposure to these chemicals was implicated in the development of illnesses including genitourinary disorders among many veterans of the Persian Gulf War. Previous studies from this laboratory have shown that exposure to combination of these chemicals produced greater toxicity compared to single components. Exposure to stress alone did not cause any significant histopathological alterations in the testes. Administration of combination of these chemicals induced apoptosis in rat testicular germ cells, Sertoli cells, and Leydig cells, as well as in the endothelial lining of the blood vessels. Testicular damage was significantly augmented when the animals were further exposed to a combination of chemicals and stress. Histopathological examination of testicular tissue sections showed that apoptosis was confined to the basal germ cells and spermatocytes, indicating suppression of spermatogenesis. Increased apoptosis of testicular cells coincided, in timing and localization, with increased expression of the apoptosis-promoting proteins Bax and p53. Furthermore, significant increase of 3-nitrotyrosine immunostaining in the testis revealed oxidative and/or nitrosation induction of cell death. In conclusion, combined exposure to real-life doses of test compounds caused germ-cell apoptosis that was significantly enhanced by stress.

------------------------------------------------------------------------------------------------------------------------

(2003) Sensorimotor deficits and increased brain nicotinic acetylcholine receptors following exposure to chlorpyrifos and/or nicotine in rats.
Despite well-known adverse effects associated with cigarette smoking, approximately 20% of the US population continues to smoke and many more are exposed to environmental tobacco smoke. Many of the same individuals are also exposed to environmental neurotoxic chemicals such as the organophosphorus insecticide chlorpyrifos. In the present study, the effects of exposure to low doses of nicotine and chlorpyrifos alone and in combination, were studied on the central cholinergic system and sensorimotor performance in rats. Male Sprague-Dawley rats (250-300 g) were treated with nicotine (1 mg/kg s.c., in normal saline), chlorpyrifos (0.1 mg/kg dermally, in 0.1 ml 70% ethanol), or a combination of both, daily for 30 days. Control rats were treated with saline and dermally with ethanol. Sensorimotor behavior was evaluated 24 h following the last dose using a battery of tests. There was a significant deficit in incline plane performance, beam-walk score and beam-walk time following exposure to each chemical, alone or in combination. The deficit in incline plane performance was greater when the two chemicals were given in combination than with either compound alone. Biochemical analysis showed a decrease in cerebellar and an increase in midbrain acetylcholinesterase (AChE) activity following combined exposure. Exposure to nicotine alone resulted in a significant increase in AChE activity in brainstem and midbrain, whereas there was no significant change after exposure to chlorpyrifos, alone. A significant increase in ligand binding to nicotinic acetylcholine receptors (nAChR) was observed in brainstem and cortex following exposure to nicotine or chlorpyrifos. This was further augmented with combined exposure, which caused a modest but significant increase in m2 muscarinic acetylcholine receptors (m2-mAChR) ligand binding in the cortex. These data suggest that exposure to either nicotine or chlorpyrifos or a combination of the two may impair neurobehavioral performance and affect the central nervous system cholinergic pathways.


Organophosphorus compounds are potent neurotoxic chemicals that are widely used in medicine, industry, and agriculture. The neurotoxicity of these chemicals has been documented in accidental human poisoning, epidemiological studies, and animal models. Organophosphorus compounds have 3 distinct neurotoxic actions. The primary action is the irreversible inhibition of acetylcholinesterase, resulting in the accumulation of acetylcholine and subsequent overstimulation of the nicotinic and muscarinic acetylcholine receptors, resulting in cholinergic effects. Another action of some of these compounds, arising from single or repeated exposure, is a delayed onset of ataxia, accompanied by a Wallerian-type degeneration of the axon and myelin in the most distal portion of the longest tracts in both the central and peripheral nervous systems, and is known as organophosphorus ester-induced delayed neurotoxicity (OPIDN). In addition, since the introduction and extensive use of synthetic organophosphorus compounds in agriculture and industry half a century ago, many studies have reported long-term, persistent, chronic neurotoxicity symptoms in
individuals as a result of acute exposure to high doses that cause acute cholinergic toxicity, or from long-term, low-level, subclinical doses of these chemicals. The author attempts to define the neuronal disorder that results from organophosphorus ester-induced chronic neurotoxicity (OPICN), which leads to long-term neurological and neurobehavioral deficits. Although the mechanisms of this neurodegenerative disorder have yet to be established, the sparse available data suggest that large toxic doses of organophosphorus compounds cause acute necrotic neuronal cell death in the brain, whereas sublethal or subclinical doses produce apoptotic neuronal cell death and involve oxidative stress.


The carcinogenic effects of 1,3-butadiene (BD), a chemical widely used in the rubber industry, are thought to be due to its epoxide metabolites. In humans, these epoxides are detoxified predominantly by hydrolysis, a reaction mediated by the microsomal epoxide hydrolase (mEH) enzyme. The mEH gene is polymorphic and the most common mEH coding-region variants detected in human populations are the two amino acid polymorphisms Tyr113His and His139Arg. Polymorphic amino acid substitutions at residues 113 and 139 in the human mEH protein can associate in four distinct combinations: Tyr113/His139, Tyr113/Arg139, His113/His139, and His113Arg139. In vitro studies have shown that each of these genotypes has a unique mEH protein level that can affect net mEH enzymatic activity. In the current study, we examined the relationships among the genotypes involving these two polymorphisms and the mutagenic responses associated with occupational exposure to BD. We studied 49 nonsmoking workers from two styrene-butadiene rubber facilities in southeast Texas using the autoradiographic HPRT mutant lymphocyte assay as a biomarker of genotoxic effect. We genotyped the study participants simultaneously for both polymorphisms, using a multiplex PCR assay developed in our laboratory, and the subjects were assigned to a specific group based on the predicted mEH activity associated with their genotypes (low, intermediate, and high). In the study population, 67% were exposed to low BD levels of <150 ppb (measured by personal badge dosimeters) and 33% were exposed to >150 ppb (mean 2,244 ppb). In the BD low-exposure group, the mEH genotypes had no significant effect on the HPRT variant (mutant) frequency (Vf). In the high-exposure group (BD > 150 ppb), individuals with genotypes associated with low mEH activity had a significant (P < 0.05) 3-fold increase in HPRT Vf (Vf +/- SEM = 13.95 +/- 2.15 x 10(-6)) compared to high-activity individuals (4.41 +/- 1.19 x 10(-6)), and a 2-fold increase in Vf compared to intermediate-activity individuals (6.44 +/- 2.09 x 10(-6)). Our results indicate that mEH genotypes may play a significant role in human sensitivity to the genotoxic effects of exposure to BD.
(2003) Increased expression of glial fibrillary acidic protein in cerebellum and hippocampus: differential effects on neonatal brain regional acetylcholinesterase following maternal exposure to combined chlorpyrifos and nicotine.

Cigarette smoking and environmental exposure to chlorpyrifos during pregnancy could lead to developmental toxicity in the offspring. In the present study, pregnant female Sprague-Dawley rats (300-350 g) were treated daily with nicotine (1 mg/kg, sc) or chlorpyrifos (0.1 mg/kg, dermal) or a combination of nicotine and chlorpyrifos from gestational days (GD) 4-20. Control animals were treated with saline and ethanol. Male offspring from the mothers treated with nicotine alone gained significantly less weight on postnatal day (PND) 30 as compared to control. On PND 7, there was a significant increase in brain acetylcholinesterase (AChE) activity in pups from nicotine- and chlorpyrifos-treated dams, whereas plasma butyrylcholinesterase (BChE) activity was significantly elevated in pups of mothers treated with either chlorpyrifos alone or pesticide combined with nicotine. On PND 30 there was a significant increase in AChE activity in brainstem and cerebellum in all treated male pups. In female pups on PND 30 there was a significant rise in AChE activity in brainstem of chlorpyrifos alone and in cerebellum of the combination nicotine and chlorpyrifos group. Histopathological evaluation demonstrated an increased neuronal cell death in the cerebellum granular cell layer of female offspring from nicotine or combined nicotine with chlorpyrifos group. A rise in glial fibrillary acidic protein (GFAP) immunostaining was observed in the CA1 subfield of hippocampus and cerebellum on PND 30 in female and male offspring of mothers treated with either nicotine or nicotine in combination with chlorpyrifos, but to a lesser extent in males. Data suggest that maternal exposure to nicotine and chlorpyrifos, alone or in combination, produces differential alterations in brain regional AChE activity and expression of GFAP in cerebellum and hippocampus in offspring on PND 30.

(2003) [Economic evaluation of population health damages caused by the influence of environmental factors].
Abalkina, IL, Novikov, SM, Skovronskaia, SA and Skvortsova, NS Journal/Gig Sanit. 95-8.

---------------------------------------------------------------

Journal/Prescrire Int. 12: 127-32.

There is no reference second-line treatment for patients with rheumatoid arthritis, juvenile chronic arthritis, psoriatic arthropathy or ankylosing spondylitis after failure or intolerance of a slow-acting antirheumatic drug such as methotrexate. Etanercept, a immunosuppressant targeting TNF-alpha (like infliximab), is now approved in France for use in these situations, with the exception of spondylitis. In the second-line treatment of adults with rheumatoid arthritis, the clinical evaluation dossier on etanercept contains data from dose-finding studies and two placebo-controlled trials involving patients in whom several single-agent treatments had failed. At a dose of 25 mg subcutaneously twice a week, etanercept worked partially in about half the patients. Without direct comparisons, the place of etanercept relative to other slow-acting antirheumatic drugs is difficult to establish. From indirect comparisons, etanercept seems a slightly better treatment option than infliximab. In the first-line treatment of rheumatoid arthritis, one trial showed that etanercept worked faster than methotrexate, but there was no significant difference between the two treatments after two years. Little is known about the efficacy of etanercept in patients with juvenile chronic arthritis who do not respond adequately to methotrexate. There are no comparative trials. One double-blind placebo-controlled trial showed that etanercept, when it worked, remained active for at least 7 months. In one trial, etanercept was more effective than placebo in patients with psoriatic arthropathy and ankylosing spondylitis who continued to receive their usual treatment, which included a slow-acting antirheumatic drug in about 50% of cases. More than 50% of patients treated with etanercept have a cutaneous reaction to the injection. These reactions are usually mild or moderate. Active pharmacovigilance is needed, given its mechanism of action, and previous notifications of a wide variety of adverse effects (even though it is sometimes difficult to establish a foolproof link between etanercept and the adverse effect). Long-term studies of large numbers of patients are needed to determine the precise risk of side effects including haematological, infectious, neurological, oncological and immunological effects. In practice, methotrexate remains the first-line treatment for inflammatory arthritis. Etanercept can be a useful second-line treatment, especially in juvenile chronic arthritis.

(2002) **Activation of the RON receptor tyrosine kinase by macrophage-stimulating protein inhibits inducible cyclooxygenase-2 expression in murine macrophages.**

The RON receptor tyrosine kinase is activated by macrophage-stimulating protein, which regulates macrophage migration, phagocytosis, and nitric oxide production. We report here the inhibitory effect of RON on lipopolysaccharide (LPS)-induced cyclooxygenase (Cox)-2 expression in mouse macrophages. In RON-expressing macrophages treated with macrophage stimulating protein, LPS-induced prostaglandin E(2) (PGE(2)) production was significantly reduced. The inhibition was accompanied by reduction of Cox-2 protein and mRNA expression. Transcriptional studies indicated that RON activation inhibits LPS-induced luciferase activity driven by the Cox-2 gene promoter. To determine whether RON activation affects LPS-induced NF-kappa B pathway, which is important for Cox-2 expression. Western blot analyses were performed showing that RON activation inhibits LPS-induced I kappa B alpha degradation. The decreased I kappa B alpha degradation was due to reduced I kappa B alpha phosphorylation at Ser-32 as determined by I kappa B alpha (Ser-32) phosphor-antibody. Moreover, we found that LPS-induced IKK beta activity, an enzyme responsible for phosphorylation of I kappa B alpha, was inhibited upon RON activation. Interestingly, these inhibitory effects were not regulated by RON-mediated phosphatidylinositol-3 kinase. These results suggest that RON activation inhibits LPS-induced macrophage Cox-2 expression. The inhibitory effect is mediated by impairing LPS-activated cascade enzymes that activate NF-kappa B. The inhibition of Cox-2 expression might represent a novel mechanism for the inhibitory functions of RON in vivo against LPS-induced inflammation and septic shock.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12177064

(2002) **Immunotoxicology of organic acid anhydrides (OAAs).**

Organic acid anhydrides (OAAs) have considerable economic importance due to their extensive use in the production of alkyd, epoxy, and polyester resins. Occupational exposure to OAAs has been associated with a variety of health effects, which may be
classified into two major categories of direct toxicity/irritant and hypersensitivity. The hypersensitivity diseases associated with OAA exposure are thought to be related to the reactivity of these chemicals and in particular their ability to form protein conjugates that may be recognized as neo-antigens by the immune system. This review will present a brief discussion of the basic chemistry of these compounds and the environmental and biological monitoring methods used for exposure measurements. The clinical syndromes associated with exposure to these compounds will be discussed along with factors that may affect disease susceptibility. Finally, animal models that have been developed to examine the mechanisms of disease will be discussed.


The aim of the present study was to determine the effects of occupational and environmental exposure on respiratory symptoms in adults in rural Beijing, China. Thirty randomly selected villages in the counties of Shunyi and Tongxian, 50 km north and east, respectively, of the city of Beijing, China, participated in this study. Village doctors interviewed all residents aged \( \geq 15 \) yrs and completed the International Union Against Tuberculosis and Lung Disease Questionnaire on Bronchial Symptoms translated into Chinese with added questions on smoking and occupational and environmental exposure. Of the eligible population, 22,528 adults (98%) took part. The prevalence of all respiratory symptoms, i.e. asthma-like symptoms, asthma attacks in the last 12 months, chronic cough and chronic phlegm, was low. Significant determinants for respiratory symptoms were age, sex, smoking and county of residence. A dose-dependent relationship was found between cumulative cigarette consumption and prevalence of respiratory symptoms. After adjusting for these variables, exposure to insecticides and fertilisers significantly increased the risk of most of the respiratory symptoms, whereas exposure to indoor air pollution from domestic fuels did not. Exposure to chemicals such as insecticides and fertilisers contributed independently to the risk of respiratory symptoms in rural Beijing, China.

(2002) [Problems in staff training in environmental illness diagnosis].
Zakharchenko, MP, Ivanov, SI and Lopatin, SA Journal/Gig Sanit. 84-6.

To determine the effects of aged and diluted sidestream cigarette smoke (ADSS) as a surrogate of environmental tobacco smoke (ETS) on ozone-induced lung injury, male B6C3F1 mice were exposed to (1) filtered air (FA), (2) ADSS, (3) ozone, or (4) ADSS followed by ozone (ADSS/ozone). Exposure to ADSS at 30 mg/m3 of total suspended particulates (TSP) for 6 h/day for 3 days, followed by exposure to ozone at 0.5 ppm for 24 h was associated with a significant increase in the number of cells recovered by bronchoalveolar lavage (BAL) compared with exposure to ADSS alone or ozone alone. The proportion of neutrophils and lymphocytes, as well as total protein level in BAL, was also significantly elevated following ADSS/ozone exposure, when compared with all other groups. Within the centriacinar regions of the lungs, the percentage of proliferating cells identified by bromodeoxyuridine (BrdU) labeling was unchanged from control, following exposure to ADSS alone, but was significantly elevated following exposure to ozone (280% of control) and further augmented in a statistically significant manner in mice exposed to ADSS/ozone (402% of control). Following exposure to ozone or ADSS/ozone, the ability of alveolar macrophages (AM) to release interleukin (IL)-6 under lipopolysaccharide (LPS) stimulation was significantly decreased, while exposure to ADSS or ADSS/ozone caused a significantly increased release of tumor necrosis factor alpha from AM under LPS stimulation. We conclude that ADSS exposure enhances the sensitivity of animals to ozone-induced lung injury.

(2002) Protein levels of neurofilament subunits in the hen central nervous system following prevention and potentiation of diisopropyl phosphorofluoridate (DFP)-induced delayed neurotoxicity(1).

Diisopropyl phosphorofluoridate (DFP) is an organophosphorus ester, which produces delayed neurotoxicity (OPIDN) in hens in 7-14 days. OPIDN is characterized by mild ataxia in its initial stages and severe ataxia or paralysis in about 3 weeks. It is marked by distal swollen axons, and exhibits aggregations of neurofilaments (NFs), microtubules, proliferated smooth endoplasmic reticulum, and multivesicular bodies. These aggregations subsequently undergo disintegration, leaving empty varicosities. Previous studies in this laboratory have shown an increased level of medium-molecular weight NF (NF-M) and decreased levels of high- and low-molecular weight NF (NF-H, NF-L) proteins in the spinal cord of DFP-treated hens. The main objective of this investigation was to study the effect of DFP administration on NF subunit levels when OPIDN is prevented or potentiated by pretreatment or post-treatment with phenylmethylsulfonyl fluoride (PMSF), respectively. Hens pretreated or post-treated with PMSF were killed 1, 5, 10, and 20 days after the last treatment. The alteration in
NF subunit protein levels observed in DFP-treated hen spinal cords was not observed in protected hens. Estimation of NFs in the potentiation experiments, however, showed a different pattern of alteration in NF subunit levels. The results showed that an alteration in NF subunit levels in DFP-treated hens might be related to the development of OPIDN, since these changes were suppressed in PMSF-protected hens. However, results from PMSF post-treated hen spinal cords suggested that potentiation of OPIDN by PMSF was mediated by a mechanism different from that followed by DFP alone to produce OPIDN.

(2002) [Somatoform disorders without findings--modern syndromes].


Sensitivity to chemicals is a toxicological concept, contained in the dose-response relationship. Sensitivity also includes the concept of hypersensitivity, although controversy surrounds the nature of effects from very low exposures. The term multiple chemical sensitivity has been used to describe individuals with a debilitating, multi-organ sensitivity following chemical exposures. Many aspects of this condition extend the nature of sensitivity to low levels of exposure to chemicals, and is a designation with medical, immunological, neuropsychological and toxicological perspectives. The basis of MCS is still to be identified, although a large number of hypersensitivity, immunological, psychological, neurological and toxicological mechanisms have been suggested, including: allergy; autosuggestion; cacosomia; conditioned response; immunological; impairment of biochemical pathways involved in energy production; impairment of neurochemical pathways; illness belief system; limbic kindling; olfactory threshold sensitivity; panic disorder; psychosomatic condition; malingering; neurogenic inflammation; overload of biotransformation pathways (also linked with free radical production); psychological or psychiatric illness; airway reactivity; sensitisation of the neurological system; time dependent sensitisation, toxicant induced loss of tolerance. Most of these theories tend to break down into concepts involving: (1) disruption in immunological/allergy processes; (2) alteration in nervous system function; (3) changes in biochemical or biotransformation capacity; (4) changes in psychological/neurobehavioural function. Research into the possible mechanisms of MCS is far from complete. However, a number of promising avenues of investigation indicate that the possibility of alteration of the sensitivity of nervous system cells (neurogenic inflammation, limbic kindling, cacosomia, neurogenic switching) are a possible mechanism for MCS.
(2002) **The presence of fungi associated with sick building syndrome in North American zoological institutions.**

A total of 110 sites from five zoological institutions were examined to determine whether fungi associated with sick building syndrome (SBS) were prevalent in the exhibits or night-time holding facilities and to investigate whether the presence of these organisms was associated with declining breeding rates or increases in morbidity and mortality (or both). Each site was sampled with an Andersen two-stage air sampler using Sabourauds dextrose agar media and a Burkard personal volumetric air sampler. Suspect surfaces were also sampled. High levels of airborne Penicillium chrysogenum, a fungal species associated with poor indoor air quality, were recovered from 16 sites out of all five institutions. Five culturable growth sites of Stachybotrys chartarum, a species strongly associated with SBS and commonly known as "black mold," were recovered from surfaces at two institutions. A wide range of other fungal species was recovered in low numbers from all institutions. A Fisher exact test analysis showed a significant nonrandom association between high levels of P. chrysogenum and sites with records of poor animal health. This study indicated that significant numbers of airborne fungi associated with SBS and poor indoor air quality are present in zoological institutions and that they could affect animal health and reproduction rates and zoo staff.


(2002) **Nasal function in self-reported chemically intolerant individuals.**

Nasal function has not yet been investigated under controlled exposures in individuals with self-reported Multiple Chemical Sensitivity (sMCS). Therefore, anterior rhinomanometry and acoustic rhinometry were applied in 12 individuals with sMCS, and 12 age-matched controls. The sMCS individuals and controls were selected on the basis of a standardized questionnaire. Controlled 4-hr exposures to ethylbenzene and 2-butanone were performed during 4 sessions. Exposures were close to the current German threshold limit values, and they approximated odor thresholds. Subjects with sMCS had a significant decrease in the flow value in anterior rhinomanometry, independent of substance and doses, compared with controls. This result suggests somatic reactions to the exposure. The result must be confirmed in additional studies, and pathophysiological examinations must be performed. For these investigations,
anterior rhinomanometry was usable, but acoustic rhinometry can be recommended only after sufficient standardization has occurred. Furthermore, biochemical parameters of nasal mucosa must be considered.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12507179

(2002) [Demand for environmental medical advice at public health offices: experiences in the district aachen public health office].
Wiesmuller, GA, Etschenberg, W, Koch, T, Konteye, C and Zahmel, J Journal Gesundheitswesen. 64: 159-64.

Since November, 1999 environmental medical advice is offered to interested citizens in the Aachen district at the District Aachen Public Health Office in cooperation with the outpatient unit of environmental medicine (UEM) of the Institute of Hygiene and Environmental Medicine of the University Hospital at Aachen, Germany. Advisory cases are documented in a data bank of Microsoft(R) Access 97. Until now, all advisory cases between November, 1999 and March, 2001 have been descriptively analysed. In this period, 34 personal and two telephonic advices were performed. The frequency of advisory activities is in the lower rang of published experiences in environmental medicine. Age distribution, more frequent advice utilization by women than by men and predominance of unspecific health disorders are comparable with published environmental medical experiences. However, in respect of suspected exposures, unspecific indoor-related environmental factors are predominant. In the past this was true for wood preservatives. Judgement about possible relationships between suspected environmental factors and health disorders or diseases was positive among 11.8 % of the persons seeking advice. This percentage is higher than published experiences which mostly show values below 10 %. It must be considered that this judgement depends primarily on the physician. Other reasons may be the too small number of advice seeking persons and selective influences. Furthermore, a definite judgement can be made only after environmental medical diagnostics (biological monitoring, local inspection, ambient monitoring) and differential diagnostics. Conspicuously, 76.5 % of the advisory cases had no contact to environmental medicine prior to the environmental medical advice at the Aachen District Public Health Office. This points to an information deficit about possibilities to clarify questions concerning environmental medicine in the population. In this context a regional guide on environmental medicine may be helpful. The environmental medical advice for citizens is an excellent example of a successful cooperation between a public health office and an university, which have different special experience in environmental hygiene and environmental medicine. This cooperation brings selectively citizens seeking for advice in environment-related health risks and disorders to practitioners specialised in environmental medicine.
(2002) Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications?

BACKGROUND & AIMS: Comorbid or extraintestinal symptoms occur frequently with irritable bowel syndrome and account for up to three fourths of excess health care visits. This challenges the assumption that irritable bowel is a distinct disorder. The aims of this study were to (1) assess comorbidity in 3 areas: gastrointestinal disorders, psychiatric disorders, and nongastrointestinal somatic disorders; and (2) evaluate explanatory hypotheses. METHODS: The scientific literature since 1966 in all languages cited in Medline was systematically reviewed. RESULTS: Comorbidity with other functional gastrointestinal disorders is high and may be caused by shared pathophysiological mechanisms such as visceral hypersensitivity. Psychiatric disorders, especially major depression, anxiety, and somatoform disorders, occur in up to 94%. The nongastrointestinal nonpsychiatric disorders with the best-documented association are fibromyalgia (median of 49% have IBS), chronic fatigue syndrome (51%), temporomandibular joint disorder (64%), and chronic pelvic pain (50%). CONCLUSIONS: Multivariate statistical analyses suggest that these are distinct disorders and not manifestations of a common somatization disorder, but their strong comorbidity suggests a common feature important to their expression, which is most likely psychological. Some models explain the comorbidity of irritable bowel with other disorders by suggesting that each disorder is the manifestation of varying combinations of interacting physiological and psychological factors. An alternative hypothesis is that the irritable bowel diagnosis is applied to a heterogeneous group of patients, some of whom have a predominantly psychological etiology, whereas others have a predominantly biological etiology, and that the presence of multiple comorbid disorders is a marker for psychological influences on etiology.

Weisberg, RB, Bruce, SE, Machan, JT, Kessler, RC, Culpepper, L and Keller, MB Journal/Psychiatr Serv. 53: 848-54.

OBJECTIVE: The authors examined the relationship between posttraumatic stress disorder (PTSD), trauma, and self-reported nonpsychiatric medical conditions in a sample of 502 primary care patients with one or more anxiety disorders. METHODS: Primary care patients with one or more DSM-IV anxiety disorders were assessed for comorbid psychiatric and substance use problems and for a history of trauma. These individuals also completed a self-report measure of current and lifetime medical conditions, lifetime tobacco use, and current regular exercise. RESULTS: Of 502 participants with at least one anxiety disorder, 84 (17 percent) reported no history of
trauma, 233 (46 percent) had a history of trauma but no PTSD, and 185 (37 percent) met DSM-IV criteria for PTSD. Patients with PTSD reported a significantly greater number of current and lifetime medical conditions than did participants with other anxiety disorders but without PTSD. Primary care patients with PTSD were more likely to have had a number of specific medical problems, including anemia, arthritis, asthma, back pain, diabetes, eczema, kidney disease, lung disease, and ulcer. Possible explanations for the greater rates of medical conditions among participants with PTSD were examined as predictors in multiple regression. PTSD was found to be a stronger predictor of reported number of medical problems than trauma history, physical injury, lifestyle factors, or comorbid depression. CONCLUSIONS: These findings suggest that PTSD is associated with a higher rate of general medical complaints.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12096168


Macrophage-stimulating protein (MSP) is a serum protein belonging to the plasminogen-related growth factor family. The specific receptor for MSP is the RON (recepteur d'origine nantais) receptor tyrosine kinase - a member of the MET proto-oncogene family. Activation of RON by MSP exerts dual functions on macrophages. The stimulatory activities include the induction of macrophage spreading, migration and phagocytosis. However, MSP also inhibits lipopolysaccharide (LPS)-induced production of inflammatory mediators, including inducible nitric oxide and prostaglandins. These suppressive effects are mediated by RON-transduced signals that block LPS-induced enzymatic cascades that activate nuclear factor kappa-B (NFkappaB) pathways. Recent in vivo studies demonstrated that inactivation of the RON gene results in increased inflammatory responses and susceptibility to LPS-induced septic death in mice, suggesting that RON expression is required for attenuating the extent of inflammatory responses in vivo. Thus, MSP and RON are potential regulators that control macrophage activities during bacterial infection in vivo.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12472665

To evaluate the reliability and validity of a standardized asthma outcome coding system, we obtained medical records for 182 asthmatic children. Records were coded by trained staff using explicit and detailed criteria. Outcome variables coded included number of corticosteroid bursts, asthma-related physician contacts, emergency room visits, hospitalizations, and number of asthma episodes. Interrater reliability was excellent. Patterns of associations between the coded variables and other independently obtained outcome measures supported concurrent and construct validity. Given the intense scrutiny of health outcomes in the current managed-care marketplace, use of this system may foster further clinical research examining asthma outcomes.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12095179


BACKGROUND: Distant healing as a treatment modality is frequently used by patients and healers. Some preliminary evidence suggests possible effects. Since patients suffering from multiple chemical sensitivity and chronic fatigue syndrome have only few effective treatment options, distant healing will be offered as a treatment within a formal trial of distant healing. DESIGN AND METHOD: A four-armed randomized trial will include 400 patients with self-attributed, environmental problems who fulfil the diagnostic criteria of severe idiopathic chronic fatigue, chronic fatigue syndrome or multiple chemical sensitivity. Patients will be recruited by specialized general practitioners and environmental clinics. They will be treated by healers distributed all over Europe, coming from various healing traditions and nationalities. Each patient will be treated by 3 healers. Healers will have no contact with the patients and will only be provided with the patient's Christian name and a photograph. The patients will be randomized to one of 4 groups in a 2 x 2 factorial design. They will either receive (distant) healing or not, and either know or not know this decision. Thereby the effects of expectation and of time can be disentangled from the specific effects of healing. OUTCOME MEASURE: Primary outcome measure will be the mental health summary scale of the MOS SF-36. The measure will be taken at the beginning and at the end of a 6-month treating or waiting period, respectively. A variety of moderator variables will be considered to evaluate which of these may be predictive of outcome.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12119513
Wakefield, J Journal/Environ Health Perspect. 110: A298-305.


There is growing awareness that primary gastrointestinal pathology may play an important role in the inception and clinical expression of some childhood developmental disorders, including autism. In addition to frequent gastrointestinal symptoms, children with autism often manifest complex biochemical and immunological abnormalities. The gut-brain axis is central to certain encephalopathies of extra-cranial origin, hepatic encephalopathy being the best characterized. Commonalities in the clinical characteristics of hepatic encephalopathy and a form of autism associated with developmental regression in an apparently previously normal child, accompanied by immune-mediated gastrointestinal pathology, have led to the proposal that there may be analogous mechanisms of toxic encephalopathy in patients with liver failure and some children with autism. Aberrations in opioid biochemistry are common to these two conditions, and there is evidence that opioid peptides may mediate certain aspects of the respective syndromes. The generation of plausible and testable hypotheses in this area may help to identify new treatment options in encephalopathies of extra-cranial origin. Therapeutic targets for this autistic phenotype may include: modification of diet and entero-colonic microbial milieu in order to reduce toxin substrates, improve nutritional status and modify mucosal immunity; anti-inflammatory/immunomodulatory therapy; and specific treatment of dysmotility, focusing, for example, on the pharmacology of local opioid activity in the gut.

(2002) [Environmental medicine. Pollution of the environment by anthropogenic products].


The individually different effects of exposure to comparable levels of chemicals might be partly explained by dissimilar response sensitivity towards chemicals. Multiple chemical sensitivity (MCS) might be the clinical endpoint of this altered sensitivity. Concerning a subclinical range of chemical sensitivity, 'challenge studies' with people reporting chemical sensitivity are needed to improve the knowledge about such differences. The chemical and general environmental sensitivity questionnaire (CGES) is a standardized screening tool for the selection of this group. In the present study 24 healthy male volunteers, half of them classified as sMCS-subjects, were experimentally exposed to 2-butanone and ethyl benzene at different levels (TLV-level vs. odor threshold). The strength of self-reported sensory irritations (nasal and ocular) and symptoms of bad smell were assessed, prior, during, and after the 4 hours of exposure. The time courses of sensory irritations were affected by sMCS. Across all exposure periods sMCS-subjects showed increasing symptom scores while control-subjects did not. Symptoms of bad smell were affected by three exposure-related factors (substance, level, duration) without any additional influence from the sMCS factor. Starting from these results it could be concluded that the time-depending influence of reported chemical sensitivity is most prominent for subjective data of sensory irritations.


Building on two earlier experiments (Behav. Res. Ther. 34 (1996) 889; 39 (2001) 1439) the present study investigated the effects of neutralizing the consequences of an obsession-like thought in healthy participants. Just like in the earlier studies, writing out and thinking over such a thought generated anxiety. After this provocation, 40 of the 120 participants were instructed to neutralize the effects of the thought for 2 min, 40 participants did not receive a particular instruction, and the remaining 40 participants were instructed to do mental arithmetic aloud so as to prevent "spontaneous" attempts at neutralizing the thought. The no instruction group reported that they neutralized (spontaneously) to the same degree as the group that was instructed to neutralize. Within 2 min, anxiety decreased to near base line levels and there were no differences between the three conditions. When the groups were asked to bring the obsession-like thought back to consciousness again, anxiety increased slightly. Yet, contrary to expectation, this increase in anxiety did not discriminate the "neutralization prevention"
group from the other two groups. Limitations of the paradigm as a model for clinical obsessions are discussed.

(2002) **Lead encephalopathy: CT and MR findings.**

Lead is toxic to many organ systems, among them bone marrow, muscles, kidneys, endocrine glands, joints, and nervous system. Encephalopathy is a rare but severe complication of lead poisoning. Lead toxicity is much less common in adults. Adult lead poisoning results primarily from exposure by inhalation in the workplace. In this report, two cases of adult toxic encephalopathy due to lead poisoning are presented with CT and MR findings.

(2002) **T-cell reactivity in neonates: influence of environmental and genetic factors.**

(2002) **Ethanol elicits and potentiates nociceptor responses via the vanilloid receptor-1.**

The vanilloid receptor-1 (VR1) is a heat-gated ion channel that is responsible for the burning sensation elicited by capsaicin. A similar sensation is reported by patients with esophagitis when they consume alcoholic beverages or are administered alcohol by injection as a medical treatment. We report here that ethanol activates primary sensory neurons, resulting in neuropeptide release or plasma extravasation in the esophagus, spinal cord or skin. Sensory neurons from trigeminal or dorsal root ganglia as well as VR1-expressing HEK293 cells responded to ethanol in a concentration-dependent and capsazepine-sensitive fashion. Ethanol potentiated the response of VR1 to capsaicin, protons and heat and lowered the threshold for heat activation of VR1 from approximately 42 degrees C to approximately 34 degrees C. This provides a likely mechanistic explanation for the ethanol-induced sensory responses that occur at body
temperature and for the sensitivity of inflamed tissues to ethanol, such as might be found in esophagitis, neuralgia or wounds.


A PBPK/PD model was developed for the organophosphate insecticide chlorpyrifos (CPF) (O,O-diethyl-O-[3,5,6-trichloro-2-pyridyl]-phosphorothioate), and the major metabolites CPF-oxon and 3,5,6-trichloro-2-pyridinol (TCP) in rats and humans. This model integrates target tissue dosimetry and dynamic response (i.e., esterase inhibition) describing uptake, metabolism, and disposition of CPF, CPF-oxon, and TCP and the associated cholinesterase (ChE) inhibition kinetics in blood and tissues following acute and chronic oral and dermal exposure. To facilitate model development, single oral-dose pharmacokinetic studies were conducted in rats (0.5-100 mg/kg) and humans (0.5-2 mg/kg), and the kinetics of CPF, CPF-oxon, and TCP were determined, as well as the extent of blood (plasma/RBC) and brain (rats only) ChE inhibition. In blood, the concentration of analytes followed the order TCP >> CPF >> CPF-oxon; in humans CPF-oxon was not quantifiable. Simulations were compared against experimental data and previously published studies in rats and humans. The model was utilized to quantitatively compare dosimetry and dynamic response between rats and humans over a range of CPF doses. The time course of CPF and TCP in both species was linear over the dose range evaluated, and the model reasonably simulated the dose-dependent inhibition of plasma ChE, RBC acetylcholinesterase (AChE), and brain (rat only) AChE. Model simulations suggest that rats exhibit greater metabolism of CPF to CPF-oxon than humans do, and that the depletion of nontarget B-esterase is associated with a nonlinear, dose-dependent increase in CPF-oxon blood and brain concentration. This CPF PBPK/PD model quantitatively estimates target tissue dosimetry and AChE inhibition and is a strong framework for further organophosphate (OP) model development and for refining a biologically based risk assessment for exposure to CPF under a variety of scenarios.

Twenty-nine individuals with chronic health complaints following exposure to chlorpyrifos were compared with 3 control groups (i.e., 1 positive and 2 negative) with respect to the following: (1) peripheral lymphocyte phenotypes; (2) autoantibodies (nucleic acids and nucleoproteins, parietal cell, brush border, mitochondria, smooth muscle, thyroid gland, and central nervous system/peripheral nervous system myelin); (3) mitogenesis to phytohemagglutinin and concanavillin. The data revealed an increase in CD26 expression, a decrease in percentage of CD5 phenotype, decreased mitogenesis in response to phytohemagglutinin and concanavillin, and an increased frequency of autoantibodies. The alterations in these peripheral blood markers were unaffected by medications, age, sex, or season. The authors concluded that chronic exposure to chlorpyrifos causes immunological changes.


Multiple chemical sensitivity (MCS) is characterized by chemically induced symptoms from multiple organ systems. No consistent physical findings or laboratory abnormalities have been determined for the associated symptoms. Twelve patients with chemically induced airway symptoms, who satisfied Cullen's criteria for MCS, were provoked double-blind, randomized with saline and three increments of inhaled capsaicin. The recordings were compared with those of a control group of healthy individuals. The results found that the patients coughed more than the control subjects at each dose of capsaicin (P < 0.05 for 0.4 mumol/L capsaicin and P < 0.005 for 2 mumol/L and 10 mumol/L). The capsaicin provocation also induced significantly more symptoms in patients with MCS. We conclude that airway sensory reactivity is increased in patients with MCS, a finding which suggests that neurogenic factors may be of importance in this condition.


(2002) Dietary adequacy of the rotary diversified diet as a treatment for "Environmental Illness".
The rotary diversified diet, used in the management of environmental illness, consists of eliminating prohibited foods from the diet and rotating remaining non-prohibited foods and their "food families" within a regular cycle. We assessed the adequacy of nutrient intakes in 22 women prescribed the diet, described the nature of supplement use, and assessed the relationship between adherence and nutrient intake levels. Except for calcium and folacin intakes, mean nutrient intakes met or exceeded recommended levels. No subjects had calcium intakes above the adequate intake for calcium; 72.7% had folate intakes below the estimated average requirement. Intakes of other nutrients, except thiamin and magnesium, were below the estimated average requirement in less than 25% of the sample; 31.8% and 45.5% of subjects, respectively, had thiamin and magnesium intakes at this level. Those who adhered more closely to the rotary diversified diet had higher intakes of vitamin C, vitamin B6, folate, and fibre than did those who followed the diet less closely. Supplements conferred some nutritional benefits; however, supplemental niacin and magnesium intakes exceeded tolerable upper intake levels. Those prescribed the rotary diversified diet require nutrition counselling from dietitians to cope with the complexity and restrictiveness of the diet.


Idiopathic environmental intolerance (IEI), also known as multiple chemical sensitivity, is a clinical description for a cluster of symptoms of unknown etiology that have been attributed by patients to multiple environmental exposures when other medical explanations have been excluded. Because allergy has not been clearly demonstrated and current toxicological paradigms for exposure-symptom relationships do not readily accommodate IEI, psychogenic theories have been the focus of a number of investigations. A significantly higher lifetime prevalence of major depression, mood disorders, anxiety disorders, and somatization disorder has been reported among patients with environmental illness compared with that in controls. Symptoms often include anxiety, lightheadedness, impaired mentation, poor coordination, breathlessness (without wheezing), tremor, and abdominal discomfort. Responses to intravenous sodium lactate challenge or single-breath inhalation of 35% carbon dioxide versus a similar breath inhalation of clean air have shown a greater frequency of panic responses in subjects with IEI than in control subjects, although such responses did not occur in all subjects. Preliminary genetic findings suggest an increased frequency of a common genotype with panic disorder patients. The panic responses in a
significant proportion of IEI patients opens a therapeutic window of opportunity. Patients in whom panic responses may at least be a contributing factor to their symptoms might be responsive to intervention with psychotherapy to enable their desensitization or deconditioning of responses to odors and other triggers, and/or may be helped by anxiolytic medications, relaxation training, and counseling for stress management.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12194904

(2002) [Principles of the implementation of environmental health risk assessment in the socioeconomic management system]. Tarkhov, PV, Pinigin, MA, Tsarenko, OM, Shevelev, II and Shvets, SN Journal/Gig Sanit. 82-4.


There is little data on the distribution of biomonitoring parameters in patients at outpatient Units of Environmental Medicine (UEM). We evaluated the biomonitoring parameters of 646 UEM outpatients from our University Hospital 1988-1998. Few patients were exposed to specific substances. Data of patients who were not obviously exposed was analysed statistically (geometric mean, standard deviation, median, 95th percentile). Results were compared with reference values in literature. Normal distribution of biomonitoring parameters was rare. 95th percentiles for arsenic, chromium, selenium, zinc, phenol and toluene were below standard, 95th percentiles for copper and mercury above, and 95th percentiles for lead, cadmium, pentachlorophenol, lindane, and beta-hexachlorocyclohexane were within the published range of reference values. Thallium as well as most volatile organic compounds analyzed were below detection levels. Aluminum and fluorine exposure was rarely analysed. In view of these results, it is concluded that the indication for biomonitoring needs to be stringent as levels of biomonitoring parameters are generally not risen in patients of the UEM.
**(2002) Medical and social prognosis for patients with perceived hypersensitivity to electricity and skin symptoms related to the use of visual display terminals.**

Stenberg, B, Bergdahl, J, Edvardsson, B, Eriksson, N, Linden, G and Widman, L


OBJECTIVES: This study attempted to give a medical and social prognosis for patients with perceived "electrical sensitivity". METHODS: In 1980-1998, 350 patients with electrical sensitivity were registered at the University Hospital of Northern Sweden in Umea, Sweden. Those with hypersensitivity to electricity had multiple symptoms evoked by exposure to different electric environments. Those with skin symptoms related to the use of visual display terminals (VDT) predominantly had facial skin symptoms evoked by a VDT, television screens, or fluorescent light tubes. A questionnaire on civil status, current health status, care, treatment and other measures taken, consequences of the problem, eliciting factors, and current employment was sent to all the patients. The response rate was 73%. Of the 50 respondents with hypersensitivity to electricity, 38% were men and 62% were women. Of the 200 patients with skin symptoms related to VDT use, 21.5% were men and 78.5% women.

RESULTS: More women than men had turned to caregivers, including complementary therapies. A larger proportion of patients with hypersensitivity to electricity (38%) than those with skin symptoms related to VDT use (17%) was no longer gainfully employed. Both groups reported a higher symptom frequency than that reported by the general population. Over time, the medical prognosis improved in the latter group but not in the former. CONCLUSIONS: Patients with hypersensitivity to electricity, particularly women, have extensive medical problems and a considerable number of them stop working. Many patients with skin symptoms related to VDT use have a favorable prognosis. Both groups need early and consistent management.

-----------------------------------------------------------------------------------------------

**(2002) Gastric carcinoma distal to the cardia: a review of the epidemiological pathology of the precursors to a preventable cancer.**

Stemmermann, GN and Fenoglio-Preiser, C

Journal/Pathology. 34: 494-503.

A distinctive gastritis precedes the development of cancer distal to the cardia. Helicobacter pylori infection and the use of pickled foods as substitutes for fresh fruits and vegetables constitute the most important environmental factors that generate this gastritis. This review describes the anatomical changes that characterise the step-by-step evolution of a process that begins in childhood and culminates in invasive cancer in middle and old age. Progression of the gastritis can be followed by measuring the host antibody response to the H. pylori infection and by serum assays that indicate loss of parietal cell mass. Cancer of the distal stomach will disappear if adequate, sanitary housing and year-round fresh vegetables are made available to all economic levels of society. Programmes that offer these reforms must be sustained over several generations, since the anatomical changes that precede gastric cancer are probably not reversible and begin early in life. In the absence of these reforms,
death from gastric cancer may be prevented if patients with asymptomatic, early cancers are identified. High H. pylori antibody levels and serum pepsinogen assays may be used to identify persons with the extensive gastritis that favours the presence of such early cancers.

(2002) Tolerance and hormesis--increased resistance to copper in hydroids linked to hormesis.

Cultured clones of the colonial hydroid Laomedeaflexuosa have been used over some years as an experimental model to study the dynamics of growth control [J. Mar. Biol. Ass. UK (1981a) 61, 35; Aquatic Toxicology (1981b) 1, 227; Journal of Applied Toxicology (2000a) 20, 93]. Exposure to toxic agents has been an essential element of the approach, providing the stimulus to elicit adaptive control system responses. While the work has provided interpretations of physiological interest, it has also given insights to some toxicological phenomena. It is proposed that hormesis, as a stimulation of growth due to exposure to low concentrations of copper (1-10 microg l(-1)), is due to increases in the preferred rate of the growth control mechanism. This increases the capacity to counteract inhibition and confers intolerance to the inhibitor, while overcorrections to low concentrations cause hormesis.


Unexplained illnesses characterized by nonspecific, multisystem complaints are often attributed to occupational or environmental chemical exposures. This raises difficulties for the regulatory authorities, who are frequently unable to agree on the existence, nature, or source of such illnesses. It is proposed that many of these difficulties derive from an adherence to a traditional medical model of disease and that the application of a biopsychosocial approach would be more effective for both research and individual case management. A number of models derived from the field of health psychology are discussed in terms of their application to occupational and environmental syndromes. A specific example is described that relates to the health problems experienced by sheep farmers in the United Kingdom who are exposed to organophosphate-based pesticides. The source of their complaints and the responses of the health professionals and the regulatory authorities are discussed within the context of a biopsychosocial approach that focuses on illness rather than on organic disease as the unit of study and explores the interaction between the various physical and psychosocial variables involved. It is proposed that this approach, which is already well
established in the fields of human and social sciences, should be adopted more readily by those concerned with occupational and environmental epidemiology.

(2002) [Medical classification of foci of multiple and unknown chemical affections].

The purpose of this work was to define the diagnostic methods in unspecific syndromes of exogenous intoxication and their use for conduction of medical classification in the foci of polychemical and unknown chemical affections. Detection of unspecific syndromes of extreme pathologic process in persons affected by dangerous chemical substances will contribute to organization of two-stage medical support, will facilitate the conduction of medical classification, determination of type and volume of medical assistance.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12479001

(2002) Sensitization as a mechanism for multiple chemical sensitivity: relationship to evolutionary theory.

Multiple chemical sensitivity (MCS) is a disorder in humans attributed to prior chemical exposure. Sensitization is an amplification of neuronal responsiveness that elicits increased behavioral responding to stimuli, and occurs in a recently developed rat model of MCS. Rats were exposed to repeated formaldehyde (Form) and their response in three behavioral tests, including locomotor activity after a cocaine challenge, conditioned fear, and behavioral avoidance of Form, was assessed. In all three tests, rats demonstrated sensitized behaviors, implicating amplified responding within specific limbic brain regions. Evolutionary theory in the context of MCS specifies how the behavioral strategies of those with MCS are consistent with the notion that their self-perceived sense of survival and reproductive fitness may be threatened by chemical exposures. This behavior may be mediated by the same limbic brain regions that become sensitized after repeated chemical exposure in animals.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12004954
(2002) [Dependence of nonspecific bioeffects from air chemical pollutants in children].


BACKGROUND: Studies of IV magnesium sulfate as a treatment for acute asthma have had mixed results, with some data suggesting a benefit for acute severe asthma, but not for mild-to-moderate asthma. In a multicenter cohort, this study tests the hypothesis that administration of magnesium sulfate improves pulmonary function in patients with acute severe asthma. DESIGN: Placebo-controlled, double-blind, randomized clinical trial. SETTING: Emergency departments (EDs) of eight hospitals. PATIENTS: Patients aged 18 to 60 years presenting with acute asthma and FEV1 < or = 30% predicted on arrival to the ED. INTERVENTION: All patients received nebulized albuterol at regular intervals and IV methylprednisolone. Two grams of IV magnesium sulfate or placebo were administered 30 min after ED arrival. The primary efficacy end point was FEV1 at 240 min, and the data analysis was intent to treat. RESULTS: Two hundred forty-eight patients were included, and the mean FEV1 on ED arrival was 22.9% predicted. At 240 min, patients receiving magnesium had a mean FEV1 of 48.2% predicted, compared to 43.5% predicted in the placebo-treated group (mean difference, 4.7%; 95% confidence interval [CI], 0.29 to 9.3%; p = 0.045). A regression model confirmed the effect of magnesium compared to placebo was greater in patients with a lower initial FEV1 (p < 0.05). If the initial FEV1 was < 25% predicted, the final FEV1 was 45.3% predicted in the magnesium-treated group and 35.6% predicted in the placebo-treated group (mean difference, 9.7%; 95% CI, 4.0 to 15.3%; p = 0.001). If the initial FEV was > or = 25% predicted, magnesium administration was not beneficial; the final FEV1 was 51.1% predicted in the magnesium-treated group and 53.9% predicted in the placebo-treated group (mean difference, - 2.9%, 95% CI, - 9.4 to 3.7; p = not significant). Overall, the use of magnesium sulfate did not improve hospital admission rates. CONCLUSION: Administration of 2 g of IV magnesium sulfate improves pulmonary function when used as an adjunct to standard therapy in patients with very severe, acute asthma.

(2002) **Contributions of societal and geographical environments to "chronic Lyme disease": the psychopathogenesis and aporology of a new "medically unexplained symptoms" syndrome.**


Lyme disease is a relatively well-described infectious disease with multisystem manifestations. Because of confusion over conflicting reports, anxiety related to vulnerability to disease, and sensationalized and inaccurate lay media coverage, a new syndrome, "chronic Lyme disease," has become established. Chronic Lyme disease is the most recent in a continuing series of "medically unexplained symptoms" syndromes. These syndromes, such as fibromyalgia, chronic fatigue syndrome, and multiple chemical sensitivity, meet the need for a societally and morally acceptable explanation for ill-defined symptoms in the absence of objective physical and laboratory findings. We describe factors involved in the psychopathogenesis of chronic Lyme disease and focus on the confusion and insecurity these patients feel, which gives rise to an inability to adequately formulate and articulate their health concerns and to deal adequately with their medical needs, a state of disorganization termed aporia.

(2002) **Review of the upper airway, including olfaction, as mediator of symptoms.**


The upper airway serves as air conditioner, filter, and warning device. Two neurological modalities, olfaction and trigeminal chemoreception, inform us of the chemical qualities of the air we breathe. A number of poorly understood conditions, including nonallergic rhinitis, irritant-induced rhinitis, odor-triggered asthma, odor-triggered panic attacks, chemical-induced olfactory dysfunction, and irritant-associated vocal cord dysfunction, involve induction of symptoms by odorant and/or irritant chemicals in the upper airway. This article is a summary of the knowledge and theories about these various conditions, and highlights those aspects of nasal anatomy, physiology, and pathophysiология relevant to their understanding.

(2002) **Mass-casualty victim "surge" management. Preparing for bombings and blast-related injuries with possibility of hazardous materials exposure.**


Bombings and other blast-related events place severe demands on pre-hospital and in-hospital systems. The resulting surge of victims can overwhelm the resources of any facility not prepared for such an event. The September 11 terrorist attacks underscore the urgency of our need for preparedness. The challenges become even more
daunting when there is possible hazmat exposure as well; this means that adequate and rapid disposition of victims is even more critical in order to avoid contamination of hospitals systems or whole communities. Federal agencies have been designated and federal mandates have been issued to address mass casualty events, but federal or even regional systems cannot respond in time to address the massive and immediate needs generated by an explosion. Local communities must take the lead in developing incident command systems for initial management of such events. Hospital and pre-hospital providers play a key role in such planning. Ultimate management and disposition of large numbers of casualties, especially if contaminated, cannot follow standard patient management protocols; new protocols are needed. To avoid a total, overwhelming break down of in-hospital resources, hospitals need to assume a lead role in addressing such issues in their local communities.

(2002) [Alternative tests in the diagnosis of food allergies].
Senna, G, Gani, F, Leo, G and Schiappoli, M Journal/Recenti Prog Med. 93: 327-34.

In the last years an increase of allergic diseases has been observed whose prevalence is about 20-30% in general population of western countries. However there is a risk of an over diagnosis of allergic diseases as many different diseases (migraine, chronic urticaria, chronic inflammatory bowel diseases, chronic-fatigue syndrome etc.) are considered due to food allergy or intolerance. In many patients the diagnosis is based on the results of alternative diagnostic tests such as the cytotoxic test, the provocation neutralization sublingual or subcutaneous test, the heart-ear reflex test, the kinesiology, the biorisonance, the electro-acupuncture, and the hair analysis, or on immunological tests (immunocomplex or specific food IgG). We reviewed the scientific evidences of these tests (specificity, sensibility, rationale, reproducibility). According to most studies none of them had to be recommended as useful for the diagnosis of food allergy or intolerance. Physicians should alert patients about the risk of an indiscriminate use of these test in the diagnosis of food allergy. In fact the use of an incorrect diet could be dangerous, particularly in childhood, as recently shown.


OBJECTIVES: For risk assessments of solvents the knowledge on chemosensory irritation effects is important, but the methodological base for that is incomplete. The psychological approach measuring chemosensory irritations leans on perceived symptoms and self-reported changes of well being. Characteristics assessing the validity of such psychological approaches are presented. METHODS: The article is
based on 14 experimental inhalation studies with (mostly) 4-h exposures to acetone, 2-butanone, ethanol, ethyl acetate, ethyl benzene, iso-propanol, 1-octanol, and styrene. The profiles of exposure include constant and changing concentrations using the range of the German maximum concentrations at the workplace (MAK) list. Irritations (eyes and nose), olfactory symptoms (odour), and annoyance are the dependent variables measured by ratings. Young and healthy subjects (n=160), - partially, subjects with self-reported odour sensitivity (measured by items from the questionnaire on chemical and general environmental sensitivity) - were investigated.

RESULTS: The reliability of ratings is sufficient. Dose-response relationships for perceived odour and annoyance are stronger than those for irritations. A ranked order of the size of effect (related to the values before exposure) for the substances investigated shows correspondence between odour and annoyance; that for irritation differs. Within the limits of the MAK list, perceived irritations are not correlated to annoyance, whereas perceived bad smell correlates significantly to annoyance. Reversibility of the self-reported effects to approximately the pre-exposure level can be shown 1 h after cessation of the experimental exposure for the "normal" subjects. Influences of trait anxiety and chemical sensitivity on reports of annoyance, bad odour or irritation are only weak. CONCLUSION: The psychological approach of repeated measurements for self-reported irritation includes distinctive advantages compared with other methods, the simple and repeated availability during exposure, the sufficient reliability and dose-response relationship, and the comparability between substances by means of effect size. The extension of the concept of "chemosensory irritations" on reports for annoyance and bad smell can be recommended.


This article deals with the history of the terminological and nosological development of the concept neurasthenia introduced in 1869 by George Miller Beard and in particular with its reappearance in western medicine in the 1980 s. Beginning with its predecessors in antiquity and continuing with hypochondria, which became a fashionable disease in the 18 th century, the concept neurasthenia reached a high point and world-wide medical acceptance at the end of the 19 th/beginning of the 20 th century. However, between the 1930 s and 1960 s it declined in popularity and gradually disappeared until finally it only had a rudimentary nosological role in the term "pseudoneurasthenia". In the countries of the Far East, on the contrary, the concept of neurasthenia has been in continual use since its importation in the first decades of the last century. In the 1980 s, when an interest in the symptoms of chronic fatigue was reawakened in western medicine, the concept neurasthenia reappeared, this time to define the particular form of a neurotic disorder. Parallel to these developments increasing importance was attached to clinical descriptions of illnesses which on account of their similarity to the symptoms of neurasthenia could be termed modern
variants of the concept neurasthenia. These are "Chronic-Fatigue-Syndrome", "Fibromyalgia" and "Multiple Chemical Sensitivities" which have more or less adopted the organic inheritance of Beard's former concept of neurasthenia, despite the fact that so far the question of organicity could not be decisively answered in a single case. In order to clarify possible influences on the development of the concept neurasthenia and its variants, the theories and ideas of E. Shorter, medical historian at the University of Toronto, are discussed in the final part of the article, whereby the particular cultural background in each case has a decisive influence on the manifestation of the psychosomatic symptoms.


(2002) [Symptoms of sick house syndrome and contributory factors; study of general dwellings in Hokkaido].

OBJECTIVE: The aim of this study was to clarify the "Sick House Syndrome" which has recently received increasing attention, and to investigate relationships between symptoms and the state of general dwellings in Hokkaido. METHODS: Questionnaires were sent to residents in 1775 dwellings, mainly solitary houses built or remodeled within the past few years by 24 construction companies in Sapporo and its environs, and answers was received from 564. The questionnaires included queries about building structure and characteristics, the residents' habits in the home, and subjective symptoms. We requested one resident who had the most severe symptoms in the dwelling to answer a questionnaire about symptoms. We classified the symptoms into 11 categories, and selected those that developed or were aggravated after the building or remodeling. We defined dwellings in which inhabitants complained of one or more categories of symptoms as the group with sick-house-related disease (developed or aggravated group: DA group), and those in which the inhabitants complained of two or more symptoms as the group with sick house syndrome (more than one organic symptom group: MO group)". Associations between symptoms and dwellings were then studied. RESULTS: There were 201 dwellings for which residents complained of symptoms (37.2%). Of these, 94 were in the DA group (16.7%), and 57 (10.1%) in the MO group. The symptoms that developed or were aggravated after building or remodeling of the dwellings were throat, 7.1%, dermal, 6.9%, psychoneural, 5.3%, eye, 5.1%, and nasal problems, 4.1%. Unpleasant odors form furniture were significant in both groups (DA: crude odds ratio (OR) 2.66, MO: OR 3.24). Use of aromatics was significant in group DA (OR 1.78). Condensation on windows and mold growth in the dwellings were significant in both groups (condensation on windows; DA: OR 2.98, MO: OR 3.32, mold growth; DA: OR 3.11, MO: OR 3.24). In addition, the percentage of dwellings for which residents complained of symptoms increased with signs of dampness (condensation on windows and mold growth). On logistic regression
analysis, condensation on windows and mold growth were significant in both groups, and unpleasant odors from furniture in the MO group. CONCLUSION: It is suggested that symptoms of sick house syndrome are associated with high humidity such as condensation on windows and mold growth, odors from furniture and use of aromatics.


Rudolph, J Journal/Biochemistry. 41: 14613-23.

Cdc25 is a dual-specificity phosphatase that catalyzes the activation of the cyclin-dependent kinases, thus causing initiation and progression of successive phases of the cell cycle. Although it is not significantly homologous in sequence or structure to other dual-specificity phosphatases, Cdc25 belongs to the class of well-studied cysteine phosphatases as it contains their active site signature motif. Like other dual-specificity phosphatases, Cdc25 contains an active site cysteine whose pK(a) of 5.9 can be measured in pH-dependent kinetics using both small molecule and protein substrates such as Cdk2-pTpY/CycA. We have previously shown that the catalytic acid expected in phosphatases of this family and apparent in kinetics with the natural protein substrate does not appear to lie within the known structure of Cdc25 [Chen, W., et al. (2000) Biochemistry 39, 10781]. Here we provide experimental evidence for a novel mechanism wherein Cdc25 uses as its substrate a monoprotonated phosphate in contrast to the more typical bisanionic phosphate. Our pH-dependent studies, including one-turnover kinetics, solvent kinetic isotope effects, equilibrium perturbation, substrate depletion, and viscosity measurements, show that the monoprotonated phosphate of the protein substrate Cdk2-pTpY/CycA provides the critical proton to the leaving group. Additionally, we provide evidence that Glu474 on the Cdc25 enzyme serves an important role as a base in the transfer of the proton from the phosphate to the leaving group. Because of its greater intrinsic reactivity, the use of a monoprotonated phosphate as a phosphatase substrate is a chemically attractive solution and suggests the possibility of designing inhibitors specific for the Cdc25 dual-specificity phosphatase, an important anticancer target.
(2002) [Local and global environmental medicine--assessment by Norwegian physicians].

BACKGROUND: Local and global environmental problems are challenges to our societies and affect human health. This study examines how Norwegian physicians see these problems. MATERIAL AND METHODS: 1,260 physicians were sent a questionnaire on their knowledge, attitudes and practice related to this subject. The response rate was 88%. RESULTS: Four out of five physicians believe that the global environmental situation is a big threat to human health. Three out of five believe that physicians have a particular responsibility to contribute to a sustainable environment and development and should set an example by a sustainable lifestyle. Half of them believe that the health service has a greater responsibility for sustainability than other institutions. Only one out of three report that environmentally acceptable conditions have been focused in their workplace. Half of the general practitioners and one third of the specialists are faced with environmental health problems every week. More than every third doctor experience patients with "environmental hypochondria". Physicians feel that they need to know more about environmental medicine; mass media is their most important source of information. INTERPRETATION: The study indicates that Norwegian physicians understand the significance of the environmental situation and recognise the responsibility of the profession. However, this knowledge is to a lesser extent translated into practice.


OBJECTIVE: To report the prevalence of self reported chemical sensitivities in three cohorts of United Kingdom service personnel. METHOD: Cross sectional postal survey of three cohorts of United Kingdom military personnel comprising Gulf veterans (n=3531), those who had served in Bosnia (n=2050), and those serving during the Gulf war but not deployed there (Era cohort, n=2614). RESULTS: Sensitivity to at least one everyday chemical was reported by a considerable proportion of all three cohorts, and particularly by veterans of the Gulf war (Era: 14%; Bosnia: 13%; Gulf: 28%). CONCLUSION: Reported chemical sensitivities were common in all three military cohorts. Our understanding of chemical sensitivities remains limited and objective evidence for a causal link between low level exposures to chemicals and reported symptoms is lacking. Given their frequency in the population, further work in this area is necessary.
query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11886951


Statin treatment is widely used in both primary and secondary prevention of diseases in which hyperlipidaemia is a major risk factor, for example, ischaemic heart disease. The development of ulcerative colitis as an adverse reaction to simvastatin is reported, which, despite withdrawal of the drug, proved fatal. The adverse reaction profile of the statins is reviewed, which suggests that this is a class effect and not one limited to simvastatin.

(2002) [The use of methodology for the risk assessment during socio-hygienic monitoring in Moscow].


BACKGROUND: Testing of urines with dipsticks for proteinuria, glycosuria, etc., is common practice. A deficiency with currently available dipsticks is their lack of chemical sensitivity and underestimation of low-molecular-weight proteins such as light chains. METHODS: We experimented with a number of dyes that gave an easily recognized color change on dipsticks for various low-molecular-weight proteins such as alpha-1-glycoprotein, alpha-1- and beta-2-microglobulin, and kappa and lambda light chains. We were successful in formulating a dye for impregnating dipsticks that gave a color change with low-molecular-weight proteins. RESULTS: Most dipsticks will measure proteins down to about 1 g/l. Our composite of two dyes (described here as the "TPR" dipsticks) gave reproducible results for protein concentrations of >/=300 mg l, and detected low-molecular proteins. The TPR reagent is resistant to interferences from many compounds; also, the protein results are not altered in a given urine at a pH between 5 and 8. CONCLUSIONS: We have developed a dipstick that detects low-molecular-weight proteins. The dipsticks are easy to use and are suitable for outpatient or point-of-care testing. The precision of the dipsticks is satisfactory and is
only marginally lower than quantitative spectrophotometric methods using pyrogallol red (PYR).

(2002) [Risk coefficients of non-carcinogenic effects].
Prusakov, VM and Verzhbitskaia, EA Journal/Gig Sanit. 36-42.

(2002) Indoor allergens in Italy.

(2002) NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity.
Pall, ML Journal/Faseb J. 16: 1407-17.

Multiple chemical sensitivity (MCS) is a condition where previous exposure to hydrophobic organic solvents or pesticides appears to render people hypersensitive to a wide range of chemicals, including organic solvents. The hypersensitivity is often exquisite, with MCS individuals showing sensitivity that appears to be at least two orders of magnitude greater than that of normal individuals. This paper presents a plausible set of interacting mechanisms to explain such heightened sensitivity. It is based on two earlier theories of MCS: the elevated nitric oxide/peroxynitrite theory and the neural sensitization theory. It is also based on evidence implicating excessive NMDA activity in MCS. Four sensitization mechanisms are proposed to act synergistically, each based on known physiological mechanisms: Nitric oxide-mediated stimulation of neurotransmitter (glutamate) release; peroxynitrite-mediated ATP depletion and consequent hypersensitivity of NMDA receptors; peroxynitrite-mediated increased permeability of the blood-brain barrier, producing increased accessibility of organic chemicals to the central nervous system; and nitric oxide inhibition of cytochrome P450 metabolism. Evidence for each of these mechanisms, which may also be involved in Parkinson’s disease, is reviewed. These interacting mechanisms provide explanations for diverse aspects of MCS and a framework for hypothesis-driven MCS research.

Osterberg, K, Orbaek, P and Karlson, B Journal/Appl Neuropsychol. 9: 139-47.

To address the hypothesis of brain dysfunction as a component of the multiple chemical sensitivity (MCS) syndrome, a neuropsychological battery comprising 8 tests was given to 17 Swedish MCS patients and 34 demographically matched controls. Across the 6 tests used as indicators of brain impairment, comprising a total of 17 test variables, the MCS group performed poorer only in a complex reaction time test (mean reaction time; p = 0.002; t test). Correction for self-ratings of mental distress and trait psychasthenia did not eliminate the deviation in the reaction time test. Because the results on most tests were within normal limits, brain impairment was not evidenced. However, the similar minor deviations in neurobehavioral tests observed in several studies of MCS patients indicate the need for a study on a larger sample of MCS cases.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12584079


Personality, mental distress, and risk perception were assessed in (a) cases of multiple chemical sensitivity (MCS; n = 17), (b) chemically intolerant toxic encephalopathy cases (TE), type 2A (n = 31) and 2B (n = 26), and (c) healthy referents (n = 200). MCS cases showed elevated mental distress scores on the Depression, Interpersonal Sensitivity, Global Severity Index, and Somatization scales in the Symptom Checklist 90 (SCL-90). In the Karolinska Scales of Personality (KSP) the MCS group showed an elevation only on the Psychasthenia scale. Both TE groups showed elevations across the KSP anxiety scales Muscular Tension, Psychasthenia, and Somatic Anxiety. TE type 2B subjects also showed elevations on the Irritability and Indirect Aggression scales. However, neither MCS nor TE groups showed deviating personality characteristics in the Meta Contrast Technique test. Similarly, none of the groups deviated from referents in a risk perception inventory.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12004955
(2002) [Evidence-based health care: multiple chemical hypersensitivity or idiopathic environmental intolerance].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11809150

---------------------------------------------------------------


Since symptoms typical for multiple chemical sensitivity (MCS) are induced by exposure to low levels of chemicals, we hypothesize that MCS represents an impaired recognition of odors or an increased emotional reaction to common odors. Twenty-five subjects with MCS, 20 women and 5 men, and 50 gender-and-age matched controls participated in this study. The University of Pennsylvania Smell Identification Test (UPSIT) and the Cross-Cultural Smell Identification Test (CC-SIT) were administered. In addition to selecting the most probable odor among the four, the subjects were asked their impression of each odor. Odor identifiability evaluated by the scores of two tests, were almost equal in MCS and control groups. The mean CC-SIT odor per person with pleasant feeling was lower in MCS than in controls. The mean odor per person creating an unpleasant sensation was higher in MCS than in the controls. Gingerbread was the only odor making MCS subjects more pleasant than the controls. Nine out of 40 UPSIT odors were felt as unpleasant by MCS subjects more than by controls. This study indicates that MCS subjects are able to identify the odors equally as well as the controls but feel unpleasant to a larger number of odors than the controls. Despite unknown mechanisms of the altered odor perception in MCS, the application of these tests for diagnostic procedure of MCS is proposed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12597243

---------------------------------------------------------------


---------------------------------------------------------------
Neville, H and Bavelier, D Journal/Prog Brain Res. 138: 177-88.

The results from the language studies taken as a whole point to different developmental time courses and developmental vulnerabilities of aspects of grammatical and semantic/lexical processing. They thus provide support for conceptions of language that distinguish these subprocesses within language. Similarly, following auditory deprivation, processes associated with the dorsal visual pathway were more altered than were functions associated with the ventral pathway, providing support for conceptions of visual system organization that distinguish functions along these lines. Could the effects observed in blind and deaf adults be accounted for, at least in part, by the redundant connectivity of the immature human brain? One way we tested this hypothesis was to study the differentiation of visual and auditory sensory responses in normal development (Neville, 1995). In normal adults, auditory stimuli elicit ERP responses that are large over temporal brain regions but small or absent over occipital regions. By contrast, in 6-month-old children we observed that auditory ERPs are equally large over temporal and visual brain regions, consistent with the idea that there is less specificity and more redundancy of connections between the auditory and visual cortex at this time. Between 6 and 36 months, however, we observed a gradual decrease in the amplitude of the auditory ERP over visual areas, while the amplitude over the temporal areas was unchanged. These results suggest that early in human development, there exists a redundancy of connections between auditory and visual areas and that this overlap gradually decreases after birth. This loss of redundancy may be a boundary condition that determines when sensory deprivation can result in alterations in the organization of remaining sensory systems. The considerable variability in timing of sensitive periods may also be in part due to temporal differences in the occurrence of redundancy within different systems. Ongoing studies of infants and children employing different types of stimuli will test for the specificity of these effects (Mitchell et al., 1999). Differences in the degree of plasticity may also be due to differences in the overall level of redundant connectivity within different systems. For example, it may be that aspects of sensory systems that are specialized for high spatial acuity (e.g., central vision and central audition) exhibit fewer developmental redundancies, decreased modifiability and more specificity than those displaying less acuity and precision (e.g., peripheral representations within vision and audition). There is some evidence for this hypothesis within the visual system (Chalupa and Dreher, 1991). In addition, there may be molecular differences between systems displaying different levels and patterns of experience-dependent plasticity. It is of interest that all levels of the dorsal pathway of the visual system, which in the studies reviewed here shows a high level of modifiability, displays strong immunoreactivity for the monoclonal antibody CAT 301 in macaque monkeys (DeYoe et al., 1990). By contrast there is very little labeling within the ventral visual pathway. Moreover, the expression of CAT 301 immunoreactivity shows marked experience-dependent plasticity, suggesting it may play a role in the guidance and/or stabilization of synaptic structure (Sur et al., 1988). Further research along these lines within the auditory system and in animal models of sensory
deprivation and other developmental disorders may elucidate the role of specific molecular factors in the developmental plasticity of different neural systems. A related, more general hypothesis that may account for the different patterns of plasticity within both vision and language is that systems employing fundamentally different learning mechanisms (perhaps mediated by different anatomical and molecular substrates) display different patterns of developmental plasticity. It may be that systems that display experience-dependent change throughout life, including the topography of sensory maps (Merzenich et al., 1988; Gilbert, 1995; Kaas, 1995), lexical acquisition (i.e. object-word associations), and the establishment of form, face, and object representations (i.e., ventral pathway functions) rely upon very general, associative learning mechanisms that permit learning and adaptation throughout life. By contrast, systems that are important for computing dynamically shifting relations among locations, objects and events (including the dorsal visual pathway and the systems of the brain that mediate grammar) appear dependent on and modifiable by experience primarily during more limited periods in development. This could account for both the greater developmental deficits and enhancements of dorsal pathway function following various developmental anomalies and for the greater effects of altered language experience on grammatical functions. Further research is necessary to characterize systems that become constrained in this way and those that can be modified throughout life. This type of developmental evidence can contribute to fundamental descriptions of the architecture of different cognitive systems and can guide future studies of the cellular and molecular mechanisms important in neuroplasticity. Additionally, in the long run, they may contribute to the design of educational and habilitative programs for both normally and abnormally developing children.

(2002) [Clinical diagnosis of environmentally induced non-communicable diseases].
Nagornyi, SV, Maimulov, VG, Oleinikova, EV, Tsibul'skaia, EA, Tidgen, VP and Cherniakina, TS Journal/Gig Sanit. 53-7.

(2002) [Epidemiologic approaches to diagnosis of diseases dependent on ecologic factors].
Nagornyi, SV, Maimulov, VG, Oleinikova, EV, Malevannyi, IN, Grishanova, GI, Nechaev, VV, Tsibul'skaia, EA, Cherniakina, TS, Lomtev, A and Gorbanev, SA Journal Med Tr Prom Ekol. 31-5.

The article deals with peculiarities in diagnosis of diseases caused by environmental hazards. The diagnosis covers population level and includes evaluation of environmental quality. Analysis of health for whole population and for risk groups
enables to reveal "indicator" diseases. Social and hygienic monitoring, complex sanitary and ecologic examination recommend disclosure of facts and causes for any "nonspecific" diseases, definition of disorders caused by specific environmental hazards. The authors consider unity of hygienic and epidemiologic analysis for causative relationships in "human-environment" system in evaluation of noninfectious risk factors.


OBJECTIVE: To describe a cluster of inflammatory rheumatic diseases in an office workplace that suggests the presence of an environmental trigger. METHODS: There had been an indoor air problem in the workplace since the early 1990s. Large areas of the outer walls of the building were found to be moisture-damaged and contaminated by microbial growth. Case histories of the personnel were studied, and their working areas were related to the areas with highest microbial contamination. The incidence of inflammatory rheumatic diseases was compared with the statistics of the same geographic area. RESULTS: Ten patients with inflammatory rheumatic diseases (3 rheumatoid arthritis, 4 ankylosing spondylitis, 2 Sjogren's syndrome, and one of psoriatic arthritis) entitled to specially reimbursed medication were diagnosed in 1987-2000 (seven cases in 1995-1998). The incidence density ratio computed for the period 1987-2000 was 6.8 (95% confidence interval 3.6-13.0) for all office personnel and 13.2 (6.0-29.0) for those working close to the wall sustaining the worst damage. CONCLUSION: The accumulation of chronic inflammatory rheumatic diseases in a single workplace suggests that some environmental exposure in this damp office had triggered the diseases.

(2002) Follow-up on Trinity.

Accumulation of Advanced Glycation Endproducts (AGEs) in the brain is a feature of ageing and degeneration, especially in Alzheimer's disease (AD). Increased AGE levels explain many of the neuropathological and biochemical features of AD such as extensive protein crosslinking (beta-amyloid and MAP-tau), glial activation, oxidative stress and neuronal cell death. Oxidative stress and AGEs initiate a positive feedback loop, where normal age-related changes develop into a pathophysiological cascade. Combined intervention using antioxidants, anti-inflammatory drugs and AGE-inhibitors may be a promising neuroprotective strategy.


Moghaddam, B Journal/Biological Psychiatry. 51: 775-787.

http://www.sciencedirect.com/science/article/B6T4S-45R56K3-1/29adf082ebdd0ae6096c6765c0d197c7d

This study evaluated the association between acute poisoning with organophosphate pesticides (OPs) and quantitative tactile vibration thresholds. Thresholds of the dominant index fingers and big toes of 56 men hospitalized for acute poisoning with OPs were measured at hospital discharge (1-24 days after poisoning) and around seven weeks later (24-176 days after poisoning), and compared with those of controls. Thresholds of the big toes of men with severe intentional poisonings due to neuropathic OPs (metamidophos and chlorpyrifos) increased between the first and second examinations. Threshold impairment was not detected in the index finger regardless of poisoning agent or severity. The development of threshold impairment as a consequence of severe intentional poisonings with neuropathic OPs is consistent with other reports indicating that only severe OP poisonings produce sensory peripheral nerve effects.

-----------------------------------------------------------------------------------------------


The cellular and molecular mechanisms that enable us to sense cold are not well understood. Insights into this process have come from the use of pharmacological agents, such as menthol, that elicit a cooling sensation. Here we have characterized and cloned a menthol receptor from trigeminal sensory neurons that is also activated by thermal stimuli in the cool to cold range. This cold- and menthol-sensitive receptor, CMR1, is a member of the TRP family of excitatory ion channels, and we propose that it functions as a transducer of cold stimuli in the somatosensory system. These findings, together with our previous identification of the heat-sensitive channels VR1 and VRL-1, demonstrate that TRP channels detect temperatures over a wide range and are the principal sensors of thermal stimuli in the mammalian peripheral nervous system.


-----------------------------------------------------------------------------------------------

OBJECTIVES: Clinic studies demonstrate that people diagnosed with environmental illness experience high levels of disability and health care utilization. Even though the controversial status of this disorder attracts attention, actual prevalence estimates and estimated impact on health care systems are unclear. To address this, we sought both a prevalence estimate and a measure of the degree of health care utilization for those reporting this diagnosis. DESIGN AND METHODS: Point prevalence, as assessed by self-report of professional diagnosis, was established with data from the Nova Scotia Health Survey 1995, a stratified, random sample population survey of 3227 Nova Scotian adults. We compared medical care utilization for the year following the survey, drawn from the provincial medical insurance register, between the 24 cases with no other reported medical conditions and 48 age-, sex-, and education level-matched healthy controls. RESULTS: The adjusted point prevalence of environmental illness was 2.6%. Physician reimbursement costs across the following year were 5.5 times more likely to be above the survey average ($259 CAD) when compared to the healthy control group. CONCLUSIONS: The prevalence of environmental illness diagnoses represents a significant disability and treatment burden, justifying research into case definition and the phenomenology of environmental illness by health psychologists.

(2002) Multiple Chemical Sensitivities Under Siege. McCampbell, A Multiple Chemical Sensitivities Task Force of New Mexico. 2005:


OBJECTIVES: To describe complex interactions of multiple factors believed to contribute to fibromyalgia syndrome (FMS) at a person-centered level to enhance approaches to care, teaching, and research. The main factors addressed were central nervous system sensory sensitization, autonomic nervous system (ANS) activation, neurohumoral perturbations, and psychosocial and environmental stressors. A person-centered approach is defined as attention to major biopsychosocial issues of affected individuals. METHODS: Literature on classification, mechanistic pathways, course and outcomes, and management of FMS was reviewed to assess applications of person-centered approaches to care, teaching, and research. Various biopsychosocial influences were considered in relation to the heterogeneous subjective manifestations of this illness, including central hyperalgesia, ANS and other neurohumoral perturbations, functional hyperexcitability, nonrestorative sleep, and psychologic distress. RESULTS: A person-centered approach to FMS can expand on
and strengthen traditional biomedical concepts. Adding such a focus can help to untangle current controversies in the course, outcomes, and treatment of FMS. A person-centered approach can also help in the subgrouping of affected patients for greater specificity in care programs and in improved clinical investigations. In the biomedical model, diverse symptoms of FMS are often addressed separately and apart from their interconnectedness and linkages to the patient's individualized biopsychosocial factors. However, the causes of FMS symptomatology are not likely to be caused by uniform biologic abnormalities across populations. Rather, the syndrome likely results from personal reactivities to varied multifactorial biopsychosocial influences. Common denominators among individuals may include varying degrees of ANS activation (or personal susceptibility to ANS activation), nonrestorative sleep, negative affectivity, and other central pain sensitization mechanisms, among the pathways reviewed. CONCLUSIONS: Innovative analytical methodologies will need to be developed to more effectively investigate complex interacting biopsychosocial dynamics at a person-centered level, including qualitative research, and multifactorial and multilevel techniques. Adding person-centered approaches to biopsychosocial concepts of FMS promises to show new physiopathogenetic insights and more effective treatment than current biomedical models alone. Person-centered approaches enhance patient-physician relationships and help prioritize patients' goals in mutually derived treatment plans.

-------------------------------------------------------------------------------------------------------------------------------------


The new trend towards developing enantiospecific drugs has increased the interest in enantiospecific pharmacokinetics of chiral drugs, mainly in the case where only one of the two enantiomers is responsible for the pharmacological activity. Enantiospecific bioassays are also useful in investigating the pharmacokinetic behaviour of the two enantiomers when a given drug is marketed as racemate. The stability of the stereogenic centre in vitro and in vivo, as far as unidirectional and bidirectional inversions are concerned, is another reason for requiring stereospecific assay and bioassay. These assays are often complicated in order to achieve quantification, mainly for in vivo measurements, which are often in the low pg/ml range. This paper considers the enantiospecific bioassays, the methods and approaches used, the need for chemical derivatization, and the difficulties involved. It includes a specific discussion for the genetic polymorphic metabolism involving stereogenic centres.

-------------------------------------------------------------------------------------------------------------------------------------

Liu, L Journal/Crisp Data Base National Institutes of Health.
One of the mechanisms responsible for the therapeutic failure of alkylating agents is
the DNA repair protein, 06-alkylguanine-DNA alkyltransferase (AGT), encoded by the
MGMT gene. AGT removes the alkyl group from 06-alkylguanine in a fast and single
step reaction, thereby preventing the formation of DNA cross-links by chloroethylating
agents such as BCNU. Currently, a strategy involving the inactivation of AGT by
06-benzylguanine (BG) followed by BCNU treatment has shown evidence of
significantly increased antitumor effect of BCNU. Ongoing clinical trials are evaluating
its efficacy in tumor chemotherapy. However, repeated administration of BG and BCNU
will raise the possibility that BG resistant cells develop, subsequently, resulting in the
failure of chemotherapy. In our recent studies, we selected two MMR deficient colon
cancer cells for resistance to BG and BCNU and found two different mutations at
amino acid 165 of AGT, to form K165E and K165N mutant AGT in these two cell lines.
The cells harboring the K165 mutations have dramatically decreased AGT activity but
remarkably increased resistance to BG+BCNU. Thus, we hypothesize that MMR
deficiency leads to a high mutation frequency in DNA repair gene such as AGT gene
and that two K165 mutant AGTs predominantly confer acquired resistance either to the
combination BG+BCNU and BG+TMZ or alkylating agents alone. To test this
hypothesis, it is necessary to distinguish acquired resistance caused by mutated AG
from other resistance factors. This is of concern because the two BG-resistant AGTs
were identified in cell lines with MMR defects. Once cells lose MMR, their sensitivity to
various chemotherapeutic agents is decreased directly by impairing the ability to
recognize or process DNA damage and indirectly by increasing the mutation rate
throughout the genome. Therefore, it is possible that not only does mutation in AGT
confer drug resistance, but other mechanisms of drug resistance as well. Thus, these
specific objectives are proposed: to define whether K165 mutant AGTs are the major
factor of acquired resistance to BG and BCNU, despite low AGT activity; to define
whether colon cancer tumors with MMR deficiency are more likely to acquire resistance
to BG+BCNU through mutations in MGMT than MMR wt tumors; and to determine
whether BG-resistant AGT could be selected in the xenograft setting after mice
carrying the tumor received multiple treatments with BG and BCNU. The long-term
goal is to define the conditions in which MGMT mutations are observed in human
tumors after clinical use of BG and BCNU. Overall, this project promises to provide
novel information on the induction of BG-resistant AGT in drug treated MMR defective
tumors and the impact of the altered AGT-resistance to BG+BCNU.
(2002) **Arachidonic acid inhibition of muscarinic receptor-mediated nitric oxide production occurs at the level of calcium mobilization in Chinese hamster ovary cells.**
Linden, DR and el-Fakahany, EE Journal/Neurochem Res. 27: 441-9.

Strong evidence supports that nitric oxide (NO) alters cell signaling pathways involving arachidonic acid (AA). Little is known, however, about the reciprocal modulation of nitrergic pathways by AA. The effects of exogenous AA on signal transduction of M1 muscarinic acetylcholine receptors were investigated in a model system of stably transfected Chinese hamster ovary cells. AA concentration-dependently inhibited the effects of carbachol in producing NO (IC50 = 191 microM) but did not alter inositol phosphate production or M1 receptor binding. AA inhibited both carbachol-induced transient and sustained increase in intracellular calcium concentration ([Ca2+]; IC50 = 11 and 12 microM, respectively). Furthermore, AA-induced increase in [Ca2+]i cross-desensitizes with thapsigargin, but AA does not inhibit Ca(2+)-ATPase activity. These data support the concept that AA concentration-dependently inhibits receptor-mediated NO production at the level of calcium mobilization.

---------------------------------------------------------------

(2002) **[Factors contributing to interindividual variability to chemical toxicity].**

Recognising toxicokinetic and toxicodynamic variability is important in the risk assessment of chemicals and may help to explain individual differences in susceptibility in exposed populations. This presentation discusses the influence of age, gender, disease and genetics on toxicokinetic and toxicodynamic processes. Neonates have a reduced capacity for metabolism and elimination of xenobiotics that may enhance chemical toxicity caused by a parent chemical. Furthermore, the brain, reproductive organs and immune system have critical postnatal periods of maturation where they appear highly sensitive to toxic effects that interfere with the maturation process and may lead to permanent structural or functional organ changes. In the elderly, a combination of reduced organ function, disease and use of pharmaceuticals contributes to enhanced chemical sensitivity reflected in an increased incidence of adverse drug reactions in this population. There is a high degree of functional polymorphism in biotransforming enzymes. Such polymorphisms have been shown to contribute to interindividual variability in chemical response. During the last few years, accounts have been given of several polymorphisms in genes with importance for toxicodynamic processes, such as DNA repair genes and receptor genes. However, further information is needed in order to evaluate the functional contribution of these polymorphisms to chemical sensitivity and health risk.

---------------------------------------------------------------

Cases of alleged hypersensitivity to electromagnetic fields (EMFs) have been reported for more than 20 years, and some authors have suggested some connection with the "multiple chemical sensitivity" illness. We report the results of a telephone survey among a sample of 2,072 Californians. Being "allergic or very sensitive" to being near electrical devices was reported by 68 subjects, resulting in an adjusted prevalence of 3.2% (95% confidence interval = 2.8, 3.7). Twenty-seven subjects (1.3%) reported sensitivity to electrical devices but no sensitivity to chemicals. Characteristics of the people reporting hypersensitivity to EMFs were generally different from those of people reporting being allergic to everyday chemicals. Alleging environmental illness or multiple chemical sensitivity diagnosed by a doctor was the strongest predictor of reporting being hypersensitive to EMFs in this population. Other predictive factors apart from self-reporting chemical sensitivity were race/ethnicity other than White, Black, or Hispanic; having low income; and being unable to work. The perception of risk of exposure to EMFs through the use of hair dryers (vs. exposure to power and distribution lines) was the factor the most associated with self-reporting about hypersensitivity to EMFs. However, risk perception was not sufficient to explain the characteristics of people reporting this disorder.


Hypersensitivity to exposure to electric and magnetic fields (EMFs) has been reported for nearly 20 years; however, the literature on the subject is still very limited. Nearly all the literature published concerns a dermatological syndrome that consists of mainly subjective symptoms (itching, burning, dryness) and a few objective symptoms (redness, dryness) appearing after individuals begin working with video display units and decreasing during absence from work. Case-control studies as well as some good but limited double-blind trials have not found any clear relationship between this syndrome and exposure to EMFs. A "general syndrome" with more general symptoms has been rarely described but seems to have a worse prognosis. The symptoms often associated with skin disorders are mainly of neurasthenic type and can cover a lot of nonspecific symptoms present in other atypical syndromes such as multiple chemical sensitivity or chronic fatigue. Most of these symptoms are allegedly triggered by exposure to different sources of EMFs, but there have been no valid etiological studies.
published on this more general syndrome. It appears that the so-called hypersensitivity to environmental electric and magnetic fields is an unclear health problem whose nature has yet to be determined.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12194895

(2002) Increased alveolar nitric oxide concentration in asthmatic patients with nocturnal symptoms.

Nocturnal asthma symptoms and impaired lung function at night are related to inflammatory activity in the peripheral lung compartment. Exhaled nitric oxide (NO) measurement at multiple exhalation flow rates can be used to separately assess alveolar and bronchial NO production and inflammation. The authors hypothesised that asthmatic patients with nocturnal symptoms have a higher alveolar NO concentration than those with only daytime symptoms. The authors asked 40 patients with newly-diagnosed steroid-naive asthma about their nocturnal asthma symptoms through the use of a written questionnaire. Alveolar NO concentration and bronchial NO flux were assessed in the 40 asthmatics and 40 healthy controls. Nineteen of the 40 patients reported nocturnal symptoms. Patients with nocturnal symptoms had a higher alveolar NO concentration (1.7+/−0.3 (mean+/−SEM) parts per billion (ppb)) than patients without nocturnal symptoms (0.8+/−0.3 ppb, p=0.012) or healthy controls (1.0+−0.1 ppb, p=0.032). Bronchial NO flux was higher both in patients with (2.4+/−0.4 nL x s(-1), p<0.001) and without (2.6+/−0.4 nL x s(-1), p<0.001) nocturnal symptoms, compared to controls (0.7+/−0.1 nL x s(-1)). Nocturnal symptoms in asthmatic patients are related to a higher alveolar nitric oxide concentration. The results suggest that assessment of alveolar nitric oxide concentration can be used to detect the parenchymal inflammation in asthmatic patients with nocturnal symptoms.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12412673

Lee, SK, Ou, YC and Yang, RS Journal/Toxicol Sci. 65: 26-34.

Polychlorinated biphenyls (PCBs) are ubiquitous environmental contaminants that can induce neurological defects in infants and children via placental and lactational transfer. To investigate the lactational transfer of PCBs and compare pharmacokinetic
interactions among nonpregnant, lactating mice and suckling pups, quantitative

time-course measurements of PCB accumulation in tissues were performed. On

postnatal day 1, nonpregnant and lactating C57BL/6 mice were exposed to PCB 153

(2,2',4,4',5,5'-hexachlorobiphenyl, 20 mg/kg) alone or a mixture of PCB 153 (20 mg/kg)

and PCB 126 (3,3',4,4',5-pentachlorobiphenyl, 0.2 mg/kg) by oral gavage. At 1, 3, 6,

and 13 days after treatment, PCB 153 and PCB 126 were determined in nonpregnant

and maternal tissues as well as in neonatal tissues by gas chromatography (GC).

Coadministration of PCB 153 and PCB 126 increased PCB 153 retention in the liver

and decreased PCB 153 accumulation in the fat of nonpregnant mice. Lactational

transfer was confirmed to be an efficient elimination mechanism for the lactating mice

but a major source of exposure in the pups. However, little or no significant

pharmacokinetic interactions were observed in lactating mice and suckling pups. To

describe pharmacokinetic interactions between PCB 153 and PCB 126, a

physiologically based pharmacokinetic model for PCB 153 disposition was developed.

The effects of PCB 126 on the fat content in liver and a diffusion permeation constant

in fat were incorporated into the physiologically based pharmacokinetic (PBPK) model.

This model successfully describes PCB 153 disposition altered by PCB 126 in

nonpregnant mice.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11752682

(2002) Site-directed mutagenesis of a potential catalytic and formyl phosphate

binding site and substrate inhibition of N10-formyltetrahydrofolate synthetase.

Leaphart, AB, Trent Spencer, H and Lovell, CR Journal/Arch Biochem Biophys. 408:

137-43.

Structural studies of N(10)-formyltetrahydrofolate synthetase (FTHFS) have indicated

the involvement of Arg 97 in the binding of the formyl phosphate intermediate. Two

site-directed mutants were constructed to test this hypothesis: R97S (Ser substitution)

and R97E (Glu substitution). The k(cat) of R97S was approximately 60% that of the

wild-type enzyme and had K(m) for ATP and formate twofold higher than those of wild

type. R97E was completely inactive and had a K(m) for ATP nearly six times that of

wild type. Substrate inhibition by tetrahydrofolate was shown to occur in wild-type and

R97S enzymes using both steady-state and transient-state kinetic approaches. These

results lend greater insight into the mechanistic function of FTHFS by confirming the

interaction of both ATP and formate with Arg 97 and introducing the aspect of

substrate inhibition by tetrahydrofolate with regard to substrate binding and dissociation.

Nonspecific symptoms and a general feeling of ill health that is difficult to objectify are the commonest health problems with which patients present to an Environmental Medicine Outpatient Department (OPD). Of this group, a great proportion meets the classification criteria for Chronic Fatigue Syndrome (CFS) or Functional Memory Disorders in association with Idiopathic Chronic Fatigue (FMD-ICF). This is a longitudinal study of the OPD of Environmental Medicine, Freiburg University Hospital, Germany, to determine the feasibility and impact of an interdisciplinary therapeutic approach (self-help program, acupuncture, psychosomatic support by group interventions) in 8 patients with CFS, FMD-ICF, or CFS in association with self-reported Multiple Chemical Sensitivities (sr-MCS). The intervention took into consideration the patients' need for treatment of physical aspects of their disease. This is an important step to motivate patients into required psychosomatic support. Although none of the patients was willing to accept psychosomatic support or psychotherapy at study outset, acceptance of psychosomatic group interventions was high during the study course. Additionally five patients started with personal counseling at the Psychosomatic Clinic, and, without feeling stigmatized, 4 patients started with specific psychotherapy. The patients' quality of life showed no increase after four months, but, as shown by the Sum-Score of SF-36, it had improved significantly at the end of the study, which covered eight months' treatment (p = 0.015). Two follow-up investigations showed that this improvement probably persisted in part (mainly in the dimensions mental health, social function, physical role function, and vitality). In conclusion our interdisciplinary therapeutic approach indicates successful treatment of patients attributing CFS, CFS/sr-MCS, and FMD-ICF to environmental poisoning. We now plan to conduct a randomized controlled trial in the future.

---------------------------------------------------------------

Kuchma, VR Journal/Gig Sanit. 51-3.

---------------------------------------------------------------

Kroesen, K, Baldwin, CM, Brooks, AJ and Bell, IR Journal/Fam Pract. 19: 57-64.
BACKGROUND: Use of complementary and alternative medicine (CAM) is growing quickly in the USA, prompting hypotheses about why people turn to CAM. One reason for increasing use of CAM modalities may be dissatisfaction with the conventional care system. However, recent studies suggest that dissatisfaction is not a major factor. OBJECTIVES: This paper provides another perspective on the possible relationship between dissatisfaction with conventional care and the use of CAM. METHODS: Qualitative data collection, in the form of 12 focus groups with 100 CAM users, was used to inquire about issues surrounding the use of CAM. Focus group participants were military veterans enrolled in the Southern Arizona VA Health Care System, and their significant others. Qualitative analysis identified key themes emerging from the focus groups. RESULTS: Although participants were satisfied in general terms with their conventional care, there were particular aspects of the conventional care system that they criticized. Dissatisfaction with aspects of conventional care, particularly its reliance on prescription medications, was an important component in their motivation to use CAM. Results also suggest that the conventional medical system's lack of holism (inadequate information regarding diet, nutrition and exercise, and ignorance of social and spiritual dimensions) is also an important motivation for turning to CAM in this particular population. CONCLUSIONS: Independent research and a sense of responsibility on the part of focus group participants for their own health seemed to be taking them outside the domain of the conventional health care system.


MCS has been studied predominantly in clinical and occupational settings. Since the mid-1990's, a few investigators have examined dimensions of this controversial syndrome in the general population. In this discussion, the role of epidemiology in learning about MCS is presented. Some of the challenges of population-based research on MCS are discussed. Specific studies are presented with regard to study population, case definition, exposure and case classification methods, interpretation, and conclusions.


Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer. The genetic factors underlying the susceptibility to this disease remain elusive. The enzymes CYP2E1, MPO and NQO1 are involved in the biotransformation of a variety of xenobiotics present in organic solvents, tobacco smoke, drugs, plastic derivatives and pesticides. They also control the level of the oxidative stress by catalyzing the formation of free radicals or by protecting cells from their deleterious effect. DNA variants in the corresponding genes have been associated with an increased susceptibility to different adult cancers, including hematologic malignancies. To investigate whether they represent risk-modifying factors in childhood ALL, we conducted a case-control study involving 174 patients and 337 controls, both of French-Canadian origin. We found that carriers of the CYP2E1*5 variant were at 2.8-fold higher risk of ALL (95%CI, 1.2-6.4) and that NQO1 alleles *2 and *3 contributed to the risk of ALL as well (OR = 1.7, 95%CI, 1.2-2.4). No such association was found with MPO alone. However, when the wild-type MPO allele was considered together with the CYP2E1 and NQO1 risk-elevating genotypes, the risk of ALL was increased further (OR = 5.4, 95%CI, 1.2-23.4) suggesting a combined effect. We also found a gene-gene interaction between the GSTM1 null genotype and NQO1 mutant alleles. It is therefore plausible that exposure to xenobiotics metabolized by these enzymes play a role in the etiology of childhood ALL.


As part of an evaluation study of the impacts of the Indonesian integrated pest management (IPM) Farmer Field Schools on farmers' health, focus group discussions were conducted with rice farmers who grew shallots in rotation. Farmers who had previously participated in IPM rice field schools and who were at the time participating in IPM shallot field schools were compared with farmers who had no experience with IPM methods. The study found that farmers' knowledge concerning the health dangers of pesticides is not sufficient to change their behaviors. Their overriding concern is crop damage that leads to economic loss, not health. IPM field-school training offers farmers a viable alternative by concretely demonstrating the health, agricultural, environmental, and economic advantages of eliminating unnecessary
pesticide use. If public health professionals aim to change behaviors through interventions, they must employ appropriate methods, meet the community's priorities and values, and offer feasible alternatives.


Symptoms, and especially those without clear underlying medical explanations, account for a large percentage of clinical encounters. Many unexplained symptoms have been organized by patients and practitioners into syndromes such as chronic fatigue syndrome, multiple chemical sensitivity, sick building syndrome, Gulf War syndrome, and the like. All these syndromes are defined solely on the basis of symptoms rather than by medical signs. Some of the above-described conditions overlap strongly with explained conditions such as asthma. The relationship of such symptoms and syndromes to environmental exposure is often sharply debated, as is the distinction between the various syndromes. This leads to problems of what type of research should be conducted and who should conduct it. It is time to develop a comprehensive research agenda to sort out nomenclature, epidemiology, and environmental causation for these conditions, moving toward comprehensive and effective public health and clinical approaches.


This monograph of peer-reviewed articles is based on presentations at the conference "Environmental Factors in Medically Unexplained Physical Symptoms and Related Syndromes" held 10-12 January 2001 in Piscataway, New Jersey, USA. The purpose of the conference was to determine research priorities for elucidating the role of environmental factors in medically unexplained symptoms and symptom syndromes. These include conditions such as chronic fatigue syndrome, multiple chemical sensitivities, sick building syndrome, Gulf War illness, and the like. Approximately 1 1/2 days were devoted to plenary talks and 1 day was devoted to break-out sessions to discuss epidemiologic, psychosocial, and experimental research. Recommendations were made for a series of epidemiologic, psychosocial, and experimental research approaches, with acknowledgment that nosology issues are clearly fundamental to advancing understanding of these conditions.
Allergic contact dermatitis (ACD) is a common occupational and environmental health issue. In common with other forms of allergy the disease progresses in two stages; an initial phase during which sensitization is acquired, followed later (after subsequent exposure to the same chemical allergen) by elicitation of a cutaneous inflammatory reaction. The development of skin sensitization is associated with, and requires, the activation and clonal expansion of allergen responsive T lymphocytes and it is these cells that orchestrate the cutaneous allergic reaction. In recent years, much has been learned of the characteristics of immune responses to skin sensitizing chemicals and of the roles played by dendritic cells, cytokines and chemokines. Some of the more interesting cellular and molecular mechanisms are reviewed briefly in this article. A more detailed appreciation of responses induced by chemical allergens has in turn facilitated the design of novel approaches to the toxicological evaluation of skin sensitization. Real progress has been made, not only in the development of improved methods for hazard identification and characterization, but also in the application of new paradigms for risk assessment. The newer methods now available and the opportunities that exist for further advances are considered. Finally, progress has been made in the characterization of skin sensitization in humans and in the clinical management of ACD. This article seeks to consider skin sensitization and ACD in holistic fashion, bridging experimental observations with clinical disease and basic mechanisms with practical toxicology.

Enhanced expression of neuronal nitric oxide synthase and phospholipase C-gamma1 in regenerating murine neuronal cells by pulsed electromagnetic field.

Pulsed electromagnetic field (PEMF) has been shown to improve the rate of peripheral nerve regeneration. In the present study we investigated the expression of neuronal nitric oxide synthase (nNOS) and phospholipase C-gamma1 (PLC-gamma1) in regenerating rat laryngeal nerves during the exposure to PEMF after surgical transection and reanastomosis. Axons were found to regenerate into the distal stump nearly twice faster in PEMF-exposed animals than in the control. Consistently, motor
function was better recovered in PEMF-treated rats. The expression of nNOS and PLC-gamma1 was highly enhanced in the regenerated nerves.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11989979

(2002) Is neurotoxicity associated with environmental trichloroethylene (TCE)?

Individuals who lived near 2 electronic manufacturing plants were exposed to odorous chlorinated solvents by inhalation (directly) and by out gassing from well water. An exposure zone was defined by concentrations of trichloroethylene, 1,1,1-trichloroethane, tetrachloroethylene, and vinyl chloride in groundwater. The author adopted trichloroethylene as a "shorthand" for the exposure designation. Residents complained of impaired recall and concentration, and of dizziness; therefore, the focus of this investigation was brain functions. Neurobehavioral functions, Profile of Mood States, frequencies of 35 symptoms, and questionnaire responses provided by 236 residents from exposure zones were compared with responses provided by 161 unexposed regional referents and by 67 Phoenix residents who lived outside the exposure zone areas. Pulmonary functions were measured with spirometry. Residents of the exposure zones were compared with regional referents, and the former had significantly (p < .05) delayed simple and choice reaction times, impaired balance, delayed blink reflex latency R-1, and abnormal color discrimination. In addition, these individuals had impaired (1) cognitive functions, (2) attention and perceptual motor speed, and (3) recall. Individuals who lived in exposure zones had airway obstructions. Adverse mood state scores and frequencies of 33 of 35 symptoms were elevated. In conclusion, individuals who lived in the exposure zones had neurobehavioral impairments, reduced pulmonary functions, elevated Profile of Mood State scores, and excessive symptom frequencies.

(2002) Recent advances in understanding the mechanisms of TCDD immunotoxicity.

TCDD is a highly immunosuppressive chemical that induces potent suppression of immune responses in laboratory animals. However, apart from the requisite role of the AhR and the identification of bone-marrow-derived cells as critical AhR-expressing targets, the specific cells and the underlying biochemical mechanisms by which TCDD disrupts immunological functions remain unclear. Recent data suggest that a new paradigm for the mechanism of immunotoxic action of TCDD may be more accurate, moving from one focused on the suppression of immune functions to one focused on
the inappropriate activation of cells, leading to anergy or death, and the consequent premature termination of the immune response. Enhanced activation of B cells, DC and CD4+ T cells by TCDD has been described as well as the earlier disappearance of the latter two populations from peripheral lymphoid organs. Although much remains to be learned about how inappropriate cellular activation via the AhR induces immune suppression, deducing this mechanism of action and the signaling pathways involved, should lead to new insight into basic mechanisms of immune regulation.


BACKGROUND: Patients with upper and lower airway symptoms and with pronounced sensitivity to chemical odours, such as perfumes, flower scents and tobacco smoke, have been suggested to have sensory hyperreactivity (SHR). The symptoms have been difficult to identify with physiological measurements and the effects of various medications are doubtful. However, these patients have been found to be more sensitive to inhalation of capsaicin than healthy people. The aim of this study was to establish limit values with the capsaicin inhalation test in patients with SHR.

METHODS: Ninety-five consecutive patients with upper and lower airway problems, who were admitted for allergy testing, underwent a capsaicin inhalation test with three different concentrations. The number of coughs was registered during each challenge. Score systems were used for symptoms and influence on social life of sensitivity to odours. In relation to scored symptoms, the patients were grouped as SHR or not, and compared with 73 healthy controls. RESULTS: All patients and controls coughed on
capsaicin in a dose-dependent manner. Symptom score of odour sensitivity in patients was positively correlated to the response of the test. Out of 95 patients, 15 (16%) were scored to SHR. Patients with SHR reacted more to the capsaicin inhalation test than the other patients and the healthy controls. The limit values for a positive capsaicin inhalation test for the SHR were determined to be 10, 35 and 55 coughs at 0.4, 2.0 and 10 microM capsaicin, respectively. CONCLUSION: The capsaicin inhalation test well reflects the degree of airway sensitivity to chemicals and to what extent the social life is influenced. The cut-off values of the test can distinguish patients with pronounced sensitivity to odours.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12243320


The number of reports on the effects induced by electromagnetic radiation (EMR) in various cellular systems is still increasing. Until now no satisfactory mechanism has been proposed to explain the biological effects of this radiation. Oxygen free radicals may play a role in mechanisms of adverse effects of EMR. This study was undertaken to investigate the influence of electromagnetic radiation of a digital GSM mobile telephone (900 MHz) on oxidant and antioxidant levels in rabbits. Adenosine deaminase, xanthine oxidase, catalase, myeloperoxidase, superoxide dismutase (SOD) and glutathione peroxidase activities as well as nitric oxide (NO) and malondialdehyde levels were measured in sera and brains of EMR-exposed and sham-exposed rabbits. Serum SOD activity increased, and serum NO levels decreased in EMR-exposed animals compared to the sham group. Other parameters were not changed in either group. This finding may indicate the possible role of increased oxidative stress in the pathophysiology of adverse effect of EMR. Decreased NO levels may also suggest a probable role of NO in the adverse effect.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12415560

(2002) The carboxyl-terminal domains of MKP-1 and MKP-2 have inhibitory effects on their phosphatase activity.

Both the mitogen-activated protein kinase (MAPK) phosphatases MKP-1 and MKP-2 exert important feedback control of MAPK-mediated signaling events. The function of
MKP-1 and MKP-2 is regulated via complex mechanisms, ranging from increased transcription of the MKP-1 and MKP-2 genes to post-translational catalytic activation of MKP-1 and MKP-2 proteins upon binding to their substrate MAPKs. In addition, MKP-1 stability increases upon ERK-dependent phosphorylation of two serine residues in its C-terminus. The C-terminal regions of MKP-1 and MKP-2, but not those of other MKPs, are homologous. To investigate the role of this domain, we have deleted the C-terminal tails from MKP-1 and MKP-2 and examined the effect of these deletions on their enzymatic activity. C-terminally truncated MKP-1 and MKP-2 exhibited, both in vivo and in vitro, substantially greater phosphatase activity towards their substrate MAPKs than did the full-length counterparts. However, C-terminal truncations did not significantly change either their substrate affinity, or their substrate-mediated catalytic activation. Basal phosphatase activity of the truncated proteins was also significantly higher than that of the wild-type counterparts. Collectively, these results suggest that the C-terminal domain may potentially play a role in the regulation of MKP-1 and MKP-2.

(2002) [Prevalence of weather sensitivity in Germany].

BACKGROUND AND OBJECTIVE: As epidemiological data on prevalence of weather-related health effects were lacking we conducted a weather sensitivity (WS) survey in Germany. SUBJECTS AND METHODS: A total of 1064 citizens (age > 16) representative of the population in Germany were interviewed in January 2001. RESULTS: The results show that 19.2% of the population believe that weather influences their health to a "high degree", 35.3% that weather has "some influence on their health". The highest prevalence of WS (high + some influence) is found in the age group of > 60 years, in 68% of the subjects. The highest frequencies of weather-related symptoms are reported for stormy weather (30%) and when it gets colder (29%). The most frequent symptoms reported by weather-sensitive subjects are headaches/migraine (61%), lethargy (47%), sleep disturbances (46%), fatigue (42%), joint pain (40%), irritation (31%), depression (27%), vertigo (26%), concentration problems (26%) and scar pain (23%). 32% of the weather-sensitive subjects have been incapable to do their regular work because of weather-related symptoms at least once last year, 22% even several times. Co-morbidity was significantly higher in weather-sensitive subjects. CONSEQUENCE: On the basis of these data we are planning studies on causal factors of weather-related health effects.

Hoge, CW, Orman, DT, Robichaux, RJ, Crandell, EO, Patterson, VJ, Engel, CC, Ritchie, EC and Milliken, CS Journal/Mil Med. 167: 44-7.

At the direction of the Army Surgeon General, the Army behavioral health consultants in psychiatry, psychology, and social work assembled in Washington, DC immediately after the September 11, 2001 attack to plan and implement a proactive behavioral health response to the Pentagon attack. The goal was to minimize the short- and long-term adverse behavioral health and related medical effects predicted to emerge based on past U.S. mass casualty scenarios. This article summarizes the goals, methods, and rationale used to develop the plan, as well as the key elements of the behavioral health intervention developed in response to the attack.


AIMS: Hypersensitivity to electricity (HE) is a common form of reported environmental illness in Sweden. Functional somatic symptoms has been attributed to exposure to activated electrical equipment, but no causal relationship to electromagnetic fields has been proved. In many cases, traumatic life events and psychosocial stress can be identified, but patients often reject psychological explanations. This study evaluates the effectiveness of a new short-term group-intervention programme. METHODS: A multidisciplinary team developed a short-term group-intervention programme, with a salutogenic approach that focuses on somatic and psychological reactions. Twenty-two patients (14 women and 8 men) who reported HE participated in eight weekly sessions of group meetings and physiotherapy. The effect of the programme was evaluated with regard to changes in work capacity, subjective well-being, coping ability, body awareness and physical fitness. RESULTS: Contrary to our hypothesis physical fitness was not remarkably low. Muscular tension was reduced and body awareness increased but no significant change in symptoms was observed. Individual differences in progress were observed. Fourteen patients chose to continue with psychotherapy or physiotherapy. CONCLUSIONS: Participants accepted the programme very well. One important result was identification of underlying contributing factors and motivation for further therapy. A multidisciplinary group-intervention programme with a salutogenic approach might be a useful approach to patients with medically unexplained symptoms in primary healthcare.


The study examined the assumption of a higher sensitivity of autonomic functions of subjects with self-reported multiple chemical sensitivity (sMCS) during environmental exposure. The hypothesis was tested in a laboratory study with standardized exposures. Twelve healthy male subjects (26.4 +/- 5.4 y) with and 12 male control subjects (25.7 +/- 3.8 y) without self-reported multiple chemical sensitivity (sMCS), selected by a questionnaire, were included in the experimental study. At four different days the subjects were exposed in a random order to solvents for four hours: 10 ppm or 98 ppm ethyl benzene, 10 ppm or 189 ppm 2-butanone. Heart rate and breathing rate were analysed for two 30-minutes periods of vigilance testing at the beginning and end of exposure. In sMCS-subjects both functions were elevated at the beginning of the testing periods with a tendency to decrease over the 30-minutes periods. Control subjects revealed a relatively constant level (breathing rate) and a small increase (heart rate) during the periods. These group differences were obvious for all experimental conditions across substances and levels of exposures. Furthermore, the mean of the breathing rate of sMCS-subjects was generally higher compared to the control subjects. While the assumption of a generally altered sensitivity of autonomic functions of sMCS-subjects to environmental changes seems to be supported, no specific reactions to the type or level of the chemical exposure were found.


Harris, R Journal/Curr Biol. 12: R122.


Health concerns related to the quality of the environment in offices, schools, homes, and residences have increased dramatically over the past 2 decades. One health problem frequently confronting medical practitioners and often attributed to environmental quality problems is idiopathic environmental intolerances (IEI). Formerly known as multiple chemical sensitivities, IEI is an acquired disorder characterized by adverse reactions attributed to exposure to a variety of substances under ordinary conditions. Alleged precipitants include solvents, pesticides, detergents, dusts, and fragrances. Symptoms include fatigue, malaise, headache, concentration and memory difficulties, lightheadedness, cough, hoarseness, and rhinitis without objective physical
signs or consistent laboratory abnormalities. The role of the environment in precipitating these complaints continues to be controversial, and no intervention or treatment has thus far been proven to be effective. While not progressive or life threatening, IEI is often functionally disabling and very distressing to affected individuals. The investigation of IEI should involve, at a minimum, a clinical evaluation of the affected person and in most cases an environmental evaluation as well. IEI should be managed without overutilization of diagnostic tests or prescription of unnecessary environmental, occupational, or dietary restrictions.


(2002) [Comment on W. Hausotter: Modern illness from the critical viewpoint].
Hakimi, R Journal/Versicherungsmedizin. 54: 149-50; author reply 150.

(2002) HPA axis dysregulation in mice overexpressing corticotropin releasing hormone.

http://www.sciencedirect.com/science/article/B6T4S-45TY871-4/21bab7fe726b863ff0ac7e201262057e4


Environmental exposures to very low levels of airborne chemicals are associated with adverse symptoms, often affecting multiple organ systems, in the phenomenon of chemical sensitivity (CS). Recent surveys suggest a significant prevalence of chemically sensitive subjects in the United States, but the mechanism linking exposure to symptoms remains unclear, despite the advancement of a variety of theoretical
models. In many of these models, exposure of the nasal respiratory system to an airborne agent is the first step in the pathway leading to symptoms. In this article, we advance the hypothesis that interactions between environmental chemicals and the vomeronasal organ (VNO) may play a role in the etiology of CS. The VNO, a bilateral, tubular organ located in the nose, serves in animals as part of a sensitive chemosensory system; however, evidence suggesting that the VNO retains a functional role in the adult human is controversial. Reported characteristics of the human VNO relevant to CS, including location, prevalence, selective sensitivity to airborne chemical exposure, and capacity to produce systemic effects, are discussed within the context of this ongoing debate. Beyond relevance to CS, the demonstration of an active, adult VNO could have significant impact on environmental toxicology.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12194902


US Navy Seabees have been among the most symptomatic Gulf War veterans. Beginning in May 1997, the authors mailed Gulf War-era Seabees a health survey in serial mailings. As of July 1, 1999, 68.6% of 17,559 Seabees contacted had returned the questionnaire. Compared with other Seabees, Gulf War Seabees reported poorer general health, a higher prevalence of all 33 medical problems assessed, more cognition difficulties, and a higher prevalence of four physician-diagnosed multisymptom conditions: chronic fatigue syndrome, posttraumatic stress disorder, multiple chemical sensitivity, and irritable bowel syndrome. Because the four multisymptom conditions were highly associated with one another, the authors aggregated them into a working case definition of Gulf War illness. Among the 3,831 (22% cases) Gulf War Seabee participants, multivariable modeling revealed that female, Reserve, and enlisted personnel and participants belonging to either of two particular Seabee units were most likely to meet the case definition. Twelve of 34 self-reported Gulf War exposures were mildly associated with meeting the definition of Gulf War illness, with exposure to fumes from munitions having the highest odds ratio (odds ratio = 1.9, 95% confidence interval: 1.5, 2.4). While these data do not implicate a specific etiologic exposure, they demonstrate a strong association and a high prevalence of self-reported multisymptom conditions in a large group of symptomatic Gulf War veterans.

(2002) **Chronic fatigue syndrome/ME.**

(2002) **[Environmental factors influencing early aging and shorter longevity in Russia].**
Gichev Iu, P Journal/Gig Sanit. 48-51.

(2002) **Risk perception, somatization, and self report of complaints related to electromagnetic fields—a randomized survey study.**

Exposure to electromagnetic fields (EMF) as well as EMF-related complaints has increased over the past decades. However, it is unclear whether these complaints are related to the electromagnetic or other physical properties of these fields per se, to salience of EMF in media, or to both. What is the prevalence of EMF-related complaints in the general population? What are the influencing factors on this prevalence? Does reporting of EMF-related symptoms depend on cognitive factors? To answer these questions, a survey with random variation of three cognitive factors was performed. As expected, EMF-related complaints were reported more by females and people with higher somatization tendency. Age had no significant linear effect on EMF-related complaints. The cognitive condition of threat produced a significant contrast effect among people with high somatization tendency on EMF-related complaints. Cognition can influence reporting of EMF-related effects. Thus, in future research of such effects, psychologically influencing factors should be included. Also risk communication should incorporate knowledge about social cognition.

(2002) **Thoracic outlet syndrome (TOS) is one of the traumatic complications of whiplash injury.**
The long-term objective of this project is to utilize microarray analysis to facilitate the evaluation of mechanisms of mammalian susceptibility to neurodevelopmental toxicants. Adverse neurodevelopment is a common congenital defect, with prevalence rates ranging from as high as 1 per 1,000. These neurodevelopmental defects (NDDS) can encompass abnormal neural tube closure resulting in anencephaly, exencephaly and spina bifida as well as microcephaly and other Central Nervous System (CNS) abnormalities including adverse functional and behavioral changes. Various agents (such as heat, methyl mercury, cadmium, valproic acid, etc. have been identified as mammalian neurodevelopmental toxicants; however, even across and within various mammalian species, differential responses have been identified. For example, SWV mice are sensitive and C57BL/6J mice are resistant to hyperthermia-induced neurodevelopmental defects. Both human and animal studies suggest that the genetic component of neurodevelopmental abnormalities is complex and likely to involve multiple loci. The etiology of such effects remains poorly understood, however, recent developments in gene expression profiling using DNA microarrays, offers the promise to screen thousands of genes simultaneously and to begin the dissection of subsets of genes that are associated with susceptibility to particular disease states. Using this technology, the investigators propose to use mouse strains differentially sensitive to teratogen induced NDDs (SWV-sensitive mice versus C57BI/6J resistant mice) to identify genes and their associated pathways that are modified by two well characterized neurodevelopmentally toxic agents, hyperthermia and methyl mercury (MeHg). The investigators will evaluate exposure and temporal characteristics of gene responses under conditions of sensitivity and resistance to NDDS. These initial studies will begin to test the investigators ultimate hypothesis that neurodevelopmental toxicants share a common pattern of gene expression that is pathognomonic for sensitivity to neurodevelopmental toxicity.
perspective has been to classify and study these symptoms and functional syndromes separately. In psychiatry, current taxonomies (Diagnostic and Statistical Manual of Mental Disorder, 4th edition, and The International Statistical Classification of Diseases and Related Health Problems, 10th revision) classify these syndromes together under the rubric of somatoform disorders. In this article we approach medically unexplained physical symptoms from a psychiatric perspective and discuss the common features that unite multiple unexplained symptoms or functional somatic syndromes as a class. Included in this article is a discussion of nosological issues, clinical assessment, how these syndromes are viewed within the various medical specialties, and clinical management and treatment.


Medically unexplained physical symptoms (MUPS) are persistent idiopathic symptoms that drive patients to seek medical care. MUPS syndromes include chronic fatigue syndrome, fibromyalgia syndrome, and multiple chemical sensitivities. When MUPS occur after an environmental exposure or injury, an adversarial social context that we call "contested causation" may ensue. Contested causation may occur publicly and involve media controversy, scientific disagreement, political debate, and legal struggles. This adversarial social context may diminish the effectiveness of the provider-patient relationship. Contested causation also may occur privately, when disagreement over the causes of MUPS takes place in the patient-provider context. These patient-provider disagreements over causation often occur because of the enigmatic nature of MUPS. We suggest that a context of contested causation may have serious negative effects on healthcare for individuals with MUPS. Context plays a larger role in MUPS care than it does for most medical care because of the uncertain nature of MUPS, the reliance of standard MUPS therapies on a potentially tenuous patient-provider partnership, and the clinical need to rely routinely on subjective MUPS assessments that often yield discordant patient and provider conclusions. Contested causation may erode patient-provider trust, test the provider's self-assurance and capacity to share power with the patient, and raise problematic issues of compensation, reparation, and blame. These issues may distract patients and providers from therapeutic goals. In occupational and military settings, the adverse impact of contested causation on the patient-provider partnership may diminish therapeutic effectiveness to a greater degree than it does in other medical settings. Contested causation therefore raises questions regarding generalizability of standard therapies for MUPS and related syndromes to these settings. Future research is needed to learn whether intuitively sensible and evidence-based MUPS therapies benefit occupational and military medical patients who are afforded care in the context of contested causation.
(2002) [Significance of environmental medicine in modern medicine].

(2002) Multiple chemical sensitivity (MCS) and others: allergological, environmental and psychological investigations in individuals with indoor air related complaints.

Clinical observations point to an expanding group of individuals attributing hypersensitivity phenomena to indoor air pollution. It was the aim of this study to characterize such subjects by an interdisciplinary approach. Sixty-five individuals, recruited by a public campaign, were studied by a thorough allergological examination and a structured psychological interview. Measurements of common indoor pollutants in the air and in the dust were performed in rooms of several selected patients. Forty-two patients (65%) revealed a sensitization to common allergens, out of these 32 (49%) to house dust mites. Thirty-eight (58%) patients showed a psychosomatic or psychotic disorder. Increased concentrations of at least one of the measured indoor air pollutants were found in 11 out of 13 investigated houses. According to these results, four groups of patients could be identified: Seventeen patients (26%) had "classic" allergic diseases treated inadequately. In 19 patients (29%) allergic diseases were superimposed by strong psychosomatic interactions. An exclusive psychosomatic or psychotic cause of the complaints was found in 19 (29%). Ten subjects (16%) had "classic" allergic diseases (e.g. allergic rhinoconjunctivitis, urticaria), however, there were additional indications of hypersensitivity reactions to components other than classical allergens. Patients presenting with hypersensitivity phenomena attributed by themselves to indoor air pollution are a heterogeneous group and need a diligent work-up including intense allergological examination. The role of increased concentrations of indoor air pollutants has to be elucidated further.


(2002) [Current methods for studying the impact of environmental pollution on the immune system].
Dmitriev, DA and Rumiantseva, EG Journal/Gig Sanit. 68-71.
query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12198913

(2002) Organic solvent exposure, genes, and risk of neuropsychological
impairment.
Dick, F, Semple, S, Osborne, A, Soutar, A, Seaton, A, Cherrie, JW, Walker, LG and

BACKGROUND: Subtle cognitive and neurological impairments have been found in
some workers exposed to organic solvents. Whether these effects occur at or below
current legal limits for occupational exposure is controversial. Aim: To determine
whether occupational solvent exposure is associated with neuropsychological
impairment and whether such risk is modified by polymorphisms in the genes for
enzymes involved in detoxification. DESIGN: Retrospective case-control analysis.
METHODS: We studied 78 former dockyard painters and 42 community controls.
Individual respiratory and dermal exposures to solvents were estimated.
Neuropsychological tests were administered, including paper and pencil tests, tests
from the Neurobehavioural Evaluation System (NES2), together with a structured
neurological examination and genotyping of polymorphic enzymes involved in
detoxification: GSTM1, GSTT1, GSTP1, NAT1, NAT2, SOD1 and CYP1A1. RESULTS:
While initial case-control analyses failed to identify any significant differences between
symptomatic and asymptomatic painters, in regression analyses increasing solvent
exposure was associated with increasing risk of cognitive impairment, after adjustment
for IQ (or age, where appropriate), smoking and alcohol. There was also an association
between exposure and reduction in grip strength. There was limited evidence of risk
modification by some enzyme polymorphisms. DISCUSSION: This association
between increasing intensity of solvent exposure and neuropsychological impairment
may be important at current exposure levels in the UK.

(2002) Exhaled nitric oxide as a diagnostic test for asthma: online versus offline
techniques and effect of flow rate.
Deykin, A, Massaro, AF, Drazen, JM and Israel, E Journal/Am J Respir Crit Care Med.
165: 1597-601.

Measurement of the fraction of exhaled nitric oxide (FENO) has been proposed as a
noninvasive assessment of asthmatic airway inflammation. The influence of the
expiratory flow rate during the collection maneuver on the ability of FENO to
discriminate healthy subjects from those with asthma is unknown. We compared online
and offline measurement of FENO at different flow rates. FENO was collected with
expiratory flows of 50-500 ml/second in 34 patients with asthma (PC(20) of less than 8 mg/ml) and 28 healthy subjects (PC(20) of more than 10 mg/ml) using offline collection techniques. In a subgroup of 18 individuals with asthma and 17 healthy subjects, we additionally measured FENO at multiple expiratory flow rates (47-250 ml/second) using online methods. FENO fell with an increasing expiratory flow rate; FENO was higher in subjects with asthma as compared with healthy subjects at each flow rate studied with both techniques (p < 0.001). Receiver operating characteristic (ROC) curves for the diagnosis of asthma indicated that FENO is a robust discriminator between individuals with asthma and healthy subjects (area under the ROC curves 0.79 +/- 0.06 to 0.86 +/- 0.06, p for significant discrimination < 0.0001). Neither expiratory flow rate nor collection technique (online versus offline) significantly altered this discriminatory capacity (area under the ROC curves = 0.84 +/- 0.07 with the slowest online method versus 0.80 +/- 0.07 with the fastest offline method, p = 0.46). These data indicate that the choice of expiratory flow rate and collection method can be based on practicality and patient comfort without compromising the utility of this test for asthma.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12070059


The 3'-terminal region of starfish Asterina pectinifera cdc25 cDNA encoding the C-terminal catalytic domain was overexpressed in Escherichia coli. The C-terminal domain consisted of 226 amino acid residues containing the signature motif HCxxxxxR, a motif highly conserved among protein tyrosine and dual-specificity phosphatases, and showed phosphatase activity toward p-nitrophenyl phosphate. The enzyme activity was strongly inhibited by SH inhibitors. Mutational studies indicated that the cysteine and arginine residues in the conserved motif are essential for activity, but the histidine residue is not. These results suggest that the enzyme catalyzes the reaction through a two-step mechanism involving a phosphocysteine intermediate like in the cases of other protein tyrosine and dual-specificity phosphatases. The C-terminal domain of Cdc25 activated the histone H1 kinase activity of the purified, inactive form of Cdc2.cyclin B complex (preMPF) from extracts of immature starfish oocytes. Synthetic diphosphorylated di- to nonadecapeptides mimicking amino acid sequences around the dephosphorylation site of Cdc2 still retained substrate activity. Phosphotyrosine and phosphothreonine underwent dephosphorylation in this order. This is the reverse order to that reported for the in vivo and in vitro dephosphorylation of preMPF. Monophosphopeptides having the same sequence served as much poorer substrates. As judged from the results with synthetic phosphopeptides, the presence of two phosphorylated residues was important for specific recognition of substrates by the Cdc25 phosphatase.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12498739

(2002) Personal and political aspects of MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12440396

Damodaran, TV, Mecklai, AA and Abou-Donia, MB Journal/Neurochem Res. 27: 177-81.

Sarin induced neurotoxicity is suspected to be one of the key factors responsible for Gulf-war syndrome. We studied the effect of a single (50 microg/kg/i.m) dose of sarin (0.5 x LD50) on the mRNA expression of alpha tubulin in the central nervous system (CNS) of rats which were sacrificed at different time points i.e. 1 and 2 hrs, as well as, 1, 3 and 7 days post-treatment. Northern data collected from CNS regions indicate differential, spatial, and temporal regulation of alpha tubulin mRNA levels. Immediate induction and persistence of alpha tubulin transcripts in sarin-treated CNS suggest that sarin-induced neurotoxicity is in part mediated by the altered expression of cytoskeletal genes which may be regulated at multiple levels.

Diisopropyl phosphorofluoridate (DFP) produces organophosphorus-ester-induced delayed neurotoxicity in sensitive species. We studied the effect of single dose of DFP on the expression of phosphorylated cAMP-response element binding protein (p-CREB), which is a well known transcription factor involved in several pathways mediating different types of external stimuli. The hens were perfused with neutral buffered formalin at different time points, i.e., 0.5, 1.0, and 2.0 hrs, as well as 1, 2, 5, and 20 days after dosing. The central nervous system regions of the whole brain were dissected and 7-micron sections were stained for either p-CREB immunopositivity or with hematoxylin and eosin. Results indicated an early differential increase of p-CREB immunopositivity in susceptible regions such as cerebellum, brainstem, and midbrain within 2 hrs. These induced levels persisted up to 5 days in these tissues, although the time course of p-CREB immunopositivity was distinctly different for each region. In the cerebellum induction of p-CREB was seen in the granular layer where both the granulocytes and the glial cells showed induction. Increased immunopositivity for p-CREB in the Purkinje cells and in some basket cells of the molecular layer was noticed over time, but the induction was not as great as in the granular layer. Of all the tissues cerebellum showed the strongest intensity of immunopositivity of the cells as well as the highest (absolute) number of pCREB-positive cells. The brainstem showed a similar fluctuating pattern like the cerebellum with the highest percentage increase of the immunoreactive cells at 5 days preceded by the lowest dip in immunopositivity at 2 days. In the midbrain, there was a time-dependent increase in the immunopositivity from 0.5 hr onwards until reaching control levels at 20 days. Immunopositivity was also noted in portions of the spina medularis and spina oblongata. The cerebrum (non-susceptible tissue) of DFP-treated hens did not show much deviation from the controls. The endothelial cells of the susceptible regions showed induction at early time points, in contrast to the absence of induction in cerebrum. Spatial and temporal differences in the immunopositivity pattern indicate probable involvement of CREB-independent pathways also. Overall, the complex induction pattern of p-CREB, along with our earlier observations of the early induction of c-fos, c-jun and Protein Kinase A (PKA) as well as the induction of Calcium2+/Calmodulin dependent Protein Kinase II (CaM kinase II) at later periods, strongly suggest an activator role of CREB mediated pathways that may lead to the clinical development of delayed neurotoxicity.

A single dose (1.7 mg/kg, s.c.) of diisopropylphosphorofluoridate (DFP) causes organophosphorus ester-induced delayed neurotoxicity (OPIDN) in susceptible species. We studied the effects of DFP administration on the mRNA expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), an important glycolytic protein, at different time points (1, 2, 5, 10 and 20 days) post-treatment. Total RNA was extracted from cerebrum, cerebellum, brainstem, midbrain, and spinal cord of the control and DFP-treated hens, and northern blots were prepared using standard protocols and hybridized with GAPDH, as well as beta-actin and 28S RNA cDNA (control) probes. There was a distinct spatial/temporal mRNA expression pattern for the different tissues studied. Non-susceptible tissue, cerebrum showed a dramatic increase in GAPDH mRNA at day 1, post-treatment and levels remained high at all time points, suggestive of protective mechanisms from the beginning. In contrast, highly susceptible tissues like brainstem, spinal cord and midbrain showed either no elevation or slight down-regulation at day 1, suggesting trauma and cell injury/cell death. Overall, there was moderate level of induction during the subsequent time points in these tissues, indicative of pathways of either recovery or degeneration. Cerebellum being the less susceptible tissue showed moderate increase initially, followed by higher induction, suggestive of rapid recovery. Our current data on GAPDH provides an important link in this complex network of molecular changes involving pathways identified by our group and others, such as nitric oxide (NO), CaM kinase-II (CaMK-II), protein kinase-A (PKA), c-fos, and phosphorylated-CREB (p-CREB) in DFP-induced OPIDN.


T-cell-derived proteins that bind nominal (non-MHC-associated) antigen specifically (TABM) express V and C region epitopes of the T-cell receptor (TCR) for antigen and have a significant similarity in amino acid sequence to TCR alpha-chain V and C region. The presence of these immunoproteins in human serum and a specific increase in serum TABM in infectious disease, chemical sensitivity, and food intolerance suggest that TABM may impact on pathogenesis through the modulation of cell-mediated immunity, the antigen-specific concentration and delivery of immunoregulatory cytokines such as TGF-beta and elastase, and the induction of the release of substance P by sensory neurons. In this Minireview update, we describe advances in the detection and quantitation of human TABM by monoclonal antibodies, and the association of increased human serum TABM titers in infectious disease, chemical sensitivity, and food intolerance. We suggest that the immunomodulatory mode of action of these immunoproteins may be the antigen-specific focusing of cytokines associated with TABM.
Ethical issues in occupational disease outbreak investigations.

Occupational disease outbreak investigations usually involve rapid, small-scale analysis of reports of diseases with a suspected occupational etiology, usually in a single workplace or among workers of a single employer. Ethical issues are similar to those encountered in epidemiologic studies in the workplace, with the added constraints of the need to respond rapidly, limited numbers of subjects, low statistical power, and the mandate to issue results even when the ability to generalize them is limited. Informed consent, voluntary participation, fairness, and confidentiality are major ethical issues in workplace outbreak investigations. The obligation to publicly report a workplace hazard when a non-disclosure statement has been signed can also present an ethical dilemma for outbreak investigators.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12225934

EUROQUEST--a questionnaire for solvent related symptoms: factor structure, item analysis and predictive validity.

The study evaluates the factor structure and predictive validity of the symptom questionnaire EUROQUEST (EQ) that had been developed with the goal of simplifying the evaluation of health effects associated with long-term solvent exposure. The EQ was added to the normal evaluation procedures for 118 male patients with suspected solvent-induced toxic encephalopathy (TE) referred to seven Swedish clinics of occupational medicine during an 18-month period. EQ was also completed by 239 males from a random sample of 400 Swedish males aged 25-64 years selected from the general population and a sample of 559 occupationally active male spray painters aged 25-64 years. Factor and item analyses of EQ responses were performed. Ordinary least square regression analysis was used to evaluate sensitivity and correlation to evaluate the specificity of EQ and the separate components. Questions concerning memory and concentration symptoms alone showed better sensitivity than the other five EQ dimensions singly or combined for the entire EQ and for a subset of questions approximating Q16, a widely used organic solvent symptom screening questionnaire. However, the diagnosis of TE required information in addition to exposure and responses to EQ and Q16-like questions. The results indicate that the subset of EQ questions concerning memory and concentration might replace the more cumbersome EQ and less sensitive Q16 in screening for TE, although none of the screening instruments alone replaces current clinical diagnostic procedures.
(2002) **Further evidence for an association of the paraoxonase 1 (PON1) Met-54 allele with Parkinson's disease.**

Paraoxonase1 (PON1) is an arylesterase mainly expressed in the liver that hydrolyzes organophosphates such as pesticides, reported risk factors for Parkinson's disease (PD), and other neurotoxins. A Leu-Met 54 polymorphism in the gene for PON1-affecting enzyme activity was recently shown, employing a new restriction enzyme technique, to be associated with Parkinson's disease. We examined the same polymorphism by automated capillary sequencing in a sample of Caucasian subjects from the Stockholm area in Sweden (127 healthy individuals and 114 patients with PD) and found similar distributions and a similar difference in our sample. The genotype distribution in our PD material was LL 36.0%, LM 45.6%, and MM 18.4%; in our control material, it was LL 45.7%, LM 44.1%, and MM 10.2%. Based on the previously established increase in allele frequencies of the lower-activity Met-variant of PON1, we could confirm a significant association using a one-sided chi(2) test. Results remained significant with a two-sided chi(2) test, allowing for both increases and decreases in frequencies. Our data confirm an association between the PON1 Leu-Met 54 polymorphism and PD by demonstrating a similar association. The distribution between familial and nonfamilial PD patients was equal. No other synonymous or nonsynonymous polymorphisms were found in the sequenced coding region of PON1.

(2002) **Symptomatology and etiology of multiple chemical sensitivities in the southeastern United States.**

A questionnaire was administered to individuals who had reported a hypersensitivity to common chemical products in an earlier epidemiological study in the Atlanta, Georgia, metropolitan area. The questionnaire investigated the nature of the symptoms and factors that potentially initiated hypersensitivity and subsequently triggered reactions. Also examined were associated lifestyle modifications and the relationships of hypersensitivity with other illnesses. The authors found that a majority of hypersensitive individuals (52.2%) experienced either "severe" or "somewhat severe" symptoms. The most common triggers of symptoms were cleaning products (88.4%), tobacco smoke (82.6%), perfume (81.2%), pesticides (81.2%), and car exhaust (72.5%). Only 1.4% of the subjects had a prior history of emotional problems, whereas 37.7% developed such problems after the emergence of their hypersensitivity. Lifestyle modifications varied;
76.8% changed their household cleaning/personal hygiene products, 47.8% began using water and/or air filtration systems, and 13% found it necessary to change residence. Although hypersensitivity was more common in females than males, the condition affects individuals in all categories of race/ethnicity, age, household income, and educational level.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12641185

(2002) Anxiety sensitivity and depression in multiple chemical sensitivities and asthma.

Patients with sensitivities to multiple chemicals report symptoms of cognitive dysfunction, respiratory distress, and mood disturbance. Lifetime and current psychiatric disorders, personality traits associated with symptom reporting, and tests of cognitive function were compared between 30 subjects with Multiple Chemical Sensitivities (MCS), 19 asthmatics, and 31 healthy controls. Relative to asthmatics and controls, more MCS subjects met criteria for current depression and somatization disorder. MCS subjects and asthmatics scored significantly higher than controls on scales of chemical odor intolerance and anxiety sensitivity, both of which were significant predictors of physical symptoms. Few differences on objective neuropsychological tests were noted. However, MCS subjects with comorbid depression performed significantly worse on a verbal memory test relative to asthmatics but not to controls. Anxiety and depression are significant contributors to the physical and cognitive symptoms of MCS subjects.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12391767


(2002) Psychiatric and somatic disorders and multiple chemical sensitivity (MCS) in 264 'environmental patients'.
BACKGROUND: An increasing number of individuals with diverse health complaints are currently seeking help in the field of environmental medicine. Multiple chemical sensitivity (MCS) or idiopathic environmental intolerances (IEI) is defined as an acquired disorder with multiple recurrent symptoms associated with environmental chemicals in low concentrations that are well tolerated by the majority of people. Their symptoms are not explained by any known psychiatric or somatic disorder. METHOD: Within a 2-year period we examined 264 of 267 consecutive patients prospectively presenting to a university based out-patient department for environmental medicine. Patients underwent routine medical examination, toxicological analysis and the structured clinical interview for DSM-IV psychiatric disorders (SCID). RESULTS: Seventy-five per cent of the patients met DSM-IV criteria for at least one psychiatric disorder and 35% of all patients suffered from somatoform disorders. Other frequent diagnoses were affective and anxiety disorders, and dependence or substance abuse. In 39% a psychiatric disorder, in 23% a somatic condition and in 19% a combination of the two were considered to provide sufficient explanation of the symptoms. Toxic chemicals were regarded as the most probable cause in only five cases. The suspected diagnosis of MCS/IEI could not be sustained in the vast majority of cases. CONCLUSION: This investigation confirms previous findings that psychiatric morbidity is high in patients presenting to specialized centres for environmental medicine. Somatoform disorders are the leading diagnostic category, and there is reason to believe that certain 'environmental' or MCS patients form a special subgroup of somatoform disorders. In most cases, symptoms can be explained by well-defined psychiatric and medical conditions other than MCS, which need specific treatment. Further studies should focus on provocation testing in order to find positive criteria for MCS and on therapeutic approaches that consider psychiatric aspects.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12455937


Patients with multiple chemical sensitivity (MCS) react to low levels of common environmental chemicals with various health complaints. The etiology and pathogenesis of MCS is not clear. Objective criteria for diagnosis are lacking. Usually there are no pathological somatic findings, while psychiatric morbidity is considerably high. Somatoform, mood and anxiety disorders are diagnosed most frequently. A subgroup of MCS patients may suffer from a special form of somatoform disorders related to the environment. Critics of a psychogenic model of MCS argue that psychiatric diagnoses are descriptive, and causality can not be derived from them. However, clinicians are expected to evaluate the most probable cause of the complaints and give therapeutic recommendations. There are promising therapeutic
concepts for somatoform and other psychiatric disorders, but not for MCS. Double-blind challenge tests, but also therapy evaluation studies could contribute to a better understanding of the pathogenesis of MCS in the future.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12491564


AIM: Multiple chemical sensitivity (MCS) is a controversially discussed symptom complex. Patients afflicted by MCS react to very low and generally non-toxic concentrations of environmental chemicals. It has been suggested that MCS leads to neurotoxic damage or neuroimmunological alteration in the brain detectable by position emission tomography (PET) and single photon emission computer tomography (SPECT). These methods are often applied to MCS patients for diagnosis, although they never proved appropriate. METHOD: We scanned 12 MCS patients with PET, hypothesizing that it would reveal abnormal findings. RESULTS: Mild glucose hypometabolism was present in one patient. In comparison with normal controls, the patient group showed no significant functional brain changes. CONCLUSION: This first systematic PET study in MCS patients revealed no hint of neurotoxic or neuroimmunological brain changes of functional significance.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12520659

(2002) Is multiple chemical sensitivity a clinically defined entity?

In 1996 a WHO/IPCS Workshop has suggested to use as an appropriate descriptor of MCS the broader term "Idiopathic Environmental Intolerances (IEI)", in order to incorporate "a number of disorders sharing similar symptomatologies". Research was strongly encouraged. The following points have been put forward as a precondition to define MCS as a clinical entity: (a) establishment of diagnostic criteria, (b) identification of pathogenic mechanisms, together with, (c) an explanation of relationship between exposures and symptoms. Against this background, progress made in the fields of sensory physiology and neurobehaviour research must be debated. In particular, recent results on processing of cognitive stimuli have to be considered. IEI/MCS patients exhibited differences vs. controls in their reactions to intranasal challenge, consistent with changes in cognitive processing of suprathreshold chemosensory information. Trait anxiety and focus of attention have clearly been identified as major
components in eliciting neurobehavioural MCS symptoms. Hence, the question as to whether MCS should be regarded as a clinically defined entity remains controversial, but important progress can be noticed in elucidating and defining the nature of this phenomenon, by a combined effort of several disciplines (toxicology and behavioural toxicology, psychology and psychophysiology, and clinical medicine). The new situation will call for a re-evaluation of traditional positions.


Bhaskaram, P Journal/Nutr Rev. 60: S40-5.

Micronutrient deficiencies and infectious diseases often coexist and exhibit complex interactions leading to the vicious cycle of malnutrition and infections among underprivileged populations of the developing countries, particularly in preschool children. Several micronutrients such as vitamin A, beta-carotene, folic acid, vitamin B12 vitamin C, riboflavin, iron, zinc, and selenium, have immunomodulating functions and thus influence the susceptibility of a host to infectious diseases and the course and outcome of such diseases. Certain of these micronutrients also possess antioxidant functions that not only regulate immune homeostasis of the host, but also alter the genome of the microbes, particularly in viruses, resulting in grave consequences like resurgence of old infectious diseases or the emergence of new infections. These micronutrient infection and immune function interactions and their clinical and public health relevance in developing countries are briefly reviewed in this article.

STUDY OBJECTIVE: We sought to compare the efficacy and safety of nebulized magnesium sulfate (MgSO(4)) plus albuterol with that of albuterol alone in adult patients with mild-to-moderate acute asthma exacerbations. METHODS: Patients were randomized to receive nebulized MgSO(4) (384 mg in 6 mL of sterile water) or an equal volume of placebo (normal saline solution) in a double-blind fashion after each dose of nebulized albuterol administered (2.5 mg/3 mL) every 20 minutes for the first hour of the study. Spirometry was performed at baseline and every 20 minutes for 2 hours. Monitoring for safety included vital signs, pulse oximetry, and serum magnesium levels. Improvement in percent predicted forced expiratory volume in 1 second was chosen as a primary efficacy end point. RESULTS: Among 74 patients enrolled, 37 were randomized to each of 2 study groups. There were no statistically or clinically significant differences between the 2 study groups in percent predicted forced expiratory volume in 1 second at any point during the trial or overall. There were no significant differences in vital signs, pulse oximetry, or serum magnesium levels at any point during the study. CONCLUSION: The combination of nebulized MgSO(4) and albuterol provides no benefit in addition to that provided by therapy with albuterol in adult patients with mild-to-moderate asthma exacerbations. The efficacy of nebulized MgSO(4) in patients with severe asthma exacerbations remains unknown.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12023699


Clinicians and researchers are increasingly using the term integrative medicine to refer to the merging of complementary and alternative medicine (CAM) with conventional biomedicine. However, combination medicine (CAM added to conventional) is not integrative. Integrative medicine represents a higher-order system of systems of care that emphasizes wellness and healing of the entire person (bio-psycho-socio-spiritual dimensions) as primary goals, drawing on both conventional and CAM approaches in the context of a supportive and effective physician-patient relationship. Using the context of integrative medicine, this article outlines the relevance of complex systems theory as an approach to health outcomes research. In this view, health is an emergent property of the person as a complex living system. Within this conceptualization, the whole may exhibit properties that its separate parts do not possess. Thus, unlike biomedical research that typically examines parts of health care and parts of the individual, one at a time, but not the complete system, integrative outcomes research advocates the study of the whole. The whole system includes the patient-provider relationship, multiple conventional and CAM treatments, and the philosophical context.
of care as the intervention. The systemic outcomes encompass the simultaneous, interactive changes within the whole person.

Bell, IR, Baldwin, CM, Schwartz, GE and Davidson, JR Journal/Homeopathy. 91: 63-74.

This study examined associations between scores for 19 different remedies on the constitutional type questionnaire (CTQ) and scores on standardized psychological and medical trait and state scales from health psychology research. Subjects were 104 young adult American college students (mean age 20 years; 67% female). Scales included the chemical intolerance index (CII) for environmental sensitivity, the NEO personality inventory, Marlowe-Crowne social desirability (MCSD) Scale for defensiveness, Harvard parental caring scale (HPCS) for perceived mother and father traits, Profile of Mood State (POMS) scale, Pennebaker symptom checklist (PSC), and a 3-item global health rating scale. The majority of CTQ constitutional type scores correlated significantly with greater NEO neuroticism, lower MCSD defensiveness, and greater psychological distress on the POMS subscales. NEO Extraversion and Openness subscales correlated with specific CTQ scores in directions consistent with clinical remedy pictures. CTQ Carcinosin differed from other remedies, showing no significant correlations with other scales. As hypothesized (a) persons high on CTQ scores for Carcinosin and low in parental caring (HPCS) had the highest symptom score; (b) those high on CTQ scores for Sulphur and low on HPCS had the poorest global health ratings; (c) individuals high on four different CTQ type scores (Carcinosin, Lachesis, Nux vomica, Sulphur) and high on environmental sensitivity (CII) exhibited the highest symptom scores. Taken together, the data offer additional validation of the CTQ and provide a foundation for studying interactions of constitutional type with both psychosocial and physicochemical environmental factors in homeopathic provers and patients.

(2002) Translating a nonlinear systems theory model for homeopathy into empirical tests.
Bell, IR, Baldwin, CM and Schwartz, GE Journal/Altern Ther Health Med. 8: 58-66.

Various investigators have proposed that nonlinear systems theory, notably chaos and complexity theory, provides a heuristically useful model for conceptualizing the way in which complementary and alternative medicine therapies, which purport to modify subtle energies, effect change throughout the individual as a whole. In this paper we
apply this theory to classical homeopathy and outline an empirical approach for testing the resultant hypotheses. Such research may advance understanding of the mechanisms of homeopathic remedy effects and provide a direction for homeopathic research that expands the previous emphasis on clinical trials and the remedies themselves. In refocusing attention on the dynamics of the patient as a nonlinear complex system, the proposed research program is consistent with the homeopathic emphasis on the individual rather than the disease. This approach may have additional applications that can elucidate similar effects of other energy medicine modalities (e.g., acupuncture) on the healing process of the person as a unified whole.


Embryos of the African clawed frog, Xenopus laevis, are used in FETAX (frog embryo teratogenesis assay-Xenopus) to assess developmental toxicity of chemicals. Halogenated aromatic hydrocarbons, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), can be potent developmental toxicants. However, several frog species are relatively resistant to TCDD toxicity. Although assessments of TCDD toxicity in X. laevis vary, some reports suggest that this species may also be relatively insensitive. In other vertebrates, TCDD toxicity is mediated by the aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor, and by ARNT (aryl hydrocarbon receptor nuclear translocator), the dimeric partner of AHR. To investigate the mechanisms of TCDD sensitivity and resistance in X. laevis, we have isolated cDNA sequences encoding AHR and ARNT from 96 hour embryos. X. laevis resembles many fish in the expression of two distinct AHR genes. However, phylogenetic analysis demonstrates that both X. laevis AHRs are orthologs of mammalian AHR1; neither resembles the AHR2 genes common to fish. The two proteins, AHR1alpha (836 aa; 94.1 kDa) and AHR1beta (833 aa; 93.4 kDa), share 86% amino acid identity, suggesting that they evolved rather recently, perhaps coincident with the tetraploidization of the Xenopus genome approximately 30 mya. X. laevis represents the first species in which multiple AHR1 genes have been observed. Analysis of the single X. laevis ARNT sequence detected revealed that it is an ARNT2 ortholog. ARNT2 is widely expressed in certain fish, but is restricted to kidney and CNS in mammals. Since sequencing multiple X. laevis ARNT clones detected only ARNT2, we suggest that it is the predominant ortholog expressed at this life stage. FETAX is used as a model for predicting the developmental toxicity of materials to other vertebrates. An understanding of the molecular mechanisms underlying sensitivity differences to halogenated aromatic hydrocarbons should contribute to the development of FETAX as a model for developmental toxicity of samples containing these compounds.

Wistar rats were trained in step-down inhibitory avoidance at the age of 3 months, and tested for retrieval either 1 day later or 3, 6, 9, 12, 15 or 19 months later, when the animals were 6, 9, 12, 15, 18 or 22 months old, respectively. Bupropion (20 or 60 mg kg) and sertraline (3.3 or 10 mg/kg) given orally 6 or 3 h before retention testing, respectively, enhanced retrieval of this task at all training-test intervals, despite the fact that retrieval at the longest intervals was practically not seen in control animals. The effect cannot be explained by influences of the drugs on locomotor activity; the treatments had no effect on open field behaviour at the age of 3, 8 or 21 months. The findings may be relevant to the use of these drugs as cognitive enhancers in elderly subjects.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12122311


BACKGROUND: Complementary and alternative medicine (CAM) use and expenditures are on the rise in the United States. Although civilian users of CAM have been well described, little is known about military veteran users of CAM. OBJECTIVE: To describe military veteran CAM users in the southwestern United States. METHODS: The study population comprised 508 military veterans randomly selected from Southern Arizona Veterans Administration Health Care System (Tucson) primary care patient lists, who had agreed to participate in a telephone interview. The chi(2) test was used to analyze CAM use by demographic characteristics, military service, military-related health outcomes, and physician-diagnosed health complaints. Logistic regression was used to determine predictor variables. RESULTS: Of the 508 subjects, 252 (49.6%) reported CAM use. Military veteran CAM users were significantly more likely to be non-Hispanic white, earn more than $50 000 per year (both P<.05), and have greater than 12 years of education (P<.01). Current high daily stress, perceived negative impact of military life on physical or mental health, and physician-diagnosed chronic illnesses (eg, gastrointestinal problems, insomnia, and asthma) were statistically associated with CAM use. Regression analysis provided adjusted odds ratios and indicated that ethnicity (non-Hispanic white), higher education, greater current daily stress, and overseas military experience were significant predictors of CAM use by these veterans (each P<.05). CONCLUSIONS: Ethnicity, education,
income, and several chronic health complaints are consistent with civilian CAM use. Findings also suggest, however, that physicians providing conventional medical care need to be aware of experiences unique to CAM-using military veterans.


Pregnant Sprague-Dawley rats (14-18 days of gestation) were treated with a single dose of 50 mg/kg (61% of oral LD50 in female rats) of chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro-2-pyridyl phosphorothioate) by oral gavage. Animals treated on day 18 of gestation were sacrificed at 1, 2, 4, 12 h after dosing. Animals treated on days 17, 16, 15, and 14 of gestation were sacrificed at 24, 48, 72, and 96 h after dosing, respectively. Maternal and fetal brain acetylcholinesterase (AchE) and plasma butyrylcholinesterase (BuChE) activities were significantly inhibited 1 h after treatment. Activity of fetal brain AChE and plasma BuChE recovered faster than that of the maternal enzymes. Peak inhibition of maternal spinal cord AChE and BuChE activities occurred 2 h and 1 h after dosing, respectively. Maternal spinal cord BuChE activity was totally recovered by 96 h compared to the partial recovery of spinal cord AChE activity. Maternal liver BuChE activity was significantly decreased within 1 h of dosing. The individual molecular forms (10S and 4S) of maternal and fetal brain AChE and BuChE activities were significantly decreased 1 h after treatment. Recovery of both forms of fetal brain AChE activity was much faster than the maternal forms. Activity of the 10S form of maternal control brain AChE was significantly higher than in the fetus control. The rapid recovery of cholinesterase enzymes in the fetus is attributed to the de novo synthesis of AChE enzymes in the fetus compared to the mother.


The ICOH has played a key role in the development of some scientific documents and policy recommendations, but it has not always been scientifically objective, particularly in regard to asbestos and other fibers and some chemicals and pesticides. Many ICOH members are employees of corporations or consultants to industry, serving multinational corporate interests to influence public health policy in the guise of a professional scientific organization. ICOH members' conflicts of interest with the public health dominate the organization and damage the standing of the ICOH. Official recognition of the ICOH compromises the credibility of the WHO and the ILO. It is inappropriate for the ICOH to continue to receive WHO and ILO recognition unless the ICOH is recognized as an industry organization.


BACKGROUND: A subset of drug-allergic patients show a marked propensity to react against several, chemically unrelated nonsteroidal anti-inflammatory drugs (NSAIDs). The pathogenesis of such multiple drug reactions is unclear. Approximately 30% of patients with chronic idiopathic urticaria, a condition frequently characterized by autoreactivity on autologous serum skin test (ASST), experience flares of hives after taking chemically unrelated NSAIDs. OBJECTIVE: To detect whether a clinically unapparent autoreactivity may represent the nonspecific mechanism facilitating drug-induced histamine release in patients with a history of urticaria/angioedema induced by several, chemically unrelated NSAIDs. METHODS: Thirty-six adults with a history of acute NSAID-induced urticaria (22 with multiple NSAID sensitivity [MNS]; 14 with single NSAID sensitivity [SNS]; and 20 atopic controls without a history of drug allergy) underwent ASST. Sera from 14 MNS and 4 SNS subjects (all ASST-positive) underwent histamine release assay with basophils from normal donors. Sera from five MNS patients were tested on autologous basophils as well. RESULTS: Twenty of 22 (91%) MNS subjects versus 5 of 14 (36%) SNS subjects were positive on ASST (P < 0.01). No atopic control was ASST-positive. Sera from 4 of 14 (29%) MNS patients versus 0/4 SNS subjects (P = NS) induced significant histamine release from basophils of normal donors. The use of autologous basophils did not significantly change these results. CONCLUSION: Most patients with multiple NSAID intolerance and approximately one-third of those with single NSAID hypersensitivity are characterized by the presence of circulating histamine-releasing factors. Their nature is still unclear, but the fact that only a minority of sera from ASST+ subjects were able to induce histamine release from normal basophils in vitro suggests that these factors might not
differ from those involved in most patients with chronic urticaria. These factors might play a relevant pathogenic role in NSAID-induced urticaria reactions.

(2002) [Indoor air and human health--sick house syndrome and multiple chemical sensitivity].
Ando, M Journal/Kokuritsu Iyakuhin Shokuhin Eisei Kenkyusho Hokoku. 6-38.

The number of complaints about the quality of indoor air has increased during the past two decades. These complaints have been frequent enough that the term "Sick House Syndrome or Sick Building Syndrome" and "Multiple Chemical Sensitivity" has been coined. Complaints are likely related to the increased use of synthetic organic materials in house, furnishing, and consumer products; and the buildings, furnishings, and consumer products; and the decreased ventilation for energy conservation in homes. Approximately thousand volatile chemicals have been identified in indoor air. The main sources of these chemicals are house materials, combustion fumes, cleaning compounds, and paints or stains. Exposure to high levels of these emissions and to others, coupled with the fact that most people spend more time indoors than outdoors, raises the possibility that the risk to human health from indoor air pollution may be potentially greater than the risk posed from outdoor pollutants. The complaints most frequently voiced with respect to Sick House Syndrome are irritations of the eye, nose, and throat; cough and hoarseness of voice; headache and mental fatigue. The syndrome of multiple chemical sensitivities is controversial subject with increasing impact on the field of indoor air quality. The controversy surrounding Multiple Chemical Sensitivity includes its definition, theories of etiology and pathogenesis, diagnostic, and life style. Multiple Chemical Sensitivity is considered the hypothesis that is a disease caused by exposure to many chemically distinct environmental substances at very low.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12638182


Early efforts directed toward the development of pesticide regulations addressed serious acute illnesses associated with pesticide mixing, loading, and application. As those pesticide exposures and illnesses came under control through official regulatory action, attention has turned toward problems associated with the impacts of pesticides on communities and schools. By contrast to the early successes in bringing major acute poisoning under control, the problems of pesticide impacts on communities and schools have been especially difficult to resolve through the regulatory process. This
article discusses the dynamics of the new and emerging impacts of pesticides on communities and schools, with an emphasis upon California experiences.


---------------------------------------------------------------


Exposure to organic solvents is still common in industrial and other work environments, and increases the risk of chronic toxic encephalopathy (CTE). Genetic variation in metabolic enzymes for solvents and other xenobiotics may modify the risk of developing toxic effects. Therefore, we investigated the presence of null genotypes for glutathione S-transferases M1 and T1 (GSTM1, GSTT1) and two genetic polymorphisms of microsomal epoxide hydrolase (mEPHX) in relation to the risk for chronic toxic encephalopathy (CTE) when exposed to solvents and smoking. We genotyped 115 patients who were classified into three categories: CTE (n = 56), incipient CTE (n = 27) and non-CTE (n = 32) patients. DNA was isolated from leucocytes and the GSTM1 and GSTT1 null genotypes were determined by multiplex-polymerase chain reaction. The two polymorphisms of mEPHX were analysed by PCR-RFLP (restriction fragment length polymorphism) based assays. All analyses were performed blindly with regard to both exposure and disease status. An increased binomial regression risk ratio = 2.5, 95% confidence interval (CI) 1.5-4.2, of the GSTM1 null genotype for CTE was found in smokers and for the GSTT1 null genotype (binomial regression risk ratio 1.5, 95% CI 1.0-2.0). In nonsmokers, the GSTM1 null genotype did not confer any risk for CTE. None of the studied mEPHX polymorphisms were associated with an increased risk for CTE. We suggest that the GSTM1 null genotype in smokers is a possible risk for solvent-induced CTE.

---------------------------------------------------------------

Abu-Qare, AW and Abou-Donia, MB Journal/J Appl Toxicol. 22: 149-52.
Recently, several studies have reported on the health and environmental consequences of the use of depleted uranium. Depleted uranium is a heavy metal that is also radioactive. It is commonly used in missiles as a counterweight because of its very high density (1.6 times more than lead). Immediate health risks associated with exposure to depleted uranium include kidney and respiratory problems, with conditions such as kidney stones, chronic cough and severe dermatitis. Long-term risks include lung and bone cancer. Several published reports implicated exposure to depleted uranium in kidney damage, mutagenicity, cancer, inhibition of bone, neurological deficits, significant decrease in the pregnancy rate in mice and adverse effects on the reproductive and central nervous systems. Acute poisoning with depleted uranium elicited renal failure that could lead to death. The environmental consequences of its residue will be felt for thousands of years. It is inhaled and passed through the skin and eyes, transferred through the placenta into the fetus, distributed into tissues and eliminated in urine. The use of depleted uranium during the Gulf and Kosovo Wars and the crash of a Boeing airplane carrying depleted uranium in Amsterdam in 1992 were implicated in a health concern related to exposure to depleted uranium.

(2002) Binding of pyridostigmine bromide, N,N-diethyl-m-toluamide and permethrin, alone and in combinations, to human serum albumin.
Abu-Qare, AW and Abou-Donia, MB Journal/Arch Toxicol. 76: 203-8.

In this study we examined the interaction of the anti-nerve agent drug pyridostigmine bromide (PB, 3,3-dimethylaminocarboxyloxy- N-methylpyridiniyum bromide), the insect repellent DEET (N, N-diethyl- m-toluamide), and the insecticide permethrin [3-(2,2-dichloroethyl)-2,2-dimethylcyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester] in binding to human serum albumin (HSA). Concentrations between 500 ng/ml and 10 microg/ml PB, DEET and permethrin, alone or in combination, were incubated with HSA at 37 degrees C for 60 min. Concentrations of PB, DEET and permethrin were determined using high performance liquid chromatography (HPLC). The results showed that 81.2+/-4.2%, and 84.6+/-2.5% of the initial concentration of PB was bound to HSA when incubated alone or in combination with DEET or permethrin, respectively. DEET and permethrin did not significantly interact with HSA after 1 h of incubation. Incubation of combinations of two or three compounds did not significantly alter the binding pattern of any of the compounds with HSA. These results showed that PB is highly bound to albumin protein, while the competition between PB, DEET and permethrin on binding sites of HSA as a possible site of interaction following combined administration in vivo is not likely.

Abu-Qare, AW and Abou-Donia, MB Journal/Food Chem Toxicol. 40: 1327-33.

Sarin (O-isopropylmethylphosphonofluoridate) is a highly toxic nerve agent produced for chemical warfare. Sarin is an extremely potent acetylcholinesterase (AchE) inhibitor with high specificity and affinity for the enzyme. Death by sarin is due to anoxia resulting from airway obstruction, weakness of the muscles of respiration, convulsions and respiratory failure. The main clinical symptoms of acute toxicity of sarin are seizures, tremors and hypothermia. Exposure to sarin during incidents in Japan in 1994, 1995 and 1998, and possible exposure to low levels of sarin during the Gulf War, resulted in the deaths and injury of many people in Japan and caused possible long-term health effects on Gulf War veterans. Symptoms related to sarin poisoning in Japan still exist 1-3 years after the incident and include fatigue, asthenia, shoulder stiffness and blurred vision. Sarin produced seizures in rats and pigs. Recent studies showed that long-term exposure to low levels of sarin caused neurophysiological and behavioral alterations. Toxicity from sarin significantly increased following concurrent exposure to other chemicals such as pyridostigmine bromide. Further research to examine effects of sarin on the cellular and the molecular levels, gene transcription, endocrine system as well as its long-term impact is needed.

---------------------------------------------------------------


We investigated the effects of uranyl acetate on sensorimotor behavior, generation of nitric oxide and the central cholinergic system of rats. Male Sprague-Dawley rats were treated with intramuscular injection of 0.1 and 1 mg/kg uranyl acetate in water, daily for 7 days. Control animals received equivalent amount of water. The treatment was stopped after the seventh injection because the animals in the 1-mg/kg group appeared lethargic. The animals were maintained for an additional observation period of 30 days. The study was initiated as a dose-finding study that covered doses of 10 and 100 mg/kg, as well. However, all the animals in the 100-mg/kg treatment group died after the third and fourth injections, and all animals given 10 mg/kg died after the fifth and sixth injections. On Day 30 following the cessation of treatment, the sensorimotor functions of the animals in the 0.1- and 1-mg/kg treatment groups were evaluated using a battery of tests that included measurements of postural reflexes, limb placing, orientation to vibrissae touch, grip time, beam walking and inclined plane performance. The animals were sacrificed the same day and the cerebral cortex, brainstem, cerebellum and midbrain were dissected. The levels of nitric oxide as marker for increased oxidative stress, and the integrity of the cholinergic system as reflected in acetylcholinesterase (AChE) activity and m2 muscarinic acetylcholine receptors ligand binding, were determined. The data from behavioral observations show that there was a dose-related deficit at the 0.1- and 1-mg/kg treatment groups for
inclined plane performance. Both doses reduced grip time, but there was no significant difference between the two doses. Similarly, both beam-walk score and beam-walk time were impaired at both doses as compared with the controls. A significant increase in nitric oxide was seen at 0.1 mg/kg dose in cortex and midbrain, whereas brainstem and cerebellum showed an insignificant decrease at both the doses. Similarly, there was no significant change in nitric oxide levels in kidneys and liver of the treated animals as compared with the controls. There was a significant increase in AChE activity in the cortex of the animals treated with 1 mg/kg uranyl acetate, but not in other brain regions. Ligand binding densities for the m2 muscarinic receptor did not show any change. These results show that low-dose, multiple exposure to uranyl acetate caused prolonged neurobehavioral deficits after the initial exposure has ceased.


A myriad of neurological symptoms including muscle and joint pain, ataxia, chronic fatigue, headache, and difficulty in concentration have been reported by Persian Gulf War (PGW) veterans. A large number of these veterans were prophylactically treated with pyridostigmine bromide (PB) and possibly exposed to sarin. In the present study we investigated the effects of PB and sarin, alone and in combination, on sensorimotor performance and the central cholinergic system of rats. Male Sprague-Dawley rats were treated with PB (1.3 mg/kg, 15 daily doses, oral) and sarin (50, 75, 90, and 100 microg/kg, single im dose on day 15), alone and in combination. The animals were evaluated for postural reflexes, limb placing, orienting to vibrissae touch, incline plane performance, beam-walk time, and forepaw grip time 7 and 15 days following treatment with sarin. Treatment with either PB or sarin alone resulted in significant sensorimotor impairments. Coexposure to sarin and PB resulted in significant sensorimotor deficits that worsened over time. By 15 days following sarin treatment, plasma butyrylcholinesterase (BChE) activity returned to normal levels in the animals treated with sarin alone, whereas in the animals exposed to PB or PB plus sarin, there was an increase in the enzyme activity. Cortical acetylcholinesterase (AChE) activity remained inhibited in the animals treated with sarin alone and in combination with PB. Muscarinic acetylcholine receptor (m2 mAChR) ligand binding with [(3)H]AFDX-384 in cortex and brain stem showed significant increases (approximately 120-130% of control) following coexposure to PB and sarin at higher doses. To evaluate the potential of PB for augmentation or inhibition of the toxicity induced by acute sarin exposure, the animals were exposed to either 10 or 100 microg/kg sarin (single im injection) with or without pretreatment with PB, and sacrificed 3 h after treatment with sarin. Pretreatment with PB offered slight protection in the plasma as well as brain regional enzyme activities. Pretreatment with PB did not have any effect on sarin-inhibited brain regional AChE activity following treatment with 100 microg/kg...
sarin. These results show that prophylactic treatment with PB offers some degree of protection in peripheral cholinesterase. Furthermore, these results show that treatment with either sarin or PB alone resulted in sensorimotor impairments, while coexposure to high doses of sarin with PB caused an exacerbated deficit.


Three decades ago, cabin air quality was seemingly not an issue in commercial aviation and the incidence of disease through air borne vectors or toxic fumes was uncommon among passengers and crew. However, it is claimed that modern day jet airliners generally carry the threat of disease through the ventilator systems of these aircraft which are designed for optimum efficiency, leaving them exposed to lapses in the recycling of clean air and blocking fumes from engine exhausts of the jets from entering the inhabited parts of the aircraft. It has been claimed that aerotoxic fumes are most common in the cockpit, and that the technical crew are the most susceptible to the aerotoxic syndrome.


The pharmacokinetics and placental transfer of a single intravenous dose of 5.0 mg/kg (10 micro Ci/kg) ring-labeled [(14)C]chlorpyrifos were investigated in pregnant Sprague-Dawley rats at 11-13 days of gestation. Three rats were killed at 5, 15 or 30 min, or 1, 2, 4, 8, 12, 18, 24, 36, 48, 72 or 96 h after dosing. Radioactivity and 3,5,6-trichloropyridinol (TCP) were detected in all tissues 5 min after dosing. Chlorpyrifos was only found in maternal plasma and liver. Peak maternal plasma concentration of radioactivity (micro g chlorpyrifos equivalents/ml) was 157 at 5 min, compared with 1.9 for fetal plasma at 15 min. The maximum concentrations of radioactivity (micro g chlorpyrifos equivalents/g), detected in most tissues within 12 h of dosing, were, in descending order: liver (30), brain (29), placenta (21), and fetus (2). All peaks occurred at 5 min except for fetus and fetal plasma, which were at 15 min. TCP was detected by HPLC as the major compound identified in plasma and tissues. The maximum concentration detected was in plasma, at 12.4 micro g/ml, and for the following tissues was: liver 4.3 ng/g fresh tissue, fetus 4 ng/g, placenta 2.97 ng/g, brain 1.68 ng/g, and fetal plasma 0.52 ng/g. All TCP peaks occurred at 5 min except for fetus at 30 min and fetal plasma at 15 min. Parent chlorpyrifos was detected in maternal plasma and liver at maximum concentrations of 5.1 micro g/ml and 0.40 micro g/g,
respectively, at 5 min. Chlorpyrifos was detectable in maternal plasma up to 36 h after dosing, and in liver up to 24 h after dosing. Pharmacokinetic analysis best described radioactivity, chlorpyrifos, and TCP as disappearing biexponentially from plasma and tissues. The terminal elimination half-lives of radioactivity, chlorpyrifos and TCP from maternal plasma were 16, 18, and 16 h, respectively. The results indicate that (1). chlorpyrifos undergoes a rapid metabolism to its major metabolites (TCP); (2). chlorpyrifos and its metabolites are distributed to all maternal and fetal tissues and plasma; and (3). the elimination of chlorpyrifos and TCP is slow, with redistribution from lipid stores a likely determinant of elimination rates.

---------------------------------------------------------------


We hypothesize that a single exposure to an LD(50) dose of sarin induces widespread early neuropathological changes in the adult brain. In this study, we evaluated the early changes in the adult brain after a single exposure to different doses of sarin. Adult male rats were exposed to sarin by a single intramuscular injection at doses of 1, 0.5, 0.1 and 0.01 x LD(50). Twenty-four hours after the treatment, both sarin-treated and vehicle-treated (controls) animals were analyzed for: (i) plasma butyrylcholinesterase (BChE) activity; (ii) brain acetylcholinesterase (AChE) activity, (iii) m2 muscarinic acetylcholine receptor (m2 mAChR) ligand binding; (iv) blood brain barrier (BBB) permeability using [H(3)]hexamethonium iodide uptake assay and immunostaining for endothelial barrier antigen (EBA); and (v) histopathological changes in the brain using H&E staining, and microtubule-associated protein (MAP-2) and glial fibrillary acidic protein immunostaining. In animals treated with 1 x LD(50) sarin, the significant changes include a decreased plasma BChE, a decreased AChE in the cerebrum, brainstem, midbrain and the cerebellum, a decreased m2 mAChR ligand binding in the cerebrum, an increased BBB permeability in the cerebrum, brainstem, midbrain and the cerebellum associated with a decreased EBA expression, a diffuse neuronal cell death and a decreased MAP-2 expression in the cerebral cortex and the hippocampus, and degeneration of Purkinje neurons in the cerebellum. Animals treated with 0.5 x LD(50) sarin however exhibited only a few alterations, which include decreased plasma BChE, an increased BBB permeability in the midbrain and the brain stem but without a decrease in EBA expression, and degeneration of Purkinje neurons in the cerebellum. In contrast, animals treated with 0.1 and 0.01 x LD(50) did not exhibit any of the above changes. However, m2 mAChR ligand binding in the brainstem was increased after exposure to all doses of the sarin. Collectively, the above results indicate that, the early brain damage after acute exposure to sarin is clearly dose-dependent, and that exposure to 1 x LD(50) sarin induces detrimental changes in many regions of the adult rat brain as early as 24 hours after the exposure. The early neuropathological changes observed after a single dose of 1 x LD(50) sarin could lead to a profound long-term
neurodegenerative changes in many regions of the brain, and resulting behavioral abnormalities.

----------------------------------------------------------------------


We investigated the effects of a combined exposure to restraint stress and low doses of chemicals pyridostigmine bromide (PB), N, N-diethyl-m-toluamide (DEET), and permethrin in adult male rats, a model of Gulf-War syndrome. Animals were exposed daily to one of the following for 28 days: (i) a combination of stress and chemicals (PB, 1.3 mg/kg/day; DEET, 40 mg/kg/day; and permethrin, 0.13 mg/kg/day); (ii) stress and vehicle; (iii) chemicals alone; and (iv) vehicle alone. All animals were evaluated for: (i) the disruption of the blood-brain barrier (BBB) using intravenous horseradish peroxidase (HRP) injections and endothelial barrier antigen (EBA) immunostaining; (ii) neuronal cell death using H&E staining, silver staining, and glial fibrillary acidic protein (GFAP) immunostaining; and (iii) acetylcholinesterase (AChE) activity and m2-muscarinic acetylcholine receptors (m2-AChR). Animals subjected to stress and chemicals exhibited both disruption of the BBB and neuronal cell death in the cingulate cortex, the dentate gyrus, the thalamus, and the hypothalamus. Other regions of the brain, although they demonstrated some neuronal cell death, did not exhibit disruption of the BBB. The neuropathological changes in the above four brain regions were highly conspicuous and revealed by a large number of HRP-positive neurons (21-40% of total neurons), a decreased EBA immunostaining (42-51% reduction), a decreased number of surviving neurons (27-40% reduction), the presence of dying neurons (4-10% of total neurons), and an increased GFAP immunostaining (45-51% increase). These changes were also associated with decreased forebrain AChE activity and m2-AChR (19-25% reduction). In contrast, in animals exposed to stress and vehicle or chemicals alone, the above indices were mostly comparable to that of animals exposed to vehicle alone. Thus, a combined exposure to stress and low doses of PB, DEET, and permethrin leads to significant brain injury. The various neurological symptoms reported by Gulf-War veterans could be linked to this kind of brain injury incurred during the war.

----------------------------------------------------------------------

Fourteen states (Arizona, Connecticut, Florida, Georgia, Indiana, Mississippi, New York, Ohio, Oregon, Pennsylvania, Texas, Virginia, Washington, and West Virginia) have reported investigations of multiple schoolchildren who have developed rashes. This report summarizes the investigation by state and local health departments of these rashes, which have occurred during October 2001 through February 2002, and provides examples for four states. Preliminary findings indicate that further investigation is needed to determine whether a common etiology for these rashes exists.


Alcohol is known to modulate the activity of a variety of neuroreceptors and ion channels. Recently, neuronal nicotinic acetylcholine receptors (nnAChRs) have become a specific focus of study because not only are they potently modulated by alcohol but also they regulate the release of various transmitters, including gamma-aminobutyric acid (GABA) and dopamine, which play an important role in the behavioral effects of ethanol. Whereas the potency of normal alcohols (n-alcohols) to potentiate GABA(A) receptors and to inhibit N-methyl-D-aspartate receptors increases with carbon chain length, we have found that n-alcohols, depending on the carbon chain length, exert a dual action, potentiation and inhibition, on nnAChRs in primary cultured rat cortical neurons. The mechanism of dual action of n-alcohols on nnAChRs was further analyzed using human embryonic kidney cells expressing the alpha 4 beta 2 subunits. Shorter chain alcohols from methanol to n-propanol potentiated acetylcholine (ACh)-induced currents, whereas longer chain alcohols from n-pentanol to n-dodecanol inhibited the currents. n-Butanol either potentiated or inhibited the currents depending on the concentrations of ACh and butanol. The parameters for
both potentiation (log EC(200)) and inhibition (log IC(50)) were linearly related to carbon number, albeit with different slopes. The slope for potentiation was -0.299, indicating a change in free energy change (Delta Delta G) of 405 cal/mol/methylene group, whereas the slope for inhibition was -0.584, indicating a Delta Delta G of 792 cal mol. These results suggest that potentiating and inhibitory actions are exerted through two different binding sites. Ethanol decreased the potency of n-octanol to inhibit ACh currents, possibly resulting from an allosteric mechanism.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11562431

(2001) [Diagnosis and correlation of regional ecologically-caused states in children].
Zaitseva, NV Journal/Gig Sanit. 31-6.


(2001) Differential effects of NMDA and group I mGluR antagonists on both nociception and spinal cord protein kinase C translocation in the formalin test and a model of neuropathic pain in rats.

Coincident with nociception, both noxious chemical stimulation of the hind paw and chronic constriction injury (CCI) of the sciatic nerve produce an increase in protein kinase C (PKC) translocation in the spinal cord of rats. Noxious stimulus-induced PKC translocation likely depends on glutamate activity at either N-methyl-D-aspartate (NMDA) receptors or group I metabotropic glutamate receptors (mGluR1/5) in the spinal cord dorsal horn. This study compares nociceptive responses to, and the alterations in membrane-associated PKC, induced by noxious chemical stimulation of the hindpaw and CCI of the sciatic nerve, as well as their modulation by both NMDA and mGluR1/5 receptor antagonists. Three groups of rats were given a single intrathecal (i.t.) injection of either vehicle, dizocilpine maleate (MK-801, 60 nmol), an NMDA receptor antagonist, or (S)-4-carboxyphenylglycine (S)-4CPG, (150 nmol), an mGluR1/5 antagonist, 10 min prior to a 50 microl of 2.5% formalin injection into the
ventral surface of one hind paw. Another three groups of rats were given twice daily injections of either vehicle, MK-801 (30 nmol) or (S)-4CPG (90 nmol) i.t. for 5 days starting 30 min before CCI or sham injury of the sciatic nerve. Nociceptive responses were assessed for a 60 min period after the formalin injection in the first three groups, and tests of mechanical and cold allodynia were performed on days 4, 8, 12 and 16 after CCI for the latter three groups. Furthermore, changes in the levels of membrane-associated PKC, as assayed by quantitative autoradiography of the specific binding of [3H]-phorbol 12,13-dibutyrate ([3H]-PDBu) in the dorsal horn of the lumbar spinal cord sections, were assessed in formalin-injected rats (at 5, 25 and 60 min) and in neuropathic rats 5 days after CCI, treated (as above) with vehicle, MK-801 or (S)-4CPG. The results indicate that i.t. treatment with MK-801 significantly reduced nociceptive scores in the formalin test and also produced a significant suppression of formalin-induced increases in [3H]-PDBu binding in laminae I-II, III-VI and X of the lumbar spinal cord. In contrast, i.t. treatment with (S)-4CPG failed to significantly affect either nociceptive behaviours in the formalin test or formalin-induced increases in [3H]-PDBu binding in laminae I-II and III-VI of the lumbar spinal cord. On the other hand, i.t. treatment with either MK-801 or (S)-4CPG produced a significant reduction in mechanical and cold hypersensitivity, as well as [3H]-PDBu binding in laminae I-II and III-VI of the lumbar spinal cord, after CCI. These results suggest that while NMDA, but not mGluR1/5, receptors are involved in translocation of PKC and nociception in a model of persistent acute pain, both types of receptors influence the translocation of PKC in dorsal horn and mechanical and cold allodynia in a model of chronic neuropathic pain.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11576741


Diisopropyl phosphorofluoridate (DFP) is an organophosphorus ester, which produces mild ataxia in 7-14 days and severe ataxia or paralysis in about 20 days (OPIDN) in hens. Previous studies in this laboratory have shown enhanced temporal expression of neurofilament (NF) subunit mRNAs in the spinal cord (SC) of DFP-treated hens. The main objective of this investigation was to study the effect of DFP administration on NF subunit mRNAs expression, when OPIDN is protected or potentiated by pre-treatment or post-treatment, respectively, with phenylmethylsulfonyl fluoride (PMSF). The hens were sacrificed 1, 5, 10, and 20 days after the last treatment. In contrast with enhanced mRNA expression of NF subunits reported in OPIDN, there was no alteration in the expression of NF subunits in the SC of PMSF-protected hens that did not develop OPIDN. PMSF post-treatment of DFP-treated hens, which enhanced delayed neurotoxicity produced by a low dose of DFP, exhibited decrease in the mRNA
expression of NF subunits in SC at all time periods (1-20 days) of observation. The expression of NF subunits was also studied in the degeneration-resistant tissue cerebrum of treated hens. The results from protected hens suggested that temporal enhanced expression of NF subunit mRNAs in DFP-treated hens might be contributing to the development of OPIDN in hens. By contrast, PMSF post-treatment seemed to potentiate OPIDN by a mechanism different from that followed by DFP alone to produce OPIDN.

(2001) Alteration in cytoskeletal protein levels in sciatic nerve on post-treatment of diisopropyl phosphorofluoridate (DFP)-treated hen with phenylmethylsulfonyl fluoride.

Diisopropyl phosphorofluoridate (DFP) is an organophosphorus ester, and a single dose (1.7 mg/kg, sc.) of this compound produces mild ataxia in hens in 7-14 days and a severe ataxia or paralysis (OPIDN) in three weeks. OPIDN is associated with axonal swelling and their degeneration. We have previously observed alteration in neurofilament (NF) protein levels in the spinal cord of DFP-treated hens. The main objective of this investigation was to study NF protein levels in the sciatic nerves (SN) of hens, in which OPIDN has been potentiated by phenylmethylsulfonyl fluoride (PMSF) post-treatment. PMSF is known to protect DFP-treated (1.7 mg/kg) hens from developing OPIDN if injected before, and potentiate OPIDN if injected after the administration of DFP (0.5 mg/kg). The potentiation of OPIDN was accompanied by earlier elevation of NF proteins in the SN particulate fraction. In contrast, SN supernatant fraction showed a transient fall in NF protein levels in potentiation OPIDN. Out of the two other cytoskeletal proteins (i.e., tubulin, tau) studied in this investigation, tubulin also showed earlier elevation in its level in the particulate fraction in potentiated OPIDN. The earlier elevation of NF protein levels in SN particulate fraction in potentiated OPIDN suggested the possible involvement of NFs in delayed neurotoxicity.

(2001) [Allergies: environmental illness no. 1].

Wayment, HK, Schenk, JO and Sorg, BA Journal/J Neurosci. 21: 35-44.
In vitro rotating disk electrode (RDE) voltammetry and in vivo microdialysis were used to characterize dopamine clearance in the rat medial prefrontal cortex (mPFC). RDE studies indicate that inhibition by cocaine, specific inhibitors of the dopamine transporter (DAT) and norepinephrine transporter (NET), and low Na(+) produced a 50-70% decrease in the velocity of dopamine clearance. Addition of the monoamine (MAO) inhibitors, l-deprenyl, clorgyline, pargyline, or in vivo nialamide produced 30-50% inhibition. Combined effects of uptake inhibitors with l-deprenyl on dopamine clearance were additive (up to 99% inhibition), suggesting that at least two mechanisms may contribute to dopamine clearance. Dopamine measured extracellularly 5 min after exogenous dopamine addition to incubation mixtures revealed that most conditions of DAT/NET inhibition did not produce elevated dopamine levels above controls. Inhibition of MAO produced elevated dopamine levels only after long-term, but not short-term, incubation in vitro. Short-term incubation of l-deprenyl combined with DAT and NET uptake inhibitors increased dopamine above control levels, consistent with more than one mechanism of dopamine clearance. Local infusion of pargyline (100 or 300 microm) into the mPFC or striatum via microdialysis produced more pronounced and immediate increases in mPFC dopamine levels compared with striatum. Furthermore, dopamine elevation in the mPFC was not accompanied by a decrease in the dopamine metabolites, 3,4-dihydroxyphenylacetic acid and homovanillic acid, as found in the striatum. These findings may have revealed a unique mechanism of mPFC dopamine clearance and therefore contribute to the understanding of multiple behaviors that involve mPFC dopamine transmission, such as schizophrenia, drug abuse, and working memory function.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11150317

-------------------------------------------------------------------

(2001) mGlu5 receptors and nociceptive function II. mGlu5 receptors functionally expressed on peripheral sensory neurones mediate inflammatory hyperalgesia.

Previous studies have demonstrated that the metabotropic glutamate receptor subtype 5 (mGlu5 receptor) is expressed in the cell bodies of rat primary afferent neurones. We have further investigated the function and expression of mGlu5 receptors in primary afferent neurones, and their role in inflammatory nociception. Freund's complete adjuvant-induced inflammatory hyperalgesia of the rat hind paw was significantly reduced by intraplantar, but not by intracerebroventricular or intrathecal microinjection of the selective mGlu5 receptor antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP). Pharmacological comparison in vivo of the nociceptive effects of glutamate, and ionotropic and metabotropic glutamate (mGlu) receptor agonists applied to the rat hind paw, indicated that group I mGlu receptor agonists induce a dose-dependent
decrease in paw withdrawal threshold (mechanical hyperalgesia). Group I mGlu agonist-induced hyperalgesia was inhibited by co-microinjection of MPEP, but not by the mGlu1 receptor antagonist (S)-4-carboxy-phenylglycine (4-CPG). Carrageenan-induced inflammatory hyperalgesia was inhibited by pre-treatment of the inflamed hind paw with MPEP, but not following MPEP injection into the contralateral hind paw. Dorsal horn neurones receiving peripheral nociceptive and non-nociceptive afferent input were recorded in anaesthetized rats following microinjection of CHPG into their peripheral receptive fields. CHPG significantly increased the frequency and duration of firing of dorsal horn wide dynamic range (WDR) neurones and this activity was prevented by co-administration of CHPG and MPEP into their receptive fields. Immunohistochemical experiments revealed the co-expression of mGlu5 receptor protein and betaIII tubulin in skin from naive rats, indicating the constitutive expression of mGlu5 receptors on peripheral neurones. Double-labelling of adult rat DRG cells with mGlu5 receptor and vanilloid receptor subtype 1 antisera also supports the expression of mGlu5 receptors on peripheral nociceptive afferents. These results suggest that mGlu5 receptors expressed on the peripheral terminals of sensory neurones are involved in nociceptive processes and contribute to the hyperalgesia associated with inflammation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11077066

---------------------------------------------------------------------------------------------------------------------------------------

(2001) [Legal aspects of using economic mechanisms for protecting health of residents from environmental factors].
Volkov, SD and Grunicheva, TP Journal/Gig Sanit. 84-6.

---------------------------------------------------------------------------------------------------------------------------------------

(2001) Protein kinase C activation potentiates gating of the vanilloid receptor VR1 by capsaicin, protons, heat and anandamide.

1. The effects of activation of protein kinase C (PKC) on membrane currents gated by capsaicin, protons, heat and anandamide were investigated in primary sensory neurones from neonatal rat dorsal root ganglia (DRG) and in HEK293 cells (human embryonic kidney cell line) transiently or stably expressing the human vanilloid receptor hVR1. 2. Maximal activation of PKC by a brief application of phorbol 12-myristate 13-acetate (PMA) increased the mean membrane current activated by a low concentration of capsaicin by 1.65-fold in DRG neurones and 2.18-fold in stably transfected HEK293 cells. Bradykinin, which activates PKC, also enhanced the response to capsaicin in DRG neurones. The specific PKC inhibitor RO31-8220
prevented the enhancement caused by PMA. 3. Activation of PKC did not enhance the membrane current at high concentrations of capsaicin, showing that PKC activation increases the probability of channel opening rather than unmasking channels. 4. Application of PMA alone activated an inward current in HEK293 cells transiently transfected with VR1. The current was suppressed by the VR1 antagonist capsazepine. PMA did not, however, activate a current in the large majority of DRG neurones nor in HEK293 cells stably transfected with VR1. 5. Removing external Ca(2+) enhanced the response to a low concentration of capsaicin 2.40-fold in DRG neurones and 3.42-fold in HEK293 cells. Activation of PKC in zero Ca(2+) produced no further enhancement of the response to capsaicin in either DRG neurones or HEK293 cells stably transfected with VR1. 6. The effects of PKC activation on the membrane current gated by heat, anandamide and low pH were qualitatively similar to those on the capsaicin-gated current. 7. The absence of a current activated by PMA in most DRG neurones or in stably transfected HEK293 cells suggests that activation of PKC does not directly open VR1 channels, but instead increases the probability that they will be activated by capsaicin, heat, low pH or anandamide. Removal of calcium also potentiates activation, and PKC activation then has no further effect. The results are consistent with a model in which phosphorylation of VR1 by PKC increases the probability of channel gating by agonists, and in which dephosphorylation occurs by a calcium-dependent process.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11483711


OBJECTIVES: To study the routine diagnostic procedures used in different countries for chronic toxic encephalopathy (CTE) induced by solvents. METHODS: By means of a postal questionnaire selected international experts were asked about the methods they use to diagnose patients suspected of having CTE induced by solvents, the number of patients, entrance criteria, and the results of these diagnostic procedures. RESULTS: 18 Experts working in 18 diagnostic centres responded. Most of them agreed that a diagnostic procedure for CTE induced by solvents should contain an interview and neurological, physical, and neuropsychological examinations. However, the tests used were very different, as were the classifications for CTE. Depending on the institute, a diagnosis of CTE was made in 6%--70% of the referred patients. The proportion of patients with CTE stage I ranged from 0% to 33%, stage II from 5% to 100%, and stage III from 0% to 95%. CONCLUSION: The intentions of the two 1985 conferences that aimed at clarity and uniformity of diagnosis of CTE induced by solvents are far from reached. It is possible, now the conditions are more favourable, to
aim at this important goal and recommend some refinement of the then proposed criteria.


In this chapter, a learning account is discussed as a potential explanation for the symptoms in multiple chemical sensitivity. Clinical evidence is scarce and anecdotal. A laboratory model provides more convincing results. After a few breathing trials containing CO2-enriched air as an unconditioned stimulus in a compound with harmless odor substances as conditioned stimuli, subjective symptoms are elicited and respiratory behavior is altered by the odors only. Also, mental images can become conditioned stimuli to trigger subjective symptoms. The learning effects cannot be explained by a response bias or by conditioned arousal, and they appear to involve basic associative processes that do not overlap with aware cognition of the relationship between the odors and the CO2 inhalation. Learned symptoms generalize to new odors and they can be eliminated in a Pavlovian extinction procedure. In accordance with clinical findings, neurotic subjects and psychiatric cases are more vulnerable to learning subjective symptoms in response to odors. Consistent with a learning account, cognitive-behavioral treatment techniques appear to produce beneficial results in clinical cases. Several criticisms and unresolved questions regarding the potential role of learning mechanisms are discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000028

(2001) Sensitization, subjective health complaints, and sustained arousal.

The purpose of this presentation is to discuss the possibility that sensitization is a psychobiological mechanism underlying not only multiple chemical sensitivity (MCS), but a much more general cluster of illness, referred to as "subjective health complaints". Sustained arousal, or sustained "stress" responses, may be an important factor for the development of these conditions. Patients with subjective complaints without objective changes are sometimes referred to as having "fashionable diagnoses" or "unexplained symptoms". They may be given diagnoses like MCS, epidemic fatigue, chronic fatigue syndrome, burnout, stress, a variety of intoxications, environmental illness, radiation, multiple chemical hypersensitivity, food intolerance, functional dyspepsia, irritable bowel, myalgic encephalitis, postviral syndrome, yuppie
flu, fibromyalgia, or vital exhaustion. One issue is whether this is one general condition or separate entities. Another issue is whether sensitization may be the psychobiological mechanism for most or all of these conditions. Finally, is it likely that sustained arousal may facilitate the development of sensitization in some or many neural circuits? In this review, the main emphasis will be on musculoskeletal pain. This is the most frequent and most expensive condition for sickness compensation and disability. The comorbidity of other complaints, however, will also be taken into account.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000015

(2001) Far-reaching consequences of high level air pollution on the developing immune system.

The town of Dimitrovgrad in Bulgaria has a highly industrialized region with a developing chemical industry, cement and asbestos-cement production, as well as energy production. For over four decades, the main ecological problem was air pollution, but after 1989 a great economic crisis led to an abrupt decline in the level of air pollutants. The aim of the present study was to investigate the present state of humoral immunity in teenage children from Dimitrovgrad who lived under conditions of massive air pollution during their intrauterine development and first few years of childhood. Immunoglobulins IgA, IgM, and IgG were measured in 106 clinically healthy children (average age 12.68 +/- 0.56 y) from 3 schools in Dimitrovgrad and in 41 control subjects (average age 12.35 +/- 0.22 y) from the town of Nova Mahala, an area lacking massive sources of air pollution. Immunoglobulin concentration was determined by turbidimetry using an Optima (KONE) chemical analyzer. The average IgA, IgM, and IgG levels in children from Dimitrovgrad did not differ significantly from those of the control group.


Many studies have been published on the human health effects of cyanobacterial toxicity. As a public health concern, we have to mention that the development of contact dermatitis, asthmalike symptoms, and symptoms resembling hay fever during bathing in cyanobacterial blooms have been also described. Microcystis aeruginosa, Anabaena flos-aquae, Aphanizomenon flos-aquae, and Cylindrospermopsis raciborskii are the most common species found in Hungarian freshwaters. A sensitization test on albino guinea pigs, and intradermal reactivity, and ocular irritation test on albino
rabbits were carried out with freeze-dried algal suspension in physiological salt solution. The sensitivity of guinea pigs is similar to that of humans. Microcystis, Anabaena, Cylindrospermopsis, and Aphanizomenon bloom and strain samples were examined in sensitization and irritation tests and no correlation was found between the toxin content and the allergenic character. The most toxic one (Microcystis aeruginosa) was not the most allergenic sample, but the nontoxic Aphanizomenon was the most allergenic one. The axenic strains were not allergenic at all. The pure microcystin LR was only slightly allergenic even in high concentration (1.5 mg/ml). Water and lipid soluble fractions were obtained by water and chloroform extraction of lyophilized algal suspensions. The chloroform fraction was bound on C18 cartridges and eluted by methanol in nine fractions. Only one of the lipid soluble fractions was skin irritative whereas the strongest irritative effect was shown by the water soluble fraction.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11769249


Cases with multiple chemical sensitivity (MCS) frequently present mental symptoms. This study discusses the characteristics of the anxiety and depressive state of MCS by comparing patients of MCS with a gender and age-matched control group. In this investigation, MCS cases were selected among those satisfying the diagnostic criteria of Cullen after ruling out other physical diseases. Patients visiting ophthalmologists with other diseases were designated as the control. Evaluation of the anxiety and depressive state was performed in 48 cases of MCS and 48 controls using the Japanese version of the State-Trait Anxiety Inventory, the Self-rating Depression Scale (SDS), and the Hamilton Rating Scale for Depression. Significantly higher mean values of subjective anxiety and a depressive state were obtained in 18 MCS cases than in 18 controls for the follow-up patients, while no significant difference was observed between MCS and controls of 30 new patients for each group. Therefore, anxiety in MCS is characterized by the continuous high anxiety level. MCS is also characterized by a continuance of depressive state at a "neurotic level" category by SDS. The anxiety scores and depressive levels were highly correlated in MCS and controls at the first and subsequent appearances, except those in the follow-up control cases. In conclusion, both anxiety and a depressive state in MCS remained at high level until the subsequent examination, when those in controls decreased to a normal level.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11318027

---------------------------------------------------------------
(2001) *Embryo toxicity and teratogenicity of formaldehyde.*  
Thrasher, JD and Kilburn, KH Journal/Arch Environ Health. 56: 300-11.

C-14 formaldehyde crosses the placenta and enters fetal tissues. The incorporated radioactivity is higher in fetal organs (i.e., brain and liver) than in maternal tissues. The incorporation mechanism has not been studied fully, but formaldehyde enters the single-carbon cycle and is incorporated as a methyl group into nucleic acids and proteins. Also, formaldehyde reacts chemically with organic compounds (e.g., deoxyribonucleic acid, nucleosides, nucleotides, proteins, amino acids) by addition and condensation reactions, thus forming adducts and deoxyribonucleic acid-protein crosslinks. The following questions must be addressed: What adducts (e.g., N-methyl amino acids) are formed in the blood following formaldehyde inhalation? What role do N-methyl-amino adducts play in alkylation of nuclear and mitochondrial deoxyribonucleic acid, as well as mitochondrial peroxidation? The fact that the free formaldehyde pool in blood is not affected following exposure to the chemical does not mean that formaldehyde is not involved in altering cell and deoxyribonucleic acid characteristics beyond the nasal cavity. The teratogenic effect of formaldehyde in the English literature has been sought, beginning on the 6th day of pregnancy (i.e., rodents) (Saillenfait AM, et al. Food Chem Toxicol 1989, pp 545-48; Martin WJ. Reprod Toxicol 1990, pp 237-39; Ulsamer AG, et al. Hazard Assessment of Chemicals; Academic Press, 1984, pp 337-400; and U.S. Department of Health and Human Services. Toxicological Profile of Formaldehyde; ATSDR, 1999 [references 1-4, respectively, herein]). The exposure regimen is critical and may account for the differences in outcomes. Pregnant rats were exposed (a) prior to mating, (b) during mating, (c) or during the entire gestation period. These regimens (a) increased embryo mortality; (b) increased fetal anomalies (i.e., cryptochoardism and aberrant ossification centers); (c) decreased concentrations of ascorbic acid; and (d) caused abnormalities in enzymes of mitochondria, lysosomes, and the endoplasmic reticulum. The alterations in enzymatic activity persisted 4 mo following birth. In addition, formaldehyde caused metabolic acidosis, which was augmented by iron deficiency. Furthermore, newborns exposed to formaldehyde in utero had abnormal performances in open-field tests. Disparities in teratogenic effects of toxic chemicals are not unusual. For example, chlorpyrifos has not produced teratogenic effects in rats when mothers are exposed on days 6-15 (Katakura Y, et al. Br J Ind Med 1993, pp 176-82 [reference 5 herein]) of gestation (Breslin WJ, et al. Fund Appl Toxicol 1996, pp 119-30; and Hanley TR, et al. Toxicol Sci 2000, pp 100-08 [references 6 and 7, respectively, herein]). However, either changing the endpoints for measurement or exposing neonates during periods of neurogenesis (days 1-14 following birth) and during subsequent developmental periods produced adverse effects. These effects included neuroapoptosis, decreased deoxyribonucleic acid and ribonucleic acid synthesis, abnormalities in adenylyl cyclase cascade, and neurobehavioral effects (Johnson DE, et al. Brain Res Bull 1998, pp 143-47; Lassiter TL, et al. Toxicol Sci 1999, pp 92-100; Chakraborti TK, et al. Pharmacol Biochem Behav 1993, pp 219-24; Whitney KD, et al. Toxicol Appl Pharm 1995, pp 53-62; Chanda SM, et al. Pharmacol Biochem Behav 1996, pp 771-76; Dam K, et al. Devel Brain Res 1998, pp 39-45; Campbell CG, et al. Brain Res Bull 1997, pp 179-89; and Xong X, et al. Toxicol Appl Pharm 1997, pp
158-74 [references 8-15, respectively, herein]). Furthermore, the terata caused by thalidomide is a graphic human example in which the animal model and timing of exposure were key factors (Parman T, et al. Natl Med 1999, pp 582-85; and Brenner CA, et al. Mol Human Repro 1998, pp 887-92 [references 16 and 17, respectively, herein]). Thus, it appears that more sensitive endpoints (e.g., enzyme activity, generation of reactive oxygen species, timing of exposure) for the measurement of toxic effects of environmental agents on embryos, fetuses, and neonates are more coherent than are gross terata observations. The perinatal period from the end of organogenesis to the end of the neonatal period in humans approximates the 28th day of gestation to 4 wk postpartum. Therefore, researchers must investigate similar stages of development (e.g., neurogenesis occurs in the 3rd trimester in humans and neonatal days occur during days 1-14 in rats and mice, whereas guinea pigs behave more like humans). Finally, screening for teratogenic events should also include exposure of females before mating or shortly following mating. Such a regimen is fruitful inasmuch as environmental agents cause adverse effec


LEARNING OBJECTIVES: Recent public concern about the danger of environmental fungi has focused attention on one particular mold, Stachybotrys. The purpose of this review is to examine and critique the published literature on Stachybotrys for objective scientific and clinical evidence of disease caused by the presence of this fungal organism in the environment. DATA SOURCES: Data were obtained from all published research and reviews of Stachybotrys indexed in MEDLINE since 1966. STUDY SELECTION: The publications used for this review were those that contained information about human health effects of this microorganism. The critique of these publications is the author’s. RESULTS: Stachybotrys is a minor component of the indoor mycoflora, found on certain building material surfaces in water-damaged buildings, but airborne spores are present in very low concentrations. Published reports fail to establish inhalation of Stachybotrys spores as a cause of human disease even in water-damaged buildings. A possible exception may be mycotoxin-caused pulmonary hemorrhage/hemosiderosis in infants, although scientific evidence to date is suggestive but not conclusive. Based on old reports ingestion of food prepared from Stachybotrys-contaminated grains may cause a toxic gastroenteropathy. No convincing cases of human allergic disease or infection from this mold have been published. CONCLUSIONS: The current public concern for adverse health effects from inhalation of Stachybotrys spores in water-damaged buildings is not supported by published reports in the medical literature.


BACKGROUND: This article describes the results of a retrospective study of 3 classes of medical students who participated in a targeted occupational and environmental health curriculum at the University of Connecticut School of Medicine. PURPOSE: We wanted to determine if targeted focused curricular interventions which integrated occupational and environmental health principles into routine history taking would result in increased scores on the number of questions posed during the Clinical Skills Assessment Program in the 4th year. METHODS: We analyzed Clinical Skills Assessment Program questions for 3 graduating medical school classes from 1997 to 1999. RESULTS: It appears that intense, focused training may increase the occupational and environmental questions which students ask. By revisiting the components of the history during the 3rd year, the final assessment of 4th-year students substantially and significantly increased. CONCLUSIONS: Those who wish to stem the decline in history-taking skills as students enter their clinical years should consider reinforcing these skills using structured programs and practice in areas of the history that are traditionally neglected but recognized as essential in gathering comprehensive data on patients.


Numerous studies have investigated the health problems reported by veterans of the Persian Gulf War, but important questions remain. Epidemiologic studies have consistently indicated that Gulf War veterans report unexplained symptoms at
significantly higher rates than veteran comparison groups but that they have not experienced excess rates of disease-related mortality. Addressing unanswered questions surrounding post-Gulf-War health problems presents a complex challenge for researchers, but not an insurmountable one. Progress in understanding the role of potential etiologic factors can be made using epidemiologic approaches traditionally applied in the absence of individual exposure data, such as comparisons between veteran subgroups with differing illness profiles and deployment histories.

Staudenmayer, H Journal/Toxicol Lett. 120: 333-42.

The psychogenic theory presupposes that idiopathic environmental intolerance (IEI) is an overvalued idea explained by psychological and psychosocial processes. The polysomatic symptoms are amplifications of complaints common to the general population, psychophysiological manifestations of stress and the stress-response, or symptoms of psychiatric clinical syndromes. The psychogenic theory is supported by provocation challenge studies which demonstrate that appraisals of 'reactions' are unreliable and cognitively mediated. Clinical studies of IEI cases consistently identify greater incidence of current and premorbid lifetime psychiatric disorders and co-morbidity with functional somatic syndromes that are fashionable 'diagnoses'. The toxicogenic theory presupposes low-level chemical sensitivity or intolerance without objective signs to a plethora of diverse chemical agents. Symptoms are synonymous with disease and attributions are synonymous with cause. Hypotheses about physiological processes and mechanisms are implausible and unsupported by evidence. Advocates claim this phenomenon is so ephemeral that the principles and methods of toxicology do not apply and that a scientific paradigm shift is in order.

(2001) Time-dependent changes in orally exhaled nitric oxide and pulmonary functions induced by inhaled corticosteroids in childhood asthma.

Exhaled nitric oxide levels are elevated in asthmatic children and decrease after inhaled steroid treatment. We evaluated the time-dependent changes in fractional exhaled nitric oxide concentration (FENO) and pulmonary function parameters following inhaled steroid therapy. Thirty-nine steroid-naive atopic patients (age 11.92 +0.48 years) with mild intermittent asthma and 22 age-matched healthy controls were enrolled in the study; pulmonary functions and FE(NO) levels were measured. Low doses of inhaled steroids were prescribed to all asthmatic patients who were reevaluated in a second visit (between 10 and 40 days after the beginning of the
At the enrolment, asthmatic patients had similar forced expiratory volume in 1 sec (FEV1) and forced vital capacity (FVC) values (p > 0.05) but reduced forced expiratory flows at 25-75% of the vital capacity (FEF(25-75%)) values, as compared to controls (p < 0.05). In addition, FE(NO) levels were significantly higher in asthmatics with respect to control subjects (30.8+/−3.0 and 4.0+/−0.5 ppb, respectively; p < 0.01). All asthmatics had FE(NO) levels higher than 8.8 ppb (i.e., > 2 standard deviations of the mean in controls). After steroid treatment, patients showed significant improvement of FEV1, FVC, and FEF(25-75%) (p = 0.0001; each comparison) and a reduction of FE(NO) levels (p = 0.0001). A weak significant correlation was found between percent decrease in FE(NO) levels and percent increase in FEV1 (r = 0.33, p = 0.04) or in FEF(25-75%) (r = 0.4, p = 0.01) after treatment. When changes in FE(NO) levels and in pulmonary function parameters were corrected for days of treatment, significant correlations were still present between percent decrease in FE(NO) levels and percent increase in FEV1 (r = 0.57, p = 0.0004) or percent increase in FEF(25-75%) (r = 0.45, p = 0.006). Sixteen of the 39 asthmatic patients were evaluated on two occasions after the beginning of treatment, at days 10 and 40. The significant reduction in FE(NO) levels (p < 0.01) and the significant increase in FEV1 and FEF(25-75%) values observed (p < 0.05) after 10 days did not further improve at day 40. These data show that it is possible to demonstrate early effects of low-dose inhaled steroids in asthmatic children using objective measurements of airway caliber and inflammation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11714077


Chemical intolerance is a phenomenon observed in multiple chemical sensitivity (MCS) syndrome, an ill-defined disorder in humans attributed to exposure to volatile organic compounds. Amplification of symptoms in individuals with MCS resembles the phenomenon of psychostimulant- and stress-induced sensitization in rodents. We have recently tested in rats the hypothesis that repeated chemical exposure produces sensitization of central nervous system (CNS) circuitry. A rat model of MCS in our laboratory has employed several endpoints of CNS function after repeated formaldehyde (Form) exposure (1 h/day x 5 days/week x 4 weeks). Repeated Form exposure produced behavioral sensitization to later cocaine injection, suggesting altered dopaminergic sensitivity in mesolimbic pathways. Rats given repeated Form also demonstrated increased fear conditioning to odor paired with footshock, implicating amplification of neural circuitry guiding fear responding to a conditioned odor cue. Recent studies examining the effects of repeated Form on locomotor activity during each daily exposure showed a decrease in rearing activity after 12-15 days of Form exposure compared to air-exposed controls. EEG recordings taken 1 week after
withdrawal from daily Form revealed altered sleep architecture. Some of the differences in sleep disappeared after subsequent brief (15 min) challenge with Form the next day. Overall, the findings indicate that repeated low-level chemical exposure produces behavioral changes that may be akin to those observed in individuals with MCS, such as greater sensitivity to chemicals manifest as increased anxiety upon chemical exposure and altered sleep and/or fatigue. Study of the underlying CNS changes will provide a basis for mechanistically based animal models for MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000036

Sorg, BA and Bell, I  New York Academy of Sciences. 933:
Low-level exposure to volatile organic compounds may produce symptoms in humans reporting multiple chemical sensitivity (MCS) through altered hypothalamic-pituitary-adrenal (HPA) axis functioning. We determined whether repeated formaldehyde (Form) exposure would alter corticosterone (CORT) levels in a rat model of MCS. Male Sprague-Dawley rats were given acute chamber exposures to Air or Form (0.7 or 2.4 ppm), and trunk blood was collected 20 or 60 min later. All groups showed increased CORT levels above naive basal levels at 20 min and a return to baseline by 60 min, with no differences between treatment groups. The second experiment examined the effect of repeated Form exposure (1 h/day x 5 days/week x 2 or 4 weeks) on basal CORT levels and after a final challenge. Basal CORT was increased above naive values after 2 week exposure to Air or 0.7 ppm Form. By 4 week, CORT levels in the Air group returned to naive values, but remained elevated in the 0.7 ppm Form group. There were no differences in basal CORT levels among either 2.4 ppm exposed groups. After a final Air or Form challenge, the 2 and 4 week Air and 0.7 ppm Form groups had elevated CORT levels similar to their acute response, while the 2 and 4 week 2.4 ppm Form groups had elevated CORT levels compared to their acute response, indicating enhanced reactivity of the HPA axis to subsequent Form. These findings suggest that altered HPA axis functioning occurs after repeated low-level Form exposure, and may have implications for mechanisms mediating MCS in humans.

(2001) Exposure to repeated low-level formaldehyde in rats increases basal corticosterone levels and enhances the corticosterone response to subsequent formaldehyde.
Low-level exposure to volatile organic compounds may produce symptoms in humans reporting multiple chemical sensitivity (MCS) through altered hypothalamic-pituitary-adrenal (HPA) axis functioning. We determined whether repeated formaldehyde (Form) exposure would alter corticosterone (CORT) levels in a rat model of MCS. Male Sprague-Dawley rats were given acute chamber exposures to Air or Form (0.7 or 2.4 ppm), and trunk blood was collected 20 or 60 min later. All groups showed increased CORT levels above naive basal levels at 20 min and a return to baseline by 60 min, with no differences between treatment groups. The second experiment examined the effect of repeated Form exposure (1 h/day x 5 days/week x 2 or 4 weeks) on basal CORT levels and after a final challenge. Basal CORT was increased above naive values after 2 week exposure to Air or 0.7 ppm Form. By 4 week, CORT levels in the Air group returned to naive values, but remained elevated in the 0.7 ppm Form group. There were no differences in basal CORT levels among either 2.4 ppm exposed groups. After a final Air or Form challenge, the 2 and 4 week Air and 0.7 ppm Form groups had elevated CORT levels similar to their acute response, while the 2 and 4 week 2.4 ppm Form groups had elevated CORT levels compared to their acute response, indicating enhanced reactivity of the HPA axis to subsequent Form. These findings suggest that altered HPA axis functioning occurs after repeated low-level Form exposure, and may have implications for mechanisms mediating MCS in humans.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11306018

(2001) [Methodical aspects of assessing risk from atmospheric pollutants on health of residents in Belarus].
Sokolov, SM, Filonov, VP, Naumenko, TE and Chebotarev, PA Journal/Gig Sanit. 90-3.

(2001) Neurological and neurophysiological examinations of workers occupationally exposed to manganese.

The nervous system is the major target of the toxic effect of manganese (Mn) and its compounds. Nowadays, neurological diagnostics is directed towards early detection of symptoms and abortive forms, and the cases of serious damage of the nervous system are no longer reported. The aim of the present study was to assess the effects of manganese on the functions of the nervous system in workers exposed to this metal in the ship and electrical industries. The study covered a selected group of 75 male
workers (mean age 39.17 yr +/- 9.79; range 20-56 yr), including 62 welders and fitters, as well as 13 workers involved in the battery production. Their employment duration ranged between 1 and 41 yr (mean 17.5 yr +/- 10.81). During the welding process the air Mn concentrations varied from 0.004 to 2.67 mg/m³ (arithmetic mean, 0.399 mg m³; geometric mean, 0.154 mg/m³; standard deviation, 0.586). Of the 62 workers, 30 worked in the area with exceeding MAC value of 0.3 mg/m³. At the battery production workposts, Mn concentrations fell within 0.086-1.164 mg/m³ (arithmetic mean, 0.338 mg/m³, geometric mean, 0.261 mg/m³; standard deviation, 0.292). The values of current Mn exposure in the study group fell within the range below 0.01 and 2.67 mg m³ (arithmetic mean, 0.4 mg/m; geometric mean, 0.15 mg/m³). Of the 13 subjects, 6 worked at the Mn air concentration exceeding MAC values. In the exposed group, the values of cumulated exposure index ranged from 0.008 to 35.52 (arithmetic mean, 8.045; geometric mean, 4.615; standard deviation, 6.562). The control group consisted of 62 men non-occupationally exposed to Mn, matched by sex, age and work shift distribution. Clinically, the increased emotional irritability, dysmnesia, concentration difficulties, sleepiness and limb paresthesia predominated among the disorders of the nervous system functions in workers chronically exposed to manganese. Neither in the central nor in the peripheral nervous system, the objective examinations revealed organic lesions that could provide grounds for diagnosing toxic encephalopathy or polyneuropathy. Generalized and paroxysmal changes were the most common recordings in the abnormal electroencephalography. Visual evoked potentials examinations showed abnormalities in the response evoked, which could be a signal of the optic neuron disorders and their significant relationship with cumulated exposure. The results of the study demonstrate that Mn exposure within the range of <0.01-2.67 mg/m³ (arithmetic mean, 0.4 mg/m³; geometric mean, 0.15 mg/m³) induces subclinical effects on the nervous system.

(2001) Exhaled nitric oxide levels in non-allergic and allergic mono- or polysensitised children with asthma.

BACKGROUND: Increased fractional exhaled NO concentrations (FENO) and blood tissue eosinophilia are frequently reported in allergic children with mild asthma and are thought to reflect the intensity of the inflammation characterising the disease. The aim of this study was to investigate possible differences in FENO levels or in the intensity of the blood eosinophilia in allergic and non-allergic asthmatic children. METHODS: 112 children with stable, mild, intermittent asthma with a positive bronchial challenge to methacholine were consecutively enrolled in the study; 56 were skin prick test and RAST negative (non-sensitised) while 56 were sensitised to house dust mites (23 only to house dust mites (monosensitised) and 33 were sensitised to mites and at least another class of allergens (pollens, pet danders, or moulds)). Nineteen sex and age matched healthy children formed a control group. RESULTS: Compared with
non-allergic patients, allergic children had a significantly higher rate of blood eosinophilia (p=0.0001) with no differences between mono- and polysensitised individuals. Forced expiratory volume in 1 second (FEV(1)), forced vital capacity (FVC), forced expiratory flow at 25-75% of vital capacity (FEF(25-75%)), and the degree of bronchial reactivity to methacholine were similar in non-atopic and atopic children, with no differences between mono- and polysensitised individuals. FENO levels measured by chemiluminescence analyser were higher in asthmatic children (15.9 (14.3) ppb) than in the control group (7.6 (1.6) ppb, p=0.04) and higher in allergic patients (23.9 (2.1) ppb) than in non-allergic patients (7.9 (0.8) ppb, p=0.0001), but there were no differences between mono- and polysensitised individuals (p>0.1). Significant correlations between blood eosinophilia and FENO levels were seen only in allergic (r=0.35, p<0.01) and in polysensitised individuals (r=0.45, p<0.05). CONCLUSIONS: In children with mild asthma, a similar degree of functional disease severity may be associated with a higher inflammatory component in allergic than in non-allergic subjects.


(2001) [Rationale for a complex of correcting preclinical forms of ecologically-caused states].
Shcherbinina, NV Journal/Gig Sanit. 46-9.

(2001) [Endoecological status as the criteria for ecologically-caused illness].
Setko, NP and Abaillova, NN Journal/Gig Sanit. 93-4.

(2001) [Features of ecologo-epidemiologic study of specific ecologically-caused changes on human health status].
Revich, BA Journal/Gig Sanit. 49-53.

(2001) Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy.
BACKGROUND: Influence of household pets in the development of childhood asthma or atopy has been controversial. OBJECTIVE: The purpose of this study was to investigate whether pet exposure in early life decreases the subsequent risk of frequent wheezing and/or allergic sensitization. METHODS: This was a prospective observational birth cohort study. The setting was a large health maintenance organization in Tucson, Ariz; the subjects were a population sample of 1246 newborns enrolled at birth and followed prospectively to age 13 years. The main outcome measures were as follows: time to first report of frequent wheezing (>3 episodes in the past year), skin prick test reactivity at 6 years and 11 years of age, and total serum IgE at 9 months, 6 years, and 11 years of age. RESULTS: Children living in households with > or =1 indoor dogs at birth were less likely to develop frequent wheeze than those not having indoor dogs (P =.004). This inverse association was confined to children without parental asthma (hazard ratio = 0.47; P <.001 [Cox regression]) and was not evident for children with parental asthma (hazard ratio = 0.96; P =.87). Adjustment by potential confounders did not change the results. Indoor cat exposure was not significantly associated with the risk of frequent wheezing. Neither cat exposure in early life nor dog exposure in early life was associated with skin prick test reactivity or total serum IgE at any age. CONCLUSION: Dog exposure in early life might prevent the development of asthma-like symptoms, at least in low-risk children with no family history of asthma. Nevertheless, early pet exposure does not seem to significantly influence the development of allergic sensitization.


The objective of this study was to measure the prevalence of multiple chemical sensitivity (MCS) and chronic fatigue syndrome (CFS) in British Gulf War veterans and to investigate their association with reported exposures and psychologic morbidity. In 1997--1998, the authors undertook a cross-sectional survey of three cohorts of British military personnel comprising Gulf veterans (n = 3,531), those who had served in Bosnia (n = 2,050), and those serving during the Gulf War but not deployed there (Era cohort, n = 2,614). MCS and CFS were defined according to operational criteria. The prevalence of MCS in the Gulf, Bosnia, and Era cohorts was 1.3%, 0.3%, and 0.2%, respectively. For CFS, the prevalence was 2.1% (Gulf cohort), 0.7% (Bosnia cohort), and 1.8% (Era cohort). In Gulf veterans, MCS was strongly associated with exposure to pesticides (adjusted odds ratio = 12.3, 95% confidence interval: 5.1, 30.0). Both syndromes were associated with high levels of psychologic morbidity. These findings suggest that CFS and MCS account for some of the medically unexplained illnesses.
reported by veterans after deployment to the Gulf. MCS was particularly associated with Gulf deployment and self-reported exposure to pesticides, findings that merit further exploration given the controversial status of this diagnosis and the potential for recall bias in a questionnaire survey.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11257069


The blood levels of organochlorine pesticides and chlorinated hydrocarbon solvents were measured in 200 and 114 chemically sensitive patients respectively, and compared with blood concentrations of standard medication (non-chlorinated substances. Clonidine, Haloperidol) of comparable toxicity after therapeutically effective dosage, and with reference levels of highly potent chemicals in the blood such as hormones. It was shown that the average blood levels of the most toxic environmental pollutants are comparable with the therapeutic steady state average blood levels of medications which have similar toxicities in the animal model. In addition the toxicity levels of xenoestrogens are at least an order of magnitude higher than normal plasma estrogen or progesterone levels. These findings suggest the possibility of additive or synergistic effects of these chlorinated compounds and the aforementioned medications. Also, these findings suggest the possibility of hormone deregulation from exposure to the aforementioned toxic chlorinated compounds.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12017255

(2001) [Methodological problems of diagnosing and preventing diseases connected with the influence of environmental factors].
Rakhmanin Iu, A, Rumiantsev, GI and Novikov, SM Journal/Gig Sanit. 3-7.

The study of pain may be relevant to the study of chemical intolerance (CI) in many ways. Pain is often reported as a symptom of CI and it is defined as a subjective experience similar to many other symptoms of CI, making its objectification difficult. Furthermore, the CNS plastic changes that underlie the development of persistent pain states and abnormal pain responses may share some similarities with those involved in the sensitization to environmental chemicals. Functional brain imaging studies in humans demonstrate that acute pain evoked by nociceptive stimulation is accompanied by the activation of a widely distributed network of cerebral structures, including the thalamus and the somatosensory, insular, and anterior cingulate cortices. Abnormal activity within these regions has been associated with the experience of pain following damage to the peripheral or central nervous system (neuropathic pain) in a number of clinical populations. In normal individuals, activity within this network is correlated with subjective pain perception, is highly modifiable by cognitive interventions such as hypnosis and attention, and has been associated with emotions. Other cognitive mediators such as expectations can also produce robust changes in pain perception (e.g., in placebo analgesia). These effects likely depend on both higher-order cerebral structures and descending mechanisms modulating spinal nociceptive activity. These psychological processes can be solicited to reduce clinical pain and we speculate that they may further attenuate or promote central mechanisms involved in the transition from acute to persistent pain states. The investigation of central determinants of subjective experience is essential to assess the possibility that higher-order brain/psychological processes modulate and/or mediate the development of persistent pain states. These factors may contribute to the development of symptoms in CI.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000016

(2001) Methodologic considerations in estimating burden of disease from environmental risk factors at national and global levels.

Evidence from environmental burden-of-disease studies can provide valuable input in the decision-making process in environmental health, facilitating priority setting and cost effectiveness evaluation. This paper discusses important aspects of environmental burden-of-disease estimates in the light of published examples. To produce reliable and comparable burden-of-disease estimates for environmental and occupational risk factors, harmonized methods are needed. Such methods should address the feasibility of data collection at national, regional, and global levels, the reliability of estimates, the uncertainty around estimates, and scenario tools to investigate the health gains of options for preventive action in different domains of policy. Any such method will require a framework (i.e., causal inference model) able to
take into account the contributions of distal and proximal causes, and the possible interactions between risk factors.


We recently introduced a generic single nucleotide polymorphism (SNP) genotyping method, termed DASH (dynamic allele-specific hybridization), which entails dynamic tracking of probe (oligonucleotide) to target (PCR product) hybridization as reaction temperature is steadily increased. The reliability of DASH and optimal design rules have not been previously reported. We have now evaluated crudely designed DASH assays (sequences unmodified from genomic DNA) for 89 randomly selected and confirmed SNPs. Accurate genotype assignment was achieved for 89% of these worst-case-scenario assays. Failures were determined to be caused by secondary structures in the target molecule, which could be reliably predicted from thermodynamic theory. Improved design rules were thereby established, and these were tested by redesigning six of the failed DASH assays. This involved reengineering PCR primers to eliminate amplified target sequence secondary structures. This sophisticated design strategy led to complete functional recovery of all six assays, implying that SNPs in most if not all sequence contexts can be effectively scored by DASH. Subsequent empirical support for this inference has been evidenced by approximately 30 failure-free DASH assay designs implemented across a range of ongoing genotyping programs. Structured follow-on studies employed standardized assay conditions, and revealed that assay reproducibility (733 duplicated genotypes, six different assays) was as high as 100%, with an assay accuracy (1200 genotypes, three different assays) that exceeded 99.9%. No post-PCR assay failures were encountered. These findings, along with intrinsic low cost and high flexibility, validate DASH as an effective procedure for SNP genotyping.


OBJECTIVE: To determine whether there are specific cytochrome P450 (CYP2) alleles that increase susceptibility to scleroderma in individuals who have been exposed to organic solvents. METHODS: CYP alleles at 2 loci, 2E1 and 2C19, were compared in 7 patients who had developed scleroderma after exposure to solvents versus 71 patients
with scleroderma without solvent exposure ("sporadic" disease) and 106 population controls. RESULTS: The 2E1*3 allele was found in 2 of the 7 patients who had been exposed to organic solvents, with a greater frequency than occurred in either the disease controls or the population controls (odds ratio [95% confidence interval] 9.1 [1.5-59.1] and 10.2 [1.8-62.2], respectively). All 7 patients with solvent exposure carried the 2C19EM genotype, compared with 89% of patients with sporadic scleroderma.

CONCLUSION: Our results suggest that alleles at CYP loci may be involved in increasing susceptibility to scleroderma among subjects who have been exposed to organic solvents.


OBJECTIVES: Idiopathic environmental intolerance (IEI) is associated with unexplained symptoms attributed to non-noxious levels of environmental substances. Clinically, some of the symptoms of IEI overlap with those of panic disorder (PD). We have recently reported a link between IEI and panic responses to a single inhalation of 35% carbon dioxide (CO(2)), a reliable panic induction challenge. This study assessed depression, stress, anxiety, and agoraphobic symptoms among IEI subjects from our previous study versus healthy controls. METHODS: Thirty-six IEI and 37 control subjects with no preexisting psychiatric history were compared on self-report psychological questionnaires. RESULTS: IEI subjects scored significantly higher than controls on the Agoraphobic Cognitions Questionnaire (ACQ), Depression Anxiety Stress Scales (DASS), and Mobility Inventory for Agoraphobia (MI) (Student's t, P<.05). CONCLUSIONS: IEI subjects represent a group with morbidity significantly higher than a control population but less than what would be expected for a clinical psychiatric population.

(2001) [Status and perspectives of qualitative evaluation of the effect of atmospheric pollution on population health].
Pinigin, MA Journal/Gig Sanit. 53-8.

Animal allergens play a significant role in the pathogenesis of asthma and allergic rhinitis, and are potent causes of acute and chronic symptoms. Although cat and dog allergens are the most important, exposure to a wide variety of other furred animals is not uncommon. Recent reports state that 60% to 70% of households in the western world have at least one pet. Because of this significant exposure, hypersensitivity to animals has become increasingly important. This review focuses on the importance of animal allergens, concentrating on cat and dog allergens, but including others as well. It also discusses the pathogenesis, diagnosis, prevention, and management of animal allergy.


Chronic fatigue syndrome (CFS) patients show evidence of immune activation, as demonstrated by increased numbers of activated T lymphocytes, including cytotoxic T cells, as well as elevated levels of circulating cytokines. Nevertheless, immune cell function of CFS patients is poor, with low natural killer cell cytotoxicity (NKCC), poor lymphocyte response to mitogens in culture, and frequent immunoglobulin deficiencies, most often IgG1 and IgG3. Immune dysfunction in CFS, with predominance of so-called T-helper type 2 and proinflammatory cytokines, can be episodic and associated with either cause or effect of the physiological and psychological function derangement and/or activation of latent viruses or other pathogens. The interplay of these factors can account for the perpetuation of disease with remission/exacerbation cycles. A T-helper type 2 predominance has been seen among Gulf War syndrome patients and this feature may also be present in other related disorders, such as multiple chemical sensitivity. Therapeutic intervention aimed at induction of a more favorable cytokine expression pattern and immune status appears promising.


Various types of evidence implicate nitric oxide and an oxidant, possibly peroxynitrite, in MCS and chemical intolerance (CI). The positive feedback loops proposed earlier for CFS may explain the chronic nature of MCS (CI) as well as several of its other reported properties. These observations raise the possibility that this proposed elevated nitric oxide/peroxynitrite mechanism may be the mechanism of a new disease paradigm,
answering the question raised by Miller earlier: "Are we on the threshold of a new theory of disease?"

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000033


Various types of evidence implicate nitric oxide and an oxidant, possibly peroxynitrite, in MCS and chemical intolerance (CI). The positive feedback loops proposed earlier for CFS may explain the chronic nature of MCS (CI) as well as several of its other reported properties. These observations raise the possibility that this proposed elevated nitric oxide/peroxynitrite mechanism may be the mechanism of a new disease paradigm, answering the question raised by Miller earlier: "Are we on the threshold of a new theory of disease?"

Pall, ML Journal/Med Hypotheses. 57: 139-45.

Three types of overlap occur among the disease states chronic fatigue syndrome (CFS), fibromyalgia (FM), multiple chemical sensitivity (MCS) and posttraumatic stress disorder (PTSD). They share common symptoms. Many patients meet the criteria for diagnosis for two or more of these disorders and each disorder appears to be often induced by a relatively short-term stress which is followed by a chronic pathology, suggesting that the stress may act by inducing a self-perpetuating vicious cycle. Such a vicious cycle mechanism has been proposed to explain the etiology of CFS and MCS, based on elevated levels of nitric oxide and its potent oxidant product, peroxynitrite. Six positive feedback loops were proposed to act such that when peroxynitrite levels are elevated, they may remain elevated. The biochemistry involved is not highly tissue-specific, so that variation in symptoms may be explained by a variation in nitric oxide/peroxynitrite tissue distribution. The evidence for the same biochemical mechanism in the etiology of PTSD and FM is discussed here, and while less extensive than in the case of CFS and MCS, it is nevertheless suggestive. Evidence supporting the role of elevated nitric oxide/peroxynitrite in these four disease states is summarized, including induction of nitric oxide by common apparent inducers of these disease states, markers of elevated nitric oxide/peroxynitrite in patients and evidence
for an inductive role of elevated nitric oxide in animal models. This theory appears to be the first to provide a mechanistic explanation for the multiple overlaps of these disease states and it also explains the origin of many of their common symptoms and similarity to both Gulf War syndrome and chronic sequelae of carbon monoxide toxicity. This theory suggests multiple studies that should be performed to further test this proposed mechanism. If this mechanism proves central to the etiology of these four conditions, it may also be involved in other conditions of currently obscure etiology and criteria are suggested for identifying such conditions.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11461161


Based on their studies, the authors have proposed simple and easy-to-use methods for preclinical diagnosis of environment-related diseases.


Recently there has been increased attention among both the public and health professionals regarding the potential role of mycotoxins, primarily from fungi of the genus Stachybotrys, as etiologic agents related to illness among persons exposed in the indoor (nonindustrial) environment. Recommendations for the remediation of buildings are being made based in part on reported health effects believed to be due to mycotoxins. A search of NIOSHTIC (a literature database maintained by the National Institute for Occupational Safety and Health) and MEDLINE (from 1965 to present) for literature related to fungi, mycotoxins, and the indoor environment was conducted. References from relevant articles also were reviewed. This strategy yielded a total of 13 articles. Important issues concerning exposure assessment and case definitions are inadequately addressed in the literature reviewed, making it difficult to implicate mycotoxins as a cause of building-related illness. The literature review indicates that currently there is inadequate evidence supporting a causal relationship between symptoms or illness among building occupants and exposure to mycotoxins. Research involving the identification and isolation of specific fungal toxins in the environment and in humans is needed before a more definitive link between health outcomes and mycotoxins can be made.

The fact that only some individuals exposed to environmental chemicals develop chemical intolerance raises the possibility that genetic factors could be contributing factors. The present communication summarizes evidence from a genetic animal model of cholinergic supersensitivity that suggests that an abnormal cholinergic system could be one predisposing genetic factor. The Flinders Sensitive Line (FSL) rats were established by selective breeding for increased responses to an organophosphate. It was subsequently found that these FSL rats were also more sensitive to direct-acting muscarinic agonists and had elevated muscarinic receptors compared to the selectively bred parallel group, the Flinders Resistant Line (FRL) rats, or randomly bred control rats. Increased sensitivity to cholinergic agents has also been observed in several human populations, including individuals suffering from chemical intolerance. Indeed, the FSL rats exhibit certain behavioral characteristics such as abnormal sleep, activity, and appetite that are similar to those reported in these human populations. In addition, the FSL rats have been reported to exhibit increased sensitivity to a variety of other chemical agents. Peripheral tissues, such as intestinal and airway smooth muscle, appear to be more sensitive to both cholinergic agonists and an antigen, ovalbumin. Hypothermia, a centrally mediated response, is more pronounced in the FSL rats after nicotine and alcohol, as well as agents that are selective for the dopaminergic and serotonergic systems. In some cases, the increased sensitivity has been detected in the absence of any changes in the receptors with which the drugs interact (dopamine receptors), while receptor changes have been seen in other cases (nicotine receptors). Therefore, there may be multiple mechanisms underlying the multiple chemical sensitivity-chemical intolerance of the FSL rats. An elucidation of these mechanisms may provide useful clues to those involved in chemical intolerance in humans.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000038


Chemical intolerance (CI) in humans is a poorly understood phenomenon of uncertain etiology, seemingly influenced by multiple factors both within and between affected individuals. Several authors have suggested that the development of CI in some individuals may be due, at least in part, to Pavlovian conditioning processes in which
the expression of overt symptoms to certain substances reflects classically conditioned responses to previously neutral olfactory and contextual stimuli. In this paper, we describe the potential relationship between olfactory and contextual conditioning in experimental animals and the development and expression of CI in humans. Furthermore, as significant advances have been made in delineating the brain areas that underlie these learned responses, we also review recent research on the contributions of the amygdala and perirhinal cortical region to olfactory and contextual fear conditioning.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000029


Maternal sound stress (800 Hz; 77 dB, every other minute for 15 min/day, from day 10 to 18 of gestation), combined with forced swimming stress (15 min/day), was found to cause potentiation of sound-induced loss of locomotor activity, referred to as emotional behavior, of male offspring, but not that of female offspring, at 4 weeks of age. Maternal stress also caused an increase in the total number of errors by male, but not female offspring in the water-maze test at 6 weeks of age. These effects of stress on emotional behavior and learning behavior were abolished when dams were pretreated with buspirone (30 min before the stress, from day 8 to 18 of gestation). Thus, prenatal stress might have sex-dependent effects on emotional behavior and learning ability of neonatal rats.

Multiple Drug Allergy Syndrome (MDAS) is a frequent clinical condition characterized by reactions to more than one different class of antibiotics. Even if some studies have previously reported an increased rate of allergic reactions to drugs in patients with a history of antimicrobials and NSAIDs allergy, risk factors and pathogenesis of MDAS are still object of investigation. Moreover, in these subjects it is often difficult to prescribe a safe alternative antibiotic without a tolerance test. In this study we carried out 504 tests in 460 patients with a history of immediate adverse reactions to antibiotics. From the analysis of our results it emerges that risk factors for MDAS are female sex and intolerance to NSAIDs. Risk factors for positive tolerance test are male sex, intolerance to NSAIDs and a history of MDAS, respectively. In conclusion, it seems that tolerance test may represent a valid approach to detect a safe antibiotic in these patients.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11792020

(2001) Update on sensitivity to nonsteroidal antiinflammatory drugs.

Non steroidal antiinflammatory drugs (NSAIDs) are among the most frequently prescribed medications worldwide. These drugs are effective for the treatment of a wide spectrum of diseases: musculoskeletal disorders, headache, fever, pain, and others. Their widespread use explains the very high incidence of intolerance; reactions range from asthma, rhinitis, to urticaria/angioedema, various skin eruptions and anaphylactic shock. The pathogenesis of intolerance is still unclear: immune-mediated reactions have been reported following the use of pyrazolone derivatives and, less commonly aspirin, anthranilic-acid derivatives and diclofenac. It has been suggested that NSAIDs may induce pseudoallergic reactions, while in case of bronchial asthma the inhibition of cyclooxigenase by NSAIDs has been proposed as a pathogenetic mechanism. The diagnosis of NSAIDs sensitivity can usually be established by history; in fact skin prick tests with NSAIDs have not been successful and no reliable in vitro tests are available. The only definitive diagnostic test is oral test dosing. To identify an alternative NSAIDs in a sensitive patient a tolerance test is performed. Here we review the current state of knowledge concerning NSAIDs sensitivity, including personal data to increase awareness on this issue.

(2001) High-throughput SNP genotyping by allele-specific PCR with universal energy-transfer-labeled primers.
We have developed a new method for high-throughput genotyping of single nucleotide polymorphisms (SNPs). The technique involves PCR amplification of genomic DNA with two tailed allele-specific primers that introduce priming sites for universal energy-transfer-labeled primers. The output of red and green light is conveniently scored using a fluorescence plate reader. The new method, which was validated on nine model SNPs, is well suited for high-throughput, automated genotyping because it requires only one reaction per SNP, it is performed in a single tube with no post-PCR handling, the same energy-transfer-labeled primers are used for all analyses, and the instrumentation is inexpensive. Possible applications include multiple-candidate gene analysis, genomewide scans, and medical diagnostics.

(2001) Allergy to yucca.


In humans, activation of the primary host defense system leads to increased or decreased NREM sleep quality, depending on the degree of early immune activation. Modest elevations of certain inflammatory cytokines are found during experimental sleep loss in humans and, in addition, relatively small elevations of cytokines are seen following commencement of pharmacological treatments with clozapine, a CNS active antipsychotic agent, known to have immunomodulatory properties. Cytokines such as TNF-alpha, its soluble receptors, and IL-6, present in the periphery and the CNS, comprise a link between peripheral immune stimulation and CNS-mediated behaviors and experiences such as sleep, sleepiness, and fatigue. The debilitating fatigue experienced in chronic fatigue syndrome and related diseases may also be related to altered cytokine profiles.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000021

(2001) [Relationship between atopic factors and physical symptoms induced by gaseous formaldehyde exposure during an anatomy dissection course].
Formaldehyde (FA) is an occupational and general indoor hazard often affecting the respiratory airways. One of the main causes of multiple chemical sensitivity is gaseous FA, and it has become an important social problem in developed countries. FA concentrations in anatomy dissection classrooms are thought to be higher than under usual circumstances. The number of students developing physical symptoms during the anatomy dissection course in our university has been increasing over recent years. We planned to clarify the causes of such symptoms. Ninety-five medical students were interviewed using a questionnaire about allergic histories, physical symptoms developed during the anatomy dissection course, and symptoms related to chemical sensitivity up to three months after the course had finished. We measured total IgE, specific IgE to FA and specific IgE to house dust mites. Eighty-three percent of students had experienced symptoms, such as burning eyes, nasal discharge, sore throat, general fatigue or skin irritation during the course. Fifty percent of students had a past history of atopic disease. Fifty-eight percent of students tested positive to specific IgE to house dust mites; however, only one student, who did not complain of any symptoms during the course, tested positive to FA-IgE. Students with atopic factors (present histories of atopic diseases and higher total IgE) and/or chemical sensitivity demonstrated worse physical symptoms during the anatomy dissection course than students without such histories. In conclusion, it is suggested that gaseous FA exposure may exacerbate basic allergic symptoms, and moreover that people with chemical sensitivity demonstrated worse symptoms following gaseous FA exposure. Nevertheless, in our study we find no relationship between FA-IgE and the physical symptoms of gaseous FA exposure during or following an anatomy dissection course.

---


In science, anomalies expose the limitations of existing paradigms and drive the search for new ones. In the late 1800s, physicians observed that certain illnesses spread from sick, feverish individuals to those contacting them, paving the way for the germ theory of disease. The germ theory served as a crude, but elegant formulation that explained dozens of seemingly unrelated illnesses affecting literally every organ system. Today, we are witnessing another medical anomaly—a unique pattern of illness involving chemically exposed groups in more than a dozen countries, who subsequently report multisystem symptoms and new-onset chemical, food, and drug intolerances. These intolerances may be the hallmark for a new disease process or paradigm, just as fever is a hallmark for infection. The fact that diverse demographic groups, sharing little in common except some initial chemical exposure event, develop these intolerances is a compelling anomaly pointing to a possible new theory of disease, one that has been referred to as "Toxicant-Induced Loss of Tolerance" ("TILT"). TILT has the potential to explain certain cases of asthma, migraine headaches, and depression, as well as chronic fatigue, fibromyalgia, and "Gulf War syndrome". It appears to evolve in two
stages: (1) initiation, characterized by a profound breakdown in prior, natural tolerance resulting from either acute or chronic exposure to chemicals (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms by small quantities of previously tolerated chemicals (traffic exhaust, fragrances, gasoline), foods, drugs, and food/drug combinations (alcohol, caffeine). While the underlying dynamic remains an enigma, observations indicating that affected individuals respond to structurally unrelated drugs and experience cravings and withdrawal-like symptoms, paralleling drug addiction, suggest that multiple neurotransmitter pathways may be involved.


Miller, CS Journal/Addiction. 96: 115-37.

Drug addiction and multiple chemical intolerance (abduction) appear to be polar opposites—the former characterized by craving and dependency, the latter by aversion. However, when the two are viewed in juxtaposition similarities emerge, revealing a common underlying dynamic, one which appears to be a new paradigm of disease. TILT, or toxicant-induced loss of tolerance, bridges the gap between addiction and abduction and has the potential to explain a variety of illnesses, including certain cases of asthma, migraine headaches and depression, as well as chronic fatigue syndrome, fibromyalgia and "Gulf War syndrome". This paper argues that both addiction and chemical intolerance involve a fundamental breakdown in innate tolerance, resulting in an amplification of various biological effects, particularly withdrawal symptoms. While addicts seek further exposures so as to avoid unpleasant withdrawal symptoms, chemically intolerant individuals shun their problem exposures, but for the same reason—to avoid unpleasant withdrawal symptoms. These observations raise critical questions: do addictive drugs and environmental pollutants initiate an identical disease process? Once this process begins, can both addictants and pollutants trigger symptoms and cravings? TILT opens a new window between the fields of addiction and environmental medicine, one that has the potential to transform neighboring realms of medicine, psychology, psychiatry and toxicology.


In this study, the authors used the University of Toronto’s Health Survey self-administered questionnaire to determine discriminant validity of multiple chemical sensitivity definitions. The authors distributed a total of 4,126 questionnaires to adults who attended general, allergy, occupational, and environmental health practices. The authors then matched responses to features selected from existing case definitions posited by Thomson et al.; the National Research Council; Cullen; Ashford and Miller; Randolph; Nethercott et al.; and the 1999 Consensus (references 4-7, 2, 9, and 10, respectively, herein). The overall response rate was 61.7%. The prevalence of reported symptoms was lowest in general practices, was intermediate in occupational health and allergy practices, and was highest in environmental health practices. Features from the definitions presented by Nethercott et al. and the 1999 Consensus (references 9 and 10, respectively, herein) correctly identified more than 80% of environmental health practice patients and more than 70% of general practice patients. Combinations of 4 symptoms (i.e., having a stronger sense of smell than others, feeling dull/groggy, feeling "spacey," and having difficulty concentrating) also discriminated successfully. In summary, features from 2 of 7 case definitions assessed by the University of Toronto Health Survey achieved good discrimination and identified patients with an increased likelihood of multiple chemical sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11777021

(2001)  Re: "Assessment of deaths attributable to air pollution: should we use risk estimates based on time series or on cohort studies?"


Convincing evidence has accumulated that indicates neuroplastic changes within the spinal cord in response to repeated exposure to opioids. Such neuroplastic changes occur at both cellular and intracellular levels. It has been generally acknowledged that the activation of N-methyl-D-aspartate (NMDA) receptors plays a pivotal role in the development of neuroplastic changes following repeated opioid exposure. Intracellular cascades can also be activated subsequent to NMDA receptor activation. In particular, protein kinase C has been shown to be a key intracellular element that contributes to the behavioral manifestation of neuroplastic changes. Moreover, interactions between NMDA and opioid receptors can lead to potentially irreversible degenerative neuronal changes in the spinal cord in association with the development of opioid tolerance.
Interestingly, similar cellular and intracellular changes occur in the spinal cord following peripheral nerve injury. These findings indicate that interactions exist in the spinal cord neural structures between two seemingly unrelated conditions-chronic opioid exposure and a pathological pain state. These observations may help understand mechanisms of chemical intolerance and multiple chemical sensitivity as well as have significant clinical implications in pain management with opioid analgesics.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000019


Self-reported cacosmia (i.e. feeling ill from the odour of xenobiotic substances) was studied in 151 young, healthy workers, unexposed to unpleasant odours and working in food stores without air-conditioning. Almost half (46%) of the sample reported feeling ill from the smell of chemical materials. Chemical odour intolerance induced headache, itching eyes, irritated or congested nose, dry and/or sore throat, cough, dizziness, and itching or rash. Cacosmic subjects showed a slight prevalence of the female sex, and had significantly higher symptom scores, anxiety, and depression than non-cacosmic subjects. Cacosmia may be related to multiple chemical sensitivity, sick-building syndrome and psychopathology. Individual variability in odour tolerance may substantially bias epidemiological studies on indoor air quality and health.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11314899

(2001) Episodic exposures to chemicals: what relevance to chemical intolerance?

Episodic exposures refer to intermittent acute exposures to chemicals that ordinarily have a rapid onset and short duration of effect. There has been a long tradition in preclinical behavioral pharmacology of using episodic-exposure paradigms in order to establish dose-response functions in individual organisms. In these experiments, stable baselines of behavior are first established and then followed by administering varying doses of a drug intermittently, for example, once or twice a week. The power of this approach is well established; the within-subjects design reduces error variance, allows exploration of the entire range of effective doses, and can be used to identify individual differences in drug sensitivity. Of course, the approach is only applicable to reversibly acting compounds, and checks need to be included to insure effects of one dose are not influenced by prior exposure to another dose. We have used baseline approaches
to evaluate the effects of pesticides and solvents on the behavior of adult male rats and mice. Moreover, a novel probabilistic dose-tolerance analysis applied to the data suggests substantial individual differences in chemical sensitivity, often spanning orders of magnitude. These results suggest that individual differences in chemical sensitivity may be much greater than previously acknowledged.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000013

---------------------------------------------------------------

(2001) Neurophysiological study of patients with perceived 'electrical hypersensitivity'.

The aim of the present study was to investigate baseline neurophysiological characteristics of the central and autonomous regulation and their reactivity to different tests in a group of persons with so-called 'electrical hypersensitivity', which is often considered as a form of psychosomatic disorders. Twenty patients with combinations of neuroasthenic symptoms (general fatigue, weakness, dizziness, headache) and facial skin (itching, tingling, redness) have been investigated. An equal number of symptom-free persons served as a control group. The examination comprised self-reported measures, testing of visual functions, measurements of blood pressure, heart rate and its variability, electrodermal activity, respiration, EEG and visual evoked potentials (VEP). Several variables were found to differ between the patient and the control groups. The mean value of heart rate in rest condition was higher in the patient group compared to the controls (mean value of inter-beat intervals were 0.80 and 0.90 s, respectively). Heart rate variability and response to standing test were decreased in the patient group compared to the controls. Patients had faster onset, higher amplitudes, and left-right hand asymmetry of the sympathetic skin responses. They had a higher critical fusion frequency (43 vs. 40 Hz), and a trend to increased amplitude of steady-state VEPs at stimulation frequencies of 30-70 Hz. The data indicated that the observed group of patients had a trend to hyper sympathotone, hyperresponsiveness to sensor stimulation and heightened arousal.

---------------------------------------------------------------

(2001) Cytochrome CYP2E1 phenotyping and genotyping in the evaluation of health risks from exposure to polluted environments.

Humans are exposed to over 70,000 man-made chemicals including drugs, food additives, herbicides, pesticides, and industrial agents. It is well established that
environmental chemicals are the cause of numerous human diseases including cancer. In most cases, chemical carcinogens require metabolic activation, which is mainly achieved by P450s enzymes. CYP2E1 is of clinical relevance because it is inducible by ethanol, and it metabolizes many common organic solvents such as benzene, alcohols and halogenated solvents. Therefore, alteration in the level of CYP2E1 might influence the health effects of the environmental pollutants. This hypothesis needs to be validated by epidemiological studies and the objective of the "Biomed-2" project was to develop new tests to assess the individual metabolic capacity of workers exposed to volatile organic compounds in order to predict their occupational risk. In vivo chlorzoxazone 6-hydroxylation was validated as a non-invasive and selective test for the determination of liver CYP2E1 activity. Preliminary data in workers exposed to organic solvents indicated that chlorzoxazone metabolism may be a biomarker of occupational exposure to organic solvents. Other approaches, such as use of salicylate as catalytic probe or measurement of catalytic activity in lymphocytes, were not conclusive. Attempts to use CYP2E1 genotyping for estimating human risks from chemical exposure did not bring convincing data as genetic polymorphism of CYP2E1 could not be clearly related to its catalytic activity.


This ethnographic study investigates the experiences of living with multiple chemical sensitivity (MCS), a condition increasing in prevalence but medically contested, on which very little qualitative research has been done. Participant observation included two treatment centers, a support organization, an Internet chat room, and conversations with MCS sufferers, activists, and educators. Semistructured interviews were conducted with 33 people with MCS, recruited to reflect a broad demographic range and severity of illness variation. This article describes several methodological issues associated with doing "peer research" and then describes self-care for symptom management. With no known cure, MCS sufferers manage their symptoms through three main avenues: prevention/avoidance, detoxification, and emotional self-care. Implications include education of health care providers and a warning from those who have MCS: "We are the canaries in the coal mine; what has happened to us will happen to many others unless we clean up our environment."


Pyridostigmine bromide (PB) is a reversible cholinesterase inhibitor used for treatment of myasthenia gravis and for prophylactic protection against organophosphate nerve agent. We previously showed PB can induce apoptotic death in rat brain following systemic treatment. To study mechanisms by which PB induces brain cell death, cultured rat cerebellar granule cells were used. Cytotoxicity was determined after exposure to PB (10-1000 microM) for 24 h; a high concentration of PB (>500 microM) significantly increased lactate dehydrogenase release, which was reduced by pretreatment with the antioxidant, N-t-butyl-alpha-phenyl-nitrone (PBN). Apoptosis, as determined by TUNEL staining, was concentration dependent (10-250 microM) after a 24-h exposure and cytotoxicity was confirmed by gel electrophoresis of DNA, release of cytochrome c from mitochondria, elevation of caspase activity, and electron microscopy. The oxidant-sensitive fluorescent dye 2',7'-dichlorofluorescin diacetate was used to detect reactive oxidative species (ROS) generation. Pretreatment with PBN, superoxide dismutase, catalase, or the nitric oxide synthase inhibitor N(G)-nitro-L-arginine methyl ester (L-NAME) blocked PB-induced ROS generation and apoptotic cell death. Pretreatment with atropine or MK-801 blocked ROS generation and the subsequent neurotoxicity, showing that both muscarinic and NMDA receptors mediate the response. DNA extracted from PB-treated cells revealed oligonucleosomal fragmentation on gel electrophoresis and antioxidants attenuated the DNA fragmentation, providing further evidence for a link of ROS generation and apoptosis. These results indicate that muscarinic receptor-mediated ROS generation is an initiating factor in PB-induced apoptotic cell death and activation of the NMDA glutamate receptor is directly linked to the response.


This case study was a critical investigation of the analytical methodology and exposure assessment components of an intervention that led to the closure of a polyurethane foaming plant in Glenola, N.C., where plant neighbors reported a wide range of adverse health effects. Resident complaints and reports of nuisance odors and health effects persisted for many years, coming to a head in late 1995 and early 1996. Central to state and federal agency activities was the determination of the concentrations of air contaminants including toluene diisocyanate (TDI) at the plant fence line to establish an empirical foundation for resident complaints. Well over 2000 air concentration measurements were collected in the 18-month period prior to intervention and plant closure in September 1997. Results showed that flawed methodology, including poor quality assurance and improper interpretation of the data, may have led to improper conclusions and the inappropriate closing of this facility. Agency data did not show that
ambient air concentrations of TDI at the plant fence line exceeded any required or recommended concentration limit. Furthermore, the identity and concentration of other air contaminants were not thoroughly investigated. Key lessons learned are that such interventions must be based on well-designed and executed exposure assessments. Resultant risk determinations must be based on sound science and methods.

(2001) Inhaled fluticasone decreases bronchial but not alveolar nitric oxide output in asthma.

Exhaled nitric oxide (NO) concentration is a noninvasive measure of airway inflammation and is increased in asthma. Inhaled glucocorticoids decrease exhaled NO concentration, but the relative contributions of alveolar and bronchial levels to the decrease in exhaled NO concentration are unknown. Alveolar NO concentration and bronchial NO flux can be separately approximated by measuring exhaled NO at several exhalation flow rates. The effect of steroid treatment on alveolar and bronchial NO output in asthma was studied. Alveolar NO concentration and bronchial NO flux were assessed in 16 patients with asthma before and during treatment with inhaled fluticasone for 8 weeks and in 16 healthy controls. Before the treatment, asthmatics had increased bronchial NO flux (mean+/-SEM: 3.6+/-0.4 versus 0.7+/-0.1 nL x s(-1), p<0.001) but normal alveolar NO concentration (1.2+/-0.5 versus 1.0+/-0.2 parts per billion (ppb), p>0.05) compared with controls. Inhaled fluticasone decreased bronchial NO flux from 3.6+/-0.4 to 0.7+/-0.1 nL x s(-1) (p<0.01) but had no effect on alveolar NO concentration (before: 1.2+/-0.5; after: 1.2+/-0.1 ppb, p>0.05). The forced expiratory volume in one second improved, whereas asthma symptom score and serum levels of eosinophil cationic protein and eosinophil protein X decreased during the treatment. In conclusion, inhaled fluticasone decreases bronchial but not alveolar nitric oxide output simultaneously with clinical improvement in patients with asthma.


(2001) Serum paraoxonase (PON1) isozymes: the quantitative analysis of isozymes affecting individual sensitivity to environmental chemicals.

In a recent study on Gulf War veterans who developed delayed neurotoxicity symptoms, we found their levels of serum paraoxonase (PON1) isozyme type Q to be significantly lower than in the control, unaffected veteran group. These results were
obtained in 25 ill veterans and 20 well control subjects, of which 10 were deployed and 10 were nondeployed battalion members who remained in the United States during the Gulf War. The blood samples were also assayed for serum butyrylcholinesterase in our laboratory, and more recently in Dr. C. Broomfield's laboratory for somanase and sarinase activities. The cholinesterase activities showed no significant correlation with the PON1 isozyme levels or the severity of the clinical symptoms, but the somanase and sarinase levels ran parallel to the PON1 type Q isozyme concentrations. Although there is no direct evidence that these Gulf War veterans were directly exposed to or encountered either of these nerve gases, they may have been exposed to some environmental or chemical toxin with a similar preference for hydrolysis by the PON1 type Q isozyme. The number of subjects is relatively small, but the results should encourage other investigators to examine both the individual phenotypes and the levels of PON1 isozymes in other groups exhibiting neurological symptoms.


Epidemiologic studies indicate that prolonged exposure to high pollution levels is associated with increased risk of cancer, especially lung cancer. However, under conditions of moderate or low air pollution, epidemiologic evidence does not permit reliable conclusions. Biomarker-based population studies may serve as complementary tools providing a better understanding of the relative contribution of ambient atmospheric pollution to the overall genotoxic burden suffered by city dwellers. However, past efforts to apply biomarkers to studies of low levels exposure to urban air pollution have given inconclusive results, partly because of the absence of adequate data on personal exposure, covering a time-window which is appropriate for the biomarkers being examined, as well as a battery of biomarkers reflecting different stages of the carcinogenic process. In the present paper, the potential of biomarker-based population studies to aid the assessment of the genotoxic and carcinogenic effects of urban air pollution is reviewed by reference to the achievements and limitations of earlier reported studies. The design and methodology adopted in a recently completed large-scale population study, carried out in the context of the European Union Environment and Climate Programme, known by the short name of AULIS project, is discussed and descriptive statistics of the main findings of the project are presented. These findings indicate that for cohorts suffering moderate-to-low exposures to airborne particulate-bound polycyclic aromatic hydrocarbons (PAHs), no simple correlation with biomarkers of genotoxicity existed and suggest that additional factors made a significant contribution to the overall genotoxic burden.
Kutsogiannis, DJ and Davidoff, AL Journal/Arch Environ Health. 56: 196-207.

The lack of widely accepted, standardized, clinical and epidemiologic criteria for Multiple Chemical Sensitivity syndrome has led to confusion about the identification of the condition and has slowed pertinent research. In this article, the authors evaluated the psychometric properties of 2 sets of clinical/epidemiologic criteria for Multiple Chemical Sensitivity syndrome. In this cross-sectional survey of 1,166 patients who visited outpatient occupational, otolaryngology, allergy, and clinical ecological clinics, the authors used the aforementioned sets of criteria to (a) estimate the prevalence of the syndrome in these varied samples and (b) compare the current diagnostic practices of traditional physician specialists with those of clinical ecologists. The authors used a patient-completed questionnaire to assess the medical, psychosocial, and psychological status of patients who reported multiple chemical sensitivities. This approach enabled the formulation of 6 domains, which represented commonly observed characteristics of the syndrome. The authors used a physician-completed questionnaire to collect diagnoses of Multiple Chemical Sensitivity syndrome and other medical conditions. Domains, which were operationalized by the questionnaire and comprised the 2 sets of criteria for identification of the Multiple Chemical Sensitivity syndrome, had test-retest reliabilities that exceeded .75 and estimates of internal consistency that ranged between .59 and .94. Evidence of construct and face validity was considered acceptable. The overall clinic-based prevalences of Multiple Chemical Sensitivity syndrome, based on 6 and 4 domains, were 7% and 23%, respectively. Regardless of the identifying set of criteria used, physicians' diagnoses had relatively low sensitivities (range = 6-50%) and relatively high specificities (range = 82-99%). The study data suggested that the domains operationalized by the questionnaire had reasonable psychometric characteristics. Study data also support the fact that Multiple Chemical Sensitivity syndrome is often overlooked--even by those physicians who treat it most frequently--and that use of both sets of objective criteria for identifying the syndrome would greatly improve the sensitivity of physician diagnoses.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11480495

(2001) [Features of detecting the cause of ecologically-caused diseases in children].
Kurlandskii, BA Journal/Gig Sanit. 45-6.
The assessment of irritation using clinical methods and questionnaires.

Sensory irritant responses to chemical exposures are measured by a variety of methods; however, studies can be influenced from biases associated with study design and subject responses. This article reviews the different methods used to quantitate irritation. These methods primarily focus on eye and nasal mucosal irritation. Although methods to evaluate mouth, throat mucosal, and dermal irritation are also relevant, they are seldom used in actual practice. Measurements for eye irritation include tear film stability, epithelial damage, foam formation, blinking frequency, tear flow, inflammation, and hyperemia. Methods for detecting nasal mucosa irritation include measuring swelling of the nasal mucosa, peak airflows through the nose, acoustic rhinometry, and rhinostereometry, which measures thickness of the anterior nasal turbinate. Questionnaires are useful for defining a set of symptoms in an attempt to characterize dose-response relationships from controlled exposure studies or field studies, to compare rates of events in field studies, or to screen for disease. However, it is important to consider carefully the study design, goal of utilization, and constraints surrounding their application. Whichever method is used in medical surveillance or to evaluate effectiveness of industrial hygiene or engineering controls in preventing irritation effects from chemical exposure, the sensitivity, specificity, and predictive value of the irritation measurements are important factors in interpreting the results. This article reviews these various issues and offers some advice.


Function testing for chemical brain damage: a review.

Testing of neurobehavioral functions for evaluation of the effects of chemicals on the human brain from community (i.e., environmental) exposures is logical and may be a preferred initial step. Sensitivity is improved (1) by adjusting individual tests for influential factors, found by regression modeling and by retaining significant coefficients; and (2) by the calculation of predicted values for each test for each subject. This two-part approach allows for adjustments in age, sex, educational level, and other factors before comparisons are made. Visual fields, color discrimination, reaction time, balance, and digit symbol are the most sensitive tests, followed by 6 sensitive psychological tests and less-discriminating physiological measurements. Hydrogen sulfide, polychlorinated biphenyls, and arsenic are the most toxic chemicals, followed by chlorine, chlorpyrifos, formaldehyde, nickel carbonyl, and ammonia. The least toxic chemicals, which are hydrochloric acid and chlorine, were determined 7 wk following a community spill. The least toxic chemical among those identified herein is methyl ter butyl ether.

OBJECTIVE: To determine whether variables derived from the self-regulatory model of health and illness behavior accurately predict status as a patient or nonpatient with fibromyalgia (FM). METHODS: Subjects were 79 patients who met American College of Rheumatology (ACR) criteria for FM and 39 community residents who met ACR criteria for FM but had not sought medical care for their symptoms (nonpatients). Subjects were administered 14 measures that produced 6 domains of variables: background demographics and pain duration; psychiatric morbidity; and personality, environmental, cognitive, and health status factors. These domains were entered in 4 different hierarchical logistic regression analyses to predict status as patient or nonpatient. RESULTS: The full regression model was statistically significant (P < 0.0001) and correctly identified 90.7% of the subjects with a sensitivity of 92.4% and a specificity of 87.2%. The best individual predictors of group status were self-reports of self-efficacy, negative affect, recent stressful events, and perceived pain. Relative to nonpatients, patients reported higher levels of negative affect and perceived pain and a greater number of recent stressful experiences, as well as lower levels of self-efficacy. CONCLUSION: Consistent with the self-regulatory model of health and illness behavior, psychosocial and health status variables predict health care-seeking behavior in persons with FM independently of background demographics and psychiatric morbidity. These variables may influence the severity of symptoms experienced by persons with this disorder as well as their health care-seeking behavior, but they are not necessary to produce abnormal pain sensitivity in FM.

---------------------------------------------------------------------


A high level of hippocampal brain-derived neurotrophic factor (BDNF) in normally aged as compared with young rats suggests that it is important to maintain a considerable level of hippocampal BDNF during aging in order to keep normal hippocampal functions. To elucidate possible mechanisms of endogenous BDNF increase, changes in levels of BDNF were studied in the rat brain following systemic administration of various convulsant agents; excitotoxic glutamate agonists, NMDA, kainic acid and (+
-)-alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA); GABA receptor antagonists, picrotoxin, pentylenetetrazole (PTZ) and lindane (gamma-hexachlorocyclohexane); and L-type voltage-dependent calcium channel agonist, BAY-K 8644. Kainic acid and AMPA, but not NMDA, caused remarkable increases in BDNF protein in the rat hippocampus and entorhinal cortex. Picrotoxin, PTZ and lindane stimulated BDNF production in the entorhinal cortex and also in the hippocampus of rats showing very severe convulsions. On the other hand, BAY-K 8644 treatment increased BDNF levels in the neocortex and entorhinal cortex. Maximal levels of BDNF protein were observed at 12--24 h, 8--16 h and 6 h following administration of kainic acid, PTZ and BAY-K 8644, respectively. Kainic acid stimulated BDNF synthesis in presynaptic hippocampal granule neurons, but not in postsynaptic neurons with its receptors, while PTZ and BAY-K 8644 produced the same effects in postsynaptic neurons in the entorhinal cortex (in granule neurons in the hippocampus) and in the whole cortex, respectively. Nifedipine inhibited almost completely BAY-K 8644, but not PTZ, effects. omega-Conotoxin GVIA and DCG-IV partially blocked kainic acid-induced enhancement of BDNF, indicating involvement of L-type and N-type voltage-dependent calcium channels, respectively. In addition, BDNF levels in the hippocampus of mice deficient in D-myoinositol-1,4,5-triphosphate receptor gene were scarcely different from those in the same region of controls, suggesting little involvement of intracellular calcium increase through this receptor. BAY-K 8644, but not kainic acid or PTZ, stimulated the phosphorylation of cyclic AMP responsive element binding protein. Our results indicate convulsant-dependent stimulation of BDNF production and involvement of region-specific voltage-dependent calcium channels.

(2001) [Problems of ecologically-caused illness].
Kaptsov, VA and Pankova, VB Journal/Gig Sanit. 21-5.

The paper presents data on environmental factor-induced changes in human health. The health status was studied in rail workers living and working in the areas exposed to radiation. This demonstrated a higher incidence of neoplasms, anemias, alimentary and circulatory diseases. Children had a high incidence of chronic lymphonoid tissue diseases and anemias. It is suggested that a complex of negative environmental factors is formed not only by radiation, but also by industrial pollution of the areas and by adverse and hazardous occupational factors.

Kanter, ED, Wilkinson, CW, Radant, AD, Petrie, EC, Dobie, DJ, McFall, ME, Peskind, ER and Raskind, MA Journal/Biological Psychiatry. 50: 238-245.
Although the phenomenon of environmental sensitivities (ES) has no clear etiology nor well-accepted pathophysiology, affected individuals experience symptoms that cause varying levels of dysfunction. Through a dedicated, government-funded research and treatment center, a detailed questionnaire covering 217 symptoms in 13 systems was mailed in 1997-1998 to 812 individuals referred to the center by physicians. A total of 385 (47%) questionnaires were returned, and data were analyzed on 351 individuals. Participants tended to be women (80%), middle-aged individuals (37% age 40-49 years), and those in higher educational groups (28% completed university), but there was wide variation in demographic variables. General symptoms such as difficulty concentrating, fatigue, forgetfulness, and irritability dominated the overall prevalence of symptoms since the start of their illness. Those related to irritation such as sneezing, itchy or burning eyes, and hoarseness or loss of voice were more common after exposure to environmental irritants. Ranking of symptoms using severity scores was consistent between men and women. Overall scores were higher in women, in participants who were separated or divorced, and in low-income groups. The type and consistency of symptoms experienced after exposure to triggering substances may not fit a purely psychogenic theory.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11266327

(2001) [Indicators of antioxidant status in the problem of preclinical diagnosis].
Iudina, TV, Rakitskii, VN, Egorova, MV and Fediriva, NE Journal/Gig Sanit.  61-2.

(2001) Genetic susceptibility to adverse effects of drugs and environmental toxicants. The role of the CYP family of enzymes.
Ingelman-Sundberg, M Journal/Mutat Res.  482: 11-9.
The majority of cytochrome P450 (CYP)-dependent xenobiotic metabolism is carried out by polymorphic and inducible enzymes which can cause abolished, quantitatively or qualitatively altered or enhanced drug metabolism. Stable duplication, multi-duplication or amplification of active genes, most likely in response to dietary components causing a selection of alleles with multiple genes, has been described. Several examples exist where subjects carrying certain alleles suffer from a lack of drug efficacy due to ultra-rapid metabolism caused by multiple genes or by induction of gene expression or, alternatively, adverse effects from the drug treatment due to the presence of defective alleles. The polymorphism of CYP enzymes is expected to influence the individual sensitivity and toxicity for different environmental agents, although there is no real consensus in the literature about specific firm relationships in this regard. Dosage requirements for several commonly used drugs that have a narrow therapeutic range can differ more than 20-fold dependent on the genotype or the enzyme expression status. The incidence of serious and fatal adverse drug reactions has been found to be very high among hospitalised patients and causes over 100,000 deaths per year in the US, making it between the 4th and 6th leading cause of death. It is likely that predictive genotyping could avoid 10-20% of these deaths. In the present contribution, an overview is presented about our present knowledge about the polymorphism of xenobiotic metabolising CYPs and the importance for adverse effects of drugs and metabolic activation of xenobiotics.

(2001) [Determinants of patient satisfaction with services of the Vienna environmental medicine counseling center].

Client satisfaction is a relevant aspect for assessing the efficiency of a Medical Advisory Board. The study presented here aimed at determining the factors that guarantee satisfaction. These findings are essential for the further development of the service of the Advisory Board of the City of Vienna for Environmental Medicine ("UMB"). To this end a brief anonymous questionnaire was sent to 245 clients. This comprised elements evaluating the degree of satisfaction with the consultant service of the Advisory Board, fulfillment rate of expectations, solutions offered for various problems, and whether--if necessary--the "UMB" Advisory Board would be consulted again. A satisfactory response rate of 43% was obtained. The results show a high degree of satisfaction among the clients with the consultations (= 78%) despite unresolved or only partly resolved problems (71%) and questions that remained open for discussion (38%). Approximately 90% of the clients would again consult "UMB" for advice. The reasons for consultation did not show any significant influence on the client satisfaction. However, satisfaction of clients depended on whether or not a solution was found in respect of their problem and on the action taken by "UMB" to solve it. Summarising the findings, the analyses show that apart from on-the-spot assessment and detailed inspection, comprehensive case histories and interviews are an important basis for further clarification of problems caused by environmental factors.
In this study dosing regimens were designed such that cholinesterase inhibition following exposure to chlorpyrifos was produced in one treatment group, but was absent in the other. The higher dosing regimen inhibited plasma and brain cholinesterase activities by 51 and 70%, respectively, and resulted in decreased [3H]cis-methylidioxolane ([3H]CD) binding, which was attributable to a decrease in Bmax. No concomitant loss of [3H]quinuclidinyl benzilate ([3H]QNB) binding sites was observed, indicating that the M2 muscarinic receptor subtype to which [3H]CD binds is particularly susceptible to alterations induced by chlorpyrifos treatment. As the M2 receptor subtype is surmised to be the muscarinic autoreceptor, decreases in this receptor may exacerbate poisoning by organophosphorus agents as a result of decreased ability to terminate synaptic acetylcholine release. The ability of carbachol to inhibit striatal adenylate cyclase, which is an effector molecule associated with the M2 receptor, was unaltered in chlorpyrifos-treated rats. Decreases in M2 receptors occurred with the higher dosing regimen, in the absence of any clinical manifestations. Thus, in the absence of overt clinical signs, perturbations of the muscarinic receptor system did occur as a result of sub-chronic chlorpyrifos exposure. Such alterations may contribute to neurological impairments that develop following chronic organophosphorus exposure.


CONTEXT: Hypersensitivity to electricity is a proposed environmental illness of unknown etiology. Patients report a variety of symptoms that they relate to electric equipment. The afflicted individuals suffer from ill health. Many interventions have been tried but, to date, there is no one specific treatment that has been proven superior to other remedial actions. In general, there is a lack of controlled prospective studies. OBJECTIVE: To test the hypothesis that antioxidant therapy reduces symptoms and improves health in patients reporting hypersensitivity to electricity. DESIGN: Randomized, double-blind, crossover, placebo-controlled study. SETTING: Patients referred to the Environmental Illness Research Centre, Stockholm County Council. PATIENTS: Sixteen patients reporting hypersensitivity to electricity. INTERVENTION: Antioxidant supplementation (vitamins C and E, selenium). MAIN OUTCOME
MEASURES: Self-reported symptoms and reported degree of hypersensitivity to electricity, serum levels of uric acid and diphenylpycrylhydrazyl (DPPH). RESULTS: The results indicated no significant differences in reported symptoms, reported hypersensitivity to electricity, or oxidative status in serum between periods of antioxidant and placebo treatments. Serum levels of DPPH and uric acid showed no correlation with the reported degree of symptoms or hypersensitivity to electricity. CONCLUSIONS: The study did not show any beneficial effect of antioxidant supplementation for patients reporting hypersensitivity to electricity. The results do not support the hypothesis that oxidative stress is a major contributor to ill health in patients who report hypersensitivity to electricity.


The lack of a pathophysiological marker hinders studies on environmental illnesses of unknown origin. Hence, research focused on the identification of such a marker is a priority. This study investigated the nature and a possible etiology of fatigue in hypersensitivity to electricity (the most commonly reported environmental illness in Sweden). The aim was to test the hypothesis that perceived fatigue was due to alterations in cholinesterase activity. The study group consisted of 14 people who reported a hypersensitivity to electricity, including disabling fatigue. We assessed cholinesterase activity three times: twice based on current symptoms reported by the subjects (severe fatigue attributed to electromagnetic fields and absence of this symptom) and once at a randomly selected time. No significant reduction in acetylcholinesterase was identified in any subject. Examined on a group level, no significant reduction in activity was identified at the time of severe fatigue, and no correlation between reported degree of fatigue and cholinesterase activity was observed. Fatigue attributed to electromagnetic fields was nonphysical and showed a significant correlation to difficulties in concentrating. The results do not support the hypothesis that a change in cholinesterase activity mediates fatigue in people reporting hypersensitivity to electricity.


The most frequently used pesticide in U.S. homes, as well as in schools and day care centers, is chlorpyrifos. In 1998, this insecticide was detected in household dust from the former U.S. Forces housing estates in Frankfurt am Main, Germany, resulting from its earlier use up to 1993, i.e., at least 4 years ago. This led to great concern in the new inhabitants. To investigate their internal exposure to the substance, they were offered the opportunity of taking part in biomonitoring examinations. Children playing on the floor were assumed to be especially at risk due to increased exposure to chlorpyrifos via oral or dermal intake. A total of 1146 inhabitants took part in this voluntary investigation. All of them stated that they had never used chlorpyrifos in their homes. Spot urine samples of the study participants were analyzed for six metabolites of organophosphorous insecticides [dimethylphosphate (DMP), diethylphosphate (DEP), dimethylthiophosphate (DMTP), diethylthiophosphate (DETP), dimethyldithiophosphate (DMDTP), and diethyldithiophosphate (DEDTP)] using a very sensitive gas chromatographic method with mass-selective detection and a limit of detection of 1 microg/L. No evidence was found of increased internal exposure due to former chlorpyrifos application in these homes (>4 years ago), either in children or in adults. The median values and 95th percentiles of the urinary metabolite concentrations in 484 adults were (microg/g creatinine): DMP, 15.5 and 102.5; DMTP, 13.5 and 125.8; DMDTP, <1 and 13.1; DEP, 2.1 and 11.6; DETP, <1 and 6.4; DEDTP, both <1. The urinary metabolite concentrations in children <6 years of age were higher; this was caused mainly by lower creatinine concentrations. To conclude, no increase in internal exposure due to former indoor application of chlorpyrifos could be found, and the reference values published for internal organophosphate exposure in adults in Germany were confirmed. However, as shown in other environmental studies, the urinary excretion of organophosphorous metabolites exceeds dietary intake several fold; this has been estimated from the data in various duplicate dietary studies. This observation calls for further investigation.
Psychosomatic illness as "modern diseases" are of increasing interest to the public. Environmental illnesses, for example assumed intoxication with organic solvents, multiple chemical sensitivity, sick building syndrome, chronic fatigue syndrome, fibromyalgia, the influence of amalgam or of electromagnetic waves and ozone are often causes of anxiety. There are many hypotheses about the origin of these diseases. Some scientists emphasize an organic basis; however, this is not generally accepted. Very often with good reason a psychological cause is supposed. Objective diagnostic criteria are not available, therefore these diagnoses may only be applied after sufficient exclusion of other known organic diseases. Mostly a psychological treatment is refused by the person affected, and a scientifically based somatic concept for the therapy does not exist. The medicolegal problems are important and often the reason for prolonged forensic confrontations.

(2001) Use of structural equation modeling to test the construct validity of a case definition of Gulf War syndrome: invariance over developmental and validation samples, service branches and publicity.

To attempt to replicate the syndrome-like structure identified by exploratory factor analysis of symptom reports from 249 Gulf War veterans of a Naval reserve battalion (the developmental sample), we administered Haley's original symptom questionnaire to 335 Gulf War veterans who served primarily in active-duty US Army units living in North Texas (the validation sample). On the basis of recently validated goodness-of-fit criteria (SRMR< or= 0.08, RMSEA< or= 0.06, and CFI> or= 0.95), a structural equation model (Model 1) with four symptom scales loading on each of three first-order latent syndrome factors fit both the developmental and validation samples well and was invariant across both samples. Additional models validated a higher-order latent factor (a single Gulf War syndrome) explaining the variances and covariances of the first-order factors, four additional symptom scales loading on the higher-order factor, and four possible secondary factor loadings that also fit the data well. All structural models were invariant across cohorts of the validation sample surveyed before and after intense publicity following publication of the case definition. These findings suggest that the apparent syndrome structure of a single Gulf War syndrome with three variants may be found widely and justify a confirmatory sample survey of Gulf War-era veterans.
(2001) Gulf syndrome research has passed peer review.

---------------------------------------------------------------------

(2001) [Deadly indoor climate].

---------------------------------------------------------------------


Diisopropyl phosphorofluoridate (DFP) is a type I organophosphorus compound and produces delayed neurotoxicity (OPIDN) in adult hens. A single dose of DFP (1.7 mg kg, s.c.) produces mild ataxia in hens in 7-14 days, which develops into severe ataxia or paralysis as the disease progresses. We have previously shown altered expression of several proteins (e.g. Ca2+/calmodulin-dependent protein kinase II (CaM kinase II) alpha-subunit, tau, tubulin, neurofilament protein (NF), vimentin, GFAP) and an immediate early gene (e.g. c-fos) in DFP-treated hens. Here we show an increase in protein kinase A (PKA) protein level and activity in the spinal cord at 1-day and 5-days time periods after DFP administration. We also determined the protein levels of protein kinase C (PKC), CaM kinase II and several phosphatases (i.e. phosphatase 1 (PP1), phosphatase 2A (PP2A), phosphatase 2B (PP2B) in the spinal cord of DFP-treated hens after 1, 5, 10, and 20 days). There was increase in CaM kinase II alpha subunit level after 10 and 20 days of treatment, and decrease in PKC level at 1-day and 20-days time periods in spinal cord mitochondria. In contrast, the cerebrum, which is resistant to DFP-induced axonal degeneration, did not show change in PKA and CaM Kinase II levels at any time period DFP post-administration. No alteration was found in the protein levels of PP1, PP2A, and PP2B at any time period. An early induction in PKA, which is an important protein kinase in signal transduction, followed by that of CaM kinase might be contributing towards the development of OPIDN in DFP-treated hens.

---------------------------------------------------------------------

(2001) Nitric oxide modulates high-energy phosphates in brain regions of rats intoxicated with diisopropylphosphorofluoridate or carbofuran: prevention by N-tert-butyl-alpha-phenylnitrone or vitamin E.
Acute effects of seizure-inducing doses of the organophosphate compound diisopropylphosphorofluoridate (DFP, 1.25 mg/kg s.c.) or the carbamate insecticide carbofuran (CF, 1.25 mg/kg s.c.) on nitric oxide (NO) were studied in the brain of rats. Brain regions (pyriform cortex, amygdala, and hippocampus) were assayed for citrulline as the determinant of NO and for high-energy phosphates (ATP and phosphocreatine) as well as their major metabolites (ADP, AMP, and creatine). Rats, anesthetized with sodium pentobarbital (50 mg/kg i.p.), were killed using a head-focused microwave (power, 10 kW; duration, 1.7 s). Analyses of brain regions of controls revealed significantly higher levels of citrulline in the amygdala (289.8+/-7.0 nmol/g), followed by the hippocampus (253.8+/-5.5 nmol/g), and cortex (121.7+/-4.3 nmol/g). Levels of energy metabolites were significantly higher in cortex than in amygdala or hippocampus. Within 5 min of CF injection, the citrulline levels were markedly elevated in all three brain regions examined, while with DFP treatment, only the cortex levels were elevated at this time. With either acetylcholinesterase (AChE) inhibitor, the maximum increase in citrulline levels was noted 30 min post-injection (> 6- to 7-fold in the cortex, and > 3- to 4-fold in the amygdala or hippocampus). Within 1 h following DFP or CF injection, marked declines in ATP (36-60%) and phosphocreatine (28-53%) were seen. Total adenine nucleotides and total creatine compounds were reduced (36-58% and 28-48%, respectively). The inverse relationship between the increase in NO and the decrease in high-energy phosphates, could partly be due to NO-induced impaired mitochondrial respiration leading to depletion of energy metabolites. Pretreatment of rats with an antioxidant, the spin trapping agent N-tert-butyl-alpha-phenylnitrone (PBN, 200 mg/kg i.p.), prevented DFP- or CF-induced seizures, while the antioxidant vitamin E (100 mg/kg i.p. per day for 3 days) had no anticonvulsant effect. Both antioxidants, however, significantly prevented the increase of citrulline and the depletion of high-energy phosphates. It is concluded that seizures induced by DFP and CF produce oxidative stress due to a marked increase in NO, causing mitochondrial dysfunction, and thereby depleting neuronal energy metabolites. PBN pretreatment provides protection against AChE inhibitor-induced oxidative stress mainly by preventing seizures. Additional antioxidant actions of PBN may contribute to its protective effects. Vitamin E has direct antioxidant effects by preventing excessive NO production.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11570692


OBJECTIVE: This study was carried out to investigate the impact of the physical effects of a chemical exposure, health and chemical beliefs, and chemical sensitivities
treatment preferences on the consultation outcome at a tertiary liaison clinic.

METHOD: Eighty-five patients exposed to a range of chemicals were assessed at a joint medical toxicology and psychiatric clinic. Patient's beliefs about chemicals and health, chemical sensitivities and their treatment preferences were assessed using a 23-item questionnaire. RESULTS: Fifty-seven patients (69%) had suffered from a range of initial or delayed symptoms that were probably a clear physical consequence of the exposure (Group A), whereas 26 patients (31%) had not (Group B). There were no significant differences found between groups A and B in terms of their diagnosis and their beliefs about health, food, chemicals and chemical sensitivities treatment preferences. However, patients in Group A were significantly more likely to report moderate to severe symptoms in comparison to Group B. Consultation outcome too did not differ between the two groups. The only predictors of consultation outcome were the patients' chemical sensitivities treatment preferences. Patients who at the outset thought that their treatment should comprise of complete avoidance to chemicals, regular monitoring and the use of alternative rather than conventional medicine were significantly less likely to achieve a favourable consultation outcome. Patients' chemical sensitivities treatment preferences were related to the more general beliefs on health, food and the harmful nature of chemicals and were not related to the chemical exposure variables. CONCLUSION: These findings suggest that addressing patients' treatment preferences and the general beliefs on chemicals, food and health may enhance outcome and perhaps ought to be the target for intervention in context of such a liaison clinic.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11316505

(2001) [Sanitary characteristics of chemical risk factors under conditions of housing environment].
Gubernskii Iu, D and Kalinina, NV Journal/Gig Sanit. 21-4.


Foods can produce adverse symptoms in various ways, and the patient's history can help determine whether allergy or some other mechanism is responsible. The history has limitations, however, as it is primarily subjective. Therefore, diagnostic confirmation is very important. Strict avoidance of the allergenic food is the primary course of treatment. Education is imperative to ensure that patients understand food labels and recognize the different names used to designate a specific food. Prompt treatment with epinephrine when an acute reaction occurs can make a life-or-death difference.


There are currently a number of initiatives aimed at considering and redefining the role of environmental health. These include an effort under the auspices of the Institute of Medicine Roundtable on Environmental Health and another under the auspices of the American Schools of Public Health. Both will result in conferences to be held in the same month of the New York Academy of Sciences (NYAS) conference on "The Role of Neural Plasticity in Chemical Intolerance", for which this paper is being prepared. This questioning of our definition and of our approach to the field of environmental health is an instructive background on which to consider the issue of environmental risks and public health-the topic given to me by the organizers of the NYAS conference. My approach will be to touch on those issues related to the nervous system and to unexplained symptoms in keeping with the subject of the conference, as well as to discuss some of the broader issues surrounding environmental health.


The practice of environmental health is concerned with the protection of the community. There are a number of tools used for assessment of environmental hazards, but environmental health is most reliant on the use of risk assessment. Risk
assessment is a set of tools used to assess hazards on a community level, based on human studies, ecological studies, or toxicity testing of animals.

---------------------------------------------------------------

(2001) Does the kindling model of epilepsy contribute to our understanding of multiple chemical sensitivity?

Multiple chemical sensitivity (MCS) is a phenomenon whereby individuals report an increased sensitivity to low levels of chemicals in the environment. Kindling is a model of synaptic plasticity whereby repeated low-level electrical stimulation to a number of brain sites leads to permanent increases in seizure susceptibility. Stimulation that is initially subthreshold for subclinical seizure provocation comes, over time, to elicit full-blown motor seizures. Kindling can also be induced by chemical stimulation, and repeated exposures to some pesticides have been shown to induce signs of behavioral seizure, facilitate subsequent electrical kindling, and induce subclinical electrographic signs of hyperexcitability in the amygdala. Many of the symptoms of MCS suggest that CNS limbic pathways involved in anxiety are altered in individuals reporting MCS. Limbic structures are among the most susceptible to kindling-induced seizures, and persistent cognitive and emotional sequelae have been associated with temporal lobe epilepsy (TLE) in humans and kindling in animals. Thus, a number of parallels exist between kindling and MCS phenomena, leading to initial speculations that MCS may occur via a kindling-like mechanism. However, kindling requires the activation of electrographic seizure discharge and has thus been primarily examined as a model for TLE. Events leading to the initial evocation of a subclinical electrographic seizure have been much less well studied. It is perhaps these events that may serve as a more appropriate model for the enhanced chemical responsiveness characteristic of MCS. Alternatively, kindling may be useful as a tool to selectively increase sensitivity in subcomponents of the neural fear circuit to address questions relating the role of anxiety in the development and expression of MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000037

---------------------------------------------------------------

Garcia, SJ, Seidler, FJ, Crumpton, TL and Slotkin, TA Journal/Brain Res. 891: 54-68.

The widespread use of chlorpyrifos (CPF) has raised major concerns about its potential to cause fetal or neonatal neurobehavioral damage, even at doses that do not evoke acute toxicity. CPF has been shown to inhibit replication of brain cells, to elicit
alterations in neurotrophic signaling governing cell differentiation and apoptosis, and to evoke oxidative stress. However, the specific cell types targeted by CPF have not been clarified, an issue of vital importance in establishing the boundaries of the critical period in which the developing brain is vulnerable. In the current study, we evaluated the effects of CPF on C6 glioma cells, a well-established glial model. In undifferentiated C6 cells, CPF inhibited DNA synthesis in a concentration-dependent manner, with greater potency than had been seen previously with neuronal cell lines. Just as found after in vivo CPF treatment or with neuronal cell lines, the effects on cell replication were independent of cholinergic stimulation, as cholinergic antagonists did not block CPF-induced inhibition. CPF interfered with cell signaling mediated through adenylyl cyclase at the level of G-protein function; the effects again were greater in undifferentiated C6 cells but were still detectable in differentiating cells. In contrast, differentiation enhanced the ability of CPF to elicit the formation of reactive oxygen species and to evoke deficits in Sp1, a nuclear transcription factor essential for differentiation. These results indicate that glial-type cells are targeted by CPF through the same multiple mechanisms that have been demonstrated for the effects of CPF on brain development in vivo. Because glial development continues long after the conclusion of neurogenesis, and given that CPF targets events in both glial cell replication and the later stages of differentiation, the vulnerable period for developmental neurotoxicity of CPF is likely to extend well into childhood.


The termination of chemical neurotransmission in the CNS involves the rapid removal of neurotransmitter from synapses by specific transport systems. Such mechanism operates for the three major amino acid neurotransmitters glutamate, gamma-aminobutyric acid (GABA) and glycine. To date, five different high-affinity Na(+)–dependent glutamate (Glu) transporters have been cloned: GLT1, GLAST, EAAC1, EAAT4 and EAAT5. The first two are expressed mainly by glial cells, and seem to be the predominant Glu transporters in the brain. A major function of Glu uptake in the nervous system is to prevent extracellular Glu concentrations from raising to neurotoxic levels in which glial transporters seem to play a critical role in protecting neurons from glutamate-induced excitotoxicity. Under particular conditions, glial GluTs have been shown to release Glu by reversal of activity, in a Ca(2+)-and energy-independent fashion. Furthermore, an activity of these transporters as ion channels or transducing units coupled to G-proteins has recently been reported. The localization, stoichiometry, and regulation of glial GluTs are outlined, as well as their possible contributions to nervous system diseases as ALS, AD and ischemic damage.

The termination of chemical neurotransmission in the central nervous system (CNS) involves the rapid removal of neurotransmitter from synapses. This is fulfilled by specific transport systems in neurons and glia, including those for gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain. Glial cells express the cloned Na(+)Cl(-)-dependent, high-affinity GABA transporters (GATs) GAT1, GAT2, and GAT3, as well as the low-affinity transporter BGT1. In situ hybridization and immunocytochemistry have revealed that each transporter shows distinct regional distribution in the brain and the retina. The neuronal vs. glial localization of the different transporters is not clear-cut, and variations according to species, neighboring excitatory synapses, and developmental stage have been reported. The localization, stoichiometry, and regulation of glial GATs are outlined, and the participation of these structures in development, osmoregulation, and neuroprotection are discussed. A decrease in GABAergic neurotransmission has been implicated in the pathophysiology of several CNS disorders, particularly in epilepsy. Since drugs which selectively inhibit glial but not neuronal GABA uptake exert anticonvulsant activity, clearly the establishment of the molecular mechanisms controlling GATs in glial cells will be an aid in the chemical treatment of several CNS-related diseases.


Glia possess transport systems for the three major amino acid neurotransmitters glutamate, gamma-aminobutyric acid (GABA) and glycine, involved in the arrest of neurotransmission mediated by these compounds. Two glycine transporters have been cloned: GLYT1, mainly expressed by glial cells and shown to colocalize with NMDA receptors, and GLYT2, exclusively expressed by neurons and colocalized with the inhibitory glycine receptors. The way in which the regulation of extracellular glycine concentration by glial glycine transporters affects physiological and pathological conditions is discussed. The presence, differential pharmacology and specific regulation of glycine transporters in glial cells strongly support an important role for glia in the modulation of both, excitatory and inhibitory neurotransmission.
Sensitivities to chemicals are characterized by symptoms in multiple organ systems in response to low-level chemical exposures. This paper reviews studies of controlled exposures to odorants and to mixtures of volatile organic compounds. Sensitive subgroups include subjects who met Cullen's 1987 criteria for multiple chemical sensitivity (MCS), Gulf War veterans with chronic fatigue syndrome and chemical sensitivity (CFS/CS), and subjects with specific self-reported sensitivities to methyl terbutyl ether (MTBE) in gasoline (MTBE-sensitive). All studies include comparison of age- and sex-matched healthy controls. Studies of olfaction did not support unusual sensitivity, defined as lower odor thresholds, among MCS subjects; however, a dose-response pattern of symptoms was observed in response to suprathreshold concentrations of phenyl ethyl alcohol. In blinded, controlled exposures to clean air, gasoline, gasoline/11% MTBE, and gasoline/15% MTBE, a threshold effect was observed with MTBE-sensitive subjects reporting significantly increased symptoms to gasoline/15% MTBE exposure. Autonomic arousal (heart and respiration rate; end-tidal CO2) in response to odor of chemical mixtures may mediate symptoms for subjects with generalized chemical sensitivities, but not for those whose sensitivities are confined to specific chemicals. For example, Gulf War veterans with CFS/CS experienced reduced end-tidal CO2 when exposed to diesel fumes, while exposure to MTBE did not produce any psychophysiologic changes in MTBE-sensitive subjects. Controlled olfactory and exposure studies reveal that significant responses can be observed in chemically sensitive subjects even when de-adaptation has not occurred. However, these studies suggest that symptoms are not necessarily accompanied by changes in physiologic arousal. Subject characteristics play a critical role in outcomes.

Health risks of inhaled nasal toxicants were reviewed with emphasis on chemically induced nasal lesions in humans, sensory irritation, olfactory and trigeminal nerve toxicity, nasal immunopathology and carcinogenesis, nasal responses to chemical mixtures, in vitro models, and nasal dosimetry- and metabolism-based extrapolation of nasal data in animals to humans. Conspicuous findings in humans are the effects of
outdoor air pollution on the nasal mucosa, and tobacco smoking as a risk factor for sinonasal squamous cell carcinoma. Objective methods in humans to discriminate between sensory irritation and olfactory stimulation and between adaptation and habituation have been introduced successfully, providing more relevant information than sensory irritation studies in animals. Against the background of chemoperception as a dominant window of the brain on the outside world, nasal neurotoxicology is rapidly developing, focusing on olfactory and trigeminal nerve toxicity. Better insight in the processes underlying neurogenic inflammation may increase our knowledge of the causes of the various chemical sensitivity syndromes. Nasal immunotoxicology is extremely complex, which is mainly due to the pivotal role of nasal lymphoid tissue in the defense of the middle ear, eye, and oral cavity against antigenic substances, and the important function of the nasal passages in brain drainage in rats. The crucial role of tissue damage and reactive epithelial hyperproliferation in nasal carcinogenesis has become overwhelmingly clear as demonstrated by the recently developed biologically based model for predicting formaldehyde nasal cancer risk in humans. The evidence of carcinogenicity of inhaled complex mixtures in experimental animals is very limited, while there is ample evidence that occupational exposure to mixtures such as wood, leather, or textile dust or chromium- and nickel-containing materials is associated with increased risk of nasal cancer. It is remarkable that these mixtures are aerosols, suggesting that their "particulate nature" may be a major factor in their potential to induce nasal cancer. Studies in rats have been conducted with defined mixtures of nasal irritants such as aldehydes, using a model for competitive agonism to predict the outcome of such mixed exposures. When exposure levels in a mixture of nasal cytotoxicants were equal to or below the "No-Observed-Adverse-Effect-Levels" (NOAELs) of the individual chemicals, neither additivity nor potentiation was found, indicating that the NOAEL of the "most risky chemical" in the mixture would also be the NOAEL of the mixture. In vitro models are increasingly being used to study mechanisms of nasal toxicity. However, considering the complexity of the nasal cavity and the many factors that contribute to nasal toxicity, it is unlikely that in vitro experiments ever will be substitutes for in vivo inhalation studies. It is widely recognized that a strategic approach should be available for the interpretation of nasal effects in experimental animals with regard to potential human health risk. Mapping of nasal lesions combined with airflow-driven dosimetry and knowledge about local metabolism is a solid basis for extrapolation of animal data to humans. However, more research is needed to better understand factors that determine the susceptibility of human and animal tissues to nasal toxicants, in particular nasal carcinogens.

-------------------------------------------------------------------------------------------------------------------------------------

(2001) [Allergy and the environment].

The prevalence of allergic diseases has increased in modern Western countries during the last decades. Among the hypotheses for the reasons the idea that environmental pollutants may play a role is intensively discussed. In order to characterise the
influence of these pollutants on the development, elicitation and chronification of allergic reactions (allergotoxicology) epidemiological, clinical and experimental data have to be considered. These investigations showed that among the pollutants with an enhancing effect on allergic diseases pollution types with nitrogen oxides (NOx), ozone (O3), tobacco smoke, particulate matter and diesel exhaust particles are of special interest.

Davis, AM and Inturrisi, CE Journal/Brain Res. 894: 150-3.

N-methyl-D-aspartate (NMDA) receptor antagonists may be of value in the management of hyperalgesia. LY235959, a competitive NMDA receptor antagonist, at doses of 0.001 and 0.003 nmol, intrathecally (i.t.) blocked the hyperalgesia induced by 11.1 nmol of NMDA in rats prepared with a chronic i.t. cannula. However, LY235959 does not block the hyperalgesia produced by kainic acid (a non-NMDA glutamate receptor agonist) providing evidence of its selectivity for the NMDA receptor. Using the formalin nociceptive test, 0.001 nmol LY235959 (i.t.) significantly reduced the number of Phase 2 flinches by about 80%. LY235959 can also reduce the flinching in Phase 2 by 30% when given subcutaneously (s.c.) at the lowest dose which does not produce motor deficits (20 mmol/kg). Thus, LY235959 (i.t. or s.c.) has NMDA receptor antagonist activity as defined by its ability to prevent hyperalgesia and formalin-induced central sensitization. Moreover, it is a much more potent antihyperalgesic after i.t. as compared to s.c. administration.


Diisopropyl phosphorofluoridate (DFP) produces organophosphorus-ester induced delayed neurotoxicity (OPIDN) in the hen, human and other sensitive species. We studied the effect of single dose of DFP (1.7 mg/kg/s.c.) on the expression of alpha tubulin which is one of the major sub-unit of tubulin polymers that constitute an important constituent of cellular architecture. The hens were sacrificed at different time points i.e. 1, 2, 5, 10, and 20 days. Total RNA was extracted from the following brain regions: cerebrum, cerebellum, and brainstem as well as spinal cord. Northern blots prepared using standard protocols were hybridized with alpha tubulin as well as with
beta-actin and 28S RNA cDNA (controls) probes. The results indicate a differential spatial/temporal regulation of alpha tubulin levels which may be the result of perturbed microtubule dynamics not only in the axons but also in perikarya of neurons in the CNS of DFP treated hens. In the highly susceptible tissues like brainstem and spinal cord the initial down-regulation of mRNA levels could be attributed to DFP induced stress response resulting in inhibited cell metabolism and or cell injury/cell death. Increase in levels of mRNA at 5 days and thereafter coincided with increased tubulin transport which may be due to increased phosphorylation of tubulins in both axons and perikarya and other intraaxonal changes resulting in impaired axonal transport. DFP induced decreased rate of tubulin polymerization resulting in increased levels of free tubulin monomers may be involved in the altered alpha tubulin mRNA expression at different time points by autoregulatory circuits. Cerebellum being the less susceptible tissue showed only a moderate decline at day 2, while the alpha tubulin remained at near control levels at day 1. Delayed down-regulation may be due to the co-ordinated up or down-regulation of different sub-types of alpha and beta tubulins as well as the differential response of specialised cell types in cerebellum. Continuous overexpression of alpha tubulin in cerebrum from the beginning may be its effective protective strategy to safeguard itself from neurotoxicity. Differential expression pattern observed could be due to the differential susceptibility and variability in the rate of axonal transport of different regions besides the tubulin heterogenity of CNS. Hence our results indicte differential expression of alpha tubulin is either one of the reasons for the development of OPIDN or the result of progressive changes taking place during OPIDN.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11703163


BACKGROUND: Asthma places huge demands on health-care services, and its prevalence is increasing. Reduction of exposure to environmental allergens could offer a realistic chance for primary prevention. Our aim was to ascertain whether or not living in a low-allergen environment reduces the risk of asthma and atopic diseases in infants. METHODS: We assigned infants to four risk groups according to parental
atopic status. We enrolled 291 high-risk couples (both parents atopic, no pets) into a prospective, prenatally randomised, cohort study, and allocated them to environmental manipulation, in which measures to reduce prenatal and postnatal allergen exposure were undertaken (active HRA) \( n=145 \) or no intervention (control HRC) \( n=146 \). Two further prospective groups were studied: 161 high-risk infants with pets in the home (HRP group) and 168 low-risk infants, whose parents were both non-atopic (LR group). The main outcome measures were signs and symptoms of atopic disease at 1 year of age. FINDINGS: 103 families dropped out or were lost to follow up. At age 1 year we followed-up 133 HRA, 118 HRC, 140 HRP, and 126 LR infants. Children in the HRA group were less likely to have respiratory symptoms during the first year of life than those in the HRC group. The most pronounced differences were in the relative risks for severe wheeze with shortness of breath (relative risk 0.44 [95% CI 0.20-1.00]), prescribed medication for the treatment of wheezy attacks (0.58 [0.36-0.95]), and wheezing after vigorous playing, crying, or exertion (0.18 [0.04-0.79]). Probability of respiratory symptoms in HRC and HRP infants was similar, whereas it was much lower in the LR than in the HRC group. Cat ownership was significantly associated with sensitisation to cats (24.6 [3.04-199.05]; \( p=0.003 \)). INTERPRETATION: Environmental manipulation reduces some respiratory symptoms in the first year of life in high-risk infants. Further follow up is needed, however, to ascertain whether living in a low-allergen environment reduces allergy and asthma in later life.

(2001) **Chronic fatigue.**

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11732103

(2001) **Gene therapy to prevent organophosphate intoxication.**

The specific hydrolytic activity of PON1 paraoxonase/arylesterase enzymes in liver and blood provides a natural barrier against the entry of organophosphate toxins into the central and peripheral nervous systems. Inherited differences in PON1 enzyme concentrations may determine levels of susceptibility to organophosphate injury in humans. To test whether boosting serum levels of PON1 enzymes by gene therapy might provide increased protection, we compared the degree of inactivation of whole brain acetylcholinesterase of mice exposed to chlorpyrifos 4 days after intravenous injection of recombinant adenoviruses containing PON1-LQ or PON1-LR genes or no PON1 gene. Both recombinant viruses containing PON1 genes boosted serum
aryl esterase concentrations by approximately 60% and significantly prevented the inactivation of brain acetylcholinesterase. Some mice were completely protected. These findings indicate that boosting serum levels of PON1 enzymes by a gene delivery vector raises the threshold for organophosphate toxicity by hydrolytic destruction before the chemical can enter the brain.


The symptom of chemical intolerance may occur in isolation, but often occurs in conjunction with other chronic symptoms such as pain, fatigue, memory disturbances, etc. This frequent clustering of symptoms in individuals has led to the definition of several chronic multisymptom syndromes, such as multiple chemical sensitivity, fibromyalgia, chronic fatigue syndrome, and Gulf War illnesses. The aggregate research into these syndromes has suggested some unifying mechanisms that contribute to symptomatology. Multiple lines of evidence suggest that there is aberrant function of numerous efferent neural pathways, such as the autonomic nervous system and hypothalamic-pituitary axes, in subsets of individuals with these conditions. There is perhaps the greatest evidence for abnormal sensory processing in these syndromes, with a low "unpleasantness threshold" for multiple types of sensory stimuli. Psychological and behavioral factors are known to play a significant role in initiating or perpetuating symptoms in some persons with these illnesses. In the field of pain research, the interrelationship between physiologic and psychologic factors in symptom expression has been well studied. Using both established and novel methodologies, studies have suggested that psychologic factors such as hypervigilance and expectancy are playing a relatively minor role in most individuals with fibromyalgia and that clear evidence exists of physiologic amplification of sensory stimuli. These studies need to be extended to more sensory tasks and to larger numbers of subjects with related conditions. It is of note, though, that existing data on this spectrum of illnesses would suggest that there may be greater psychologic contributions to symptomatology if an illness is defined in part by behavior (e.g., avoidance of chemical exposures) rather than on the basis of symptoms alone.


Organo psycho syndrome (OPS) or chronic toxic encephalopathy (CTE) is a neurotoxic condition reported following long-term exposure to paints containing organic solvent and to other solvents. Lactate esters are finding wider use as solvents. Lactate esters have been well studied in standard toxicity tests, but specific neurotoxicity studies have not been conducted. No clinical signs of chronic neurotoxicity have been observed in standard toxicity tests. Lactate esters are rapidly hydrolyzed in the body to lactic acid and the corresponding alcohol. Alcohols have been reported to have acute neurotoxic effects, usually following high levels of ingestion. The literature on alcohols was reviewed to establish the no-observed-adverse-effect level (NOAEL) for acute neurotoxicity and to look for any evidence of chronic neurotoxicity from the alcohols produced by hydrolysis of the lactate esters. The NOAELs were compared with the potential amounts of alcohol produced by hydrolysis of different lactate esters at 200 mg/m(3) (the NOAEL for most of the lactate esters). In all cases neither acute nor chronic neurotoxicity would be expected based on the amounts of alcohol produced by hydrolysis of the lactate esters at their NOAELs. L-Lactic acid is a normal metabolite in the body and is not considered neurotoxic. Based on this information there is no evidence to suggest that L-lactate esters can cause any chronic neurotoxicity, OPS, or CTE.

(2001) [Approach to diagnosing and computing a massive noninfectious disease connected with environmental factors]. Chiburaev, VI, Fokin, MV and Pilishenko, VA Journal/Gig Sanit. 41-5.


We evaluated the relationship between the toxicity induced by the organophosphate mevinphos (Mev) and inducible nitric oxide synthase (iNOS) in the rostral ventrolateral medulla (RVLM), the medullary origin of sympathetic neurogenic vasomotor tone. Adult Sprague-Dawley rats that were anesthetized and maintained with propofol were used.
Laser scanning confocal microscopic analysis revealed colocalization of the M2 subtype of muscarinic receptors (M(2)R) and iNOS immunoreactivity in RVLM neurons. Comicroinjection bilaterally of Mev (10 nmol) and artificial cerebrospinal fluid (aCSF) into the RVLM elicited a progressive decline in systemic arterial pressure (SAP) and heart rate. This was accompanied during phase 1 Mev intoxication by an increase in the power density of the very high-frequency (VHF; 5-9 Hz), high-frequency (HF; 0.8-2.4 Hz), low-frequency (LF; 0.25-0.8 Hz) and very low-frequency (VLF; 0-0.25 Hz) components of SAP signals. Phase 2 exhibited a reversal of the VHF and VLF power to control levels and a further reduction in the power density of both HF and LF components to below baseline. Hypotension and bradycardia promoted by Mev were significantly blunted on coadministration into the RVLM of the selective iNOS inhibitors S-methylisothiourea (250 pmol) or aminoguanidine (250 pmol). Not only was the augmented power density of HF and LF components during phase 1 Mev intoxication further enhanced, the reduced power of these two spectral components during phase 2 was appreciably antagonized. On the other hand, the temporal changes in VHF and VLF power were essentially the same as with coadministration of Mev and aCSF. We conclude that, as a cholinesterase inhibitor, Mev may induce toxicity via nitric oxide produced by iNOS on activation of the M(2)R by the accumulated acetylcholine in the RVLM.


This review addresses the issue of how axotomy of peripheral nerve fibers leads to pain and hyperalgesia. The point of axotomy (the nerve injury site), the dorsal root ganglia, and the dorsal horn of the spinal cord are candidate sites for generation of the pain signal that is likely to be critical for maintaining the neuropathic pain state. This review considers neuropathic pain from a "systems" perspective, tracing concepts of neuropathic pain from the work of Henry Head to the present. Surprisingly, the nerve injury site and the dorsal root ganglion belonging to a transected spinal nerve do not give rise to spontaneous activity in putative C-fiber nociceptors. The intact nociceptor belonging to adjacent uninjured spinal nerves, however, does acquire abnormal spontaneous activity and a chemical sensitivity to catechols. It is suggested that partially denervated tissues in the nerve, skin, and other locations may release substances that, in turn, sensitize the intact nociceptors. These abnormalities in the intact nociceptor, which arise in the context of Wallerian degeneration, probably play a role in creating or maintaining the abnormal pain state. These considerations probably also apply to the understanding of pain arising in other neuropathies. The findings relative to the "intact" nociceptor provide a rationale by which to understand how therapies distal to the nerve injury site may diminish pain.

Molds grow readily indoors in the presence of dampness. Their visibility enables their effects to be investigated by means of questionnaire surveys, although these are subject to imprecision and potential bias. Exposure to airborne mold particles can be measured in various ways that also have disadvantages and limitations. Many surveys have been conducted on the health effects of molds; most have examined the association between molds and symptoms, although some studies have used lung function tests and other objective health indices. Most surveys suggest that indoor mold growth is associated with ill health, particularly of the respiratory tract. Knowing how important mold exposure really is in health terms is difficult, owing to the tendency for mold growth to be associated with other factors that are prejudicial to health.

(2001) Trauma and Posttraumatic Stress Disorder in Primary Care Patients. 

BACKGROUND: This article examines the nature of psychological trauma and posttraumatic stress disorder (PTSD) in 504 patients recruited from primary care settings. METHOD: Patients were screened for anxiety in waiting rooms at 14 general medical settings, and those with a sufficient number and severity of anxiety symptoms were administered a standardized diagnostic clinical interview. Those who met DSM-IV criteria for an anxiety disorder and who were willing to participate were included in this study. Of the 504 patients, 185 met DSM-IV criteria for PTSD. RESULTS: Results indicated that 418 (83%) of primary care patients in our sample reported at least 1 traumatic event in their lifetime. The most prevalent traumas experienced by the entire sample of participants were witnessing others being seriously injured or killed, serious accidents, and rape. Of those participants with PTSD, rape was the strongest predictor of a PTSD diagnosis. Analyses examining gender differences indicated that, for women, a history of other unwanted sexual contact or witnessing a sexual assault, being attacked with a weapon or with intent to kill, or witnessing someone being injured were found to be risk factors for a PTSD diagnosis. Examination of clinical characteristics indicated a high rate of comorbidity of psychiatric disorders among patients with PTSD, including high rates of alcohol/substance abuse, depression, and suicide attempts. CONCLUSION: These findings emphasize the continued need to assess patients presenting at general medical facilities about trauma history.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15014575

(1) Respiratory distress and seizures developed in an 18-month-old boy following brief exposure to low-strength (17.6%) N,N-diethyl-m-toluamide (DEET). A review of the literature revealed 17 reports of DEET-induced encephalopathy in children. The objective of this study was to test the hypothesis that the potential toxicity of DEET is high and that available repellents containing DEET, irrespective of their strength, are not safe when applied to children's skin. (2) Although this is a case report, we used the features of published reports of DEET-induced encephalopathy in children to support the diagnosis, since the evidence that the child's illness was caused by DEET was circumstantial. In the following case analysis, clinical reports of children < 16 years old have been reviewed and analyzed in an effort to relate direct DEET toxicity to various clinical, demographic, and toxic compound exposure factors (Fisher's exact test and logistic regression analysis). (3) DEET-induced encephalopathy in children (56% girls) followed not only ingestion or repeated and extensive application of repellents, but also a brief exposure to DEET (45%). Of those who reported a dermal exposure, 33% reported an exposure to a product containing DEET < 20%. Seizures, the most prominent symptom (72%), were significantly more frequent when DEET solutions were applied to the skin (P<0.01). Mortality (16.6%) did not correlate significantly with the concentration of the DEET liquid used, duration of skin exposure, pattern of use, age, or sex. (4) Data of this case analysis suggest that repellents containing DEET are not safe when applied to children's skin and should be avoided in children. Additionally, since the potential toxicity of DEET is high, less toxic preparations should be probably substituted for DEET-containing repellents, whenever possible.


Idiopathic environmental intolerances (IEI)/multiple chemical sensitivity (MCS) is characterized by various somatic symptoms which cannot be explained organically, but are attributed to the influences of toxic environmental chemicals in low, usually harmless doses. In the absence of a widely accepted definition of IEI, contradictory aetiological hypotheses and therapeutic suggestions are discussed. Some authors doubt the existence of IEI/MCS as a disease entity of its own. The label IEI does not implicate neither a diagnosis of somatic disease nor that it is caused by an avoidable exposure. Many IEI patients suffer from psychiatric diseases. A majority of them can be diagnosed as somatoform disorders. Consequently, psychiatric therapies could be effective. This review describes the current knowledge about IEI/MCS, outlines a
diagnostic algorithm and a psychotherapeutic concept for variants of IEI understood as a somatoform disorder.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11576318

(2001) **Enhanced flow-dependent vasodilatation after bed rest, a possible mechanism for orthostatic intolerance in humans.**
Bonnin, P, Ben Driss, A, Benessiano, J, Maillet, A, Pavy le Traon, A and Levy, BI

We investigated the alteration in flow-dependent-dilatation in the orthostatic intolerance occurring after bed-rest deconditioning. Eight men [aged mean (SEM) 32 (2) years] underwent two consecutive periods of 7 days of head-down-tilt (HDT, -6 degrees) during bed rest. A control age and sex matched group [n = 8, 30 (2) years], maintained its usual physical activity. Blood flow velocity (BFV) and diameter (Doppler and echotracking systems) were measured in the brachial artery, under basal conditions and during the post ischaemic hyperaemia following occlusion. The increase in BFV post-ischaemia did not change before, during and after HDT but the relative increase in the diameter was greater on the 7th day of the HDT period than before HDT [+8.8(1.6)% compared to +3.7(1.0)%, P < 0.001]. After HDT, 11 of 16 standing tests (comprising eight subjects in the two HDT periods) had to be stopped because of orthostatic intolerance. The flow-dependent-dilatation measured at the end of HDT was negatively correlated with the post-bed-rest duration of orthostatic tolerance (r = 0.78, P < 0.01). After the sublingual administration of glyceryl trinitrate, there was no change in the increase in diameter. No significant changes were observed in the control group. Bed-rest deconditioning enhances the flow-dependent vasodilatation of large arteries and might contribute to the orthostatic intolerance observed following bed-rest.

---------------------------------------------------------------

(2001) **[Microelement dysbalance as a factor for ecologically-caused disease].**
Boev, VM, Utenina, VV, Bystrykh, VV, Utenin, VV, Perepelkin, SV, Setko, AG and kuksanov, VF
Journal/Gig Sanit. 68.

---------------------------------------------------------------

(2001) **The Iowa follow-up of chemically sensitive persons.**
Black, DW, Okiishi, C and Schlosser, S
Clinical symptoms and self-reported health status in persons reporting multiple chemical sensitivities (MCS) are presented from a 9-year follow-up study. Eighteen (69%) subjects from a sample of 26 persons originally interviewed in 1988 were followed up in 1997 and given structured interviews and self-report questionnaires. In terms of psychiatric diagnosis, 15 (83%) met DSM-IV criteria for a lifetime mood disorder, 10 (56%) for a lifetime anxiety disorder, and 10 (56%) for a lifetime somatoform disorder. Seven (39%) of subjects met criteria for a personality disorder using the Personality Diagnostic Questionnaire-IV. Self-report data from the Illness Behavior Questionnaire and Symptom Checklist-90-Revised show little change from 1988. The 10 most frequent complaints attributed to MCS were headache, memory loss, forgetfulness, sore throat, joint aches, trouble thinking, shortness of breath, back pain, muscle aches, and nausea. Global assessment showed that 2 (11%) had "remitted", 8 (45%) were "much" or "very much" improved, 6 (33%) were "improved", and 2 (11%) were "unchanged/worse". Mean scores on the SF-36 health survey showed that, compared to U.S. population means, subjects reported worse physical functioning, more bodily pain, worse general health, worse social functioning, and more emotional-role impairment; self-reported mental health was better than the U.S. population mean. All subjects maintained a belief that they had MCS; 16 (89%) acknowledged that the diagnosis was controversial. It is concluded that the subjects remain strongly committed to their diagnosis of MCS. Most have improved since their original interview, but many remain symptomatic and continue to report ongoing lifestyle changes.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000035

(2001) Etiology of uveitis in rural and urban areas of mid-eastern Poland.

The aim of this study was to assess and compare the frequencies of uveitis etiology in inhabitants of rural and urban areas of mid-eastern Poland. We reviewed the cases of 563 patients (263 males, 300 females; aged 2-87) with uveitis, treated at the 1st Department of Ophthalmology at the Medical Academy in Lublin and at the District Ophthalmic Hospital in Kielce, Poland, from January 1996-December 2000. Anatomical classification of uveitis was used according to the International Uveitis Study Group and etiological classification including uveitis associated with trauma, infection, systemic disease, non-associated with a systemic disease and masquerade syndromes. Data regarding age, gender, place of residence, anatomical location and etiology of uveitis were obtained. Statistical analyses were performed using Pearson's chi-square test, Spearman's rank correlation test and logistic regression. Etiology of uveitis was established in 70.0% of cases. The most common cause of uveitis was infection. Patients from rural areas were significantly more likely to have uveitis of infectious origin whereas patients from urban areas significantly more likely to have
uveitis associated with a systemic disease. In conclusion, the pattern of uveitis in mid-eastern Poland confirms the influence of environmental factors on the etiology of this heterogeneous disease.


BACKGROUND: A growing body of evidence suggests that idiopathic environmental intolerance (IEI) is a psychophysiologic disorder with prominent features of anxiety panic and somatization, although proponents of a toxicogenic explanation claim, despite a lack of convincing evidence, that symptoms arise from exposure to otherwise nonnoxious environmental agents. Patient behaviour is characterized by strenuous avoidance of perceived triggers to the point of severe impairment of normal social and vocational functioning. IEI proponents claim that previous studies showing a high prevalence of psychopathology in patients with IEI and studies showing panic responses to known panicogenic challenges merely reflect the anxiety-producing result of living with IEI. OBJECTIVE: We explored whether IEI and panic disorder, personality traits, or both shared an underlying neurogenetic basis that would predate the anxiety of IEI symptomatology. The DNA of patients with IEI was examined for the presence of known panic disorder-associated cholecystokinin B (CCK-B) receptor alleles and for personality trait-associated dopamine D4 receptor polymorphisms. METHODS: Eleven patients with typical IEI symptoms were recruited and were individually matched to normal control subjects from an existing bank for age, sex, and ethnic background. Genomic DNA was extracted from peripheral blood samples. CCK-B and dopamine D4 receptor polymorphisms were examined by using standard PCR-based techniques. RESULTS: There was a significantly higher prevalence of the panic disorder-associated CCK-B receptor allele 7 in subjects with IEI (9/22 [40.9%]) compared with control subjects (2/22 [9.1%], P = .037). There was no difference in personality trait-associated polymorphisms of the gene encoding dopamine D4 receptor between patients and control subjects. CONCLUSIONS: These findings provide preliminary evidence that IEI and panic disorder share a common neurogenetic basis, which would predate the anxiety-producing effects of IEI symptoms. Further studies with larger samples are warranted, but these results support previous studies that suggest that panic disorder may account for much of the symptomatology in at least some cases of IEI and provide a basis for rational treatment strategies.

(2001) **Environmental illness: evaluation of salivary flow, symptoms, diseases, medications, and psychological factors.**

Patients with symptoms allegedly caused by abnormal sensitivity to dental fillings and or to electromagnetic fields and other environmental factors frequently report oral complaints. Forty-four consecutive patients with these symptoms were studied. The aim was to investigate whether unstimulated salivary flow rate was associated with Candida, symptoms, disease, medication, age, sex, anxiety, depression, and stress. Furthermore, the aim was to compare the level of anxiety, depression, and stress in these patients with an age- and sex-matched control group. Fifty percent had no or low flow rate from the minor salivary glands. Candida pseudohyphae were found in 50% of the patients. Hypothyroidism and/or intake of thyroid hormones, headache, fatigue, and age were negatively associated with unstimulated salivary flow rate, and dizziness was positively associated. Unstimulated salivary flow rate was positively associated with stimulated salivary flow rate and flow rate from the minor salivary glands. Burning mouth and subjective oral dryness were reported by 48%, and 46%, respectively. The patients were more anxious, stressed, and especially more depressed than the control group. Unstimulated salivary flow rate was negatively associated with state anxiety. Measurement of salivary flow rate is important in patients with environmental illness and can be used in combination with other measurements as a diagnostic tool.

-----------------------------------

(2001) **Indicators for population and individual risk in assessing the effect of environmental factors on the health of children.**
Berdnik, OV, Serykh, LV and Antomonov, M Journal/Gig Sanit. 94-7.

Populational studies define a risk for abnormalities forming in children residing in varying polluted areas and compare it with the risk due to other health-forming factors. To define an individual risk, the authors have developed scales rating the likelihood of abnormalities that can occur in each child in relation to the biomedical or social risk factors in children, to their residence in poor environmental areas, to the child's age and sex.

-----------------------------------

(2001) **EEG beta 1 oscillation and sucrose sensitization in fibromyalgia with chemical intolerance.**

Patients with fibromyalgia (FM) have diffuse musculoskeletal pain; half report concomitant intolerance for low levels of environmental chemicals (CI). Previous
investigators have hypothesized that the chronic pain and chemical intolerance reflect sensitization of different central nervous system limbic and/or mesolimbic reward pathways. We evaluated electroencephalographic (EEG) beta activity and blood glucose responses of FM patients with and without CI and normals during three repeated sucrose ingestion sessions and during a final, water-only session (testing for conditioning). The FM with CI exhibited oscillation (reversal in direction of change from session to session) at rest and then sensitization (progressive amplification) of EEG beta 1 over time across the 3 sucrose sessions versus controls. FM with CI showed sensitization of blood glucose over the 3 sucrose sessions, which, like the EEG findings, reverted toward baseline in the final water-only session. The data suggest that the subset of FM patients with CI have increased susceptibility to oscillation and physiological sensitization without conditioning, perhaps contributing to fluctuations in their chronic course.


(2001) Sensitization studies in chemically intolerant individuals: implications for individual difference research.

Chemical intolerance (CI) is an individual difference trait in which persons report feeling ill in multiple physiological systems from low levels of a wide range of chemically unrelated environmental substances. This paper discusses the neural sensitization model for progressive host amplification of polysymptomatic responses elicited by chemical exposures following an initiating event. The sensitization model accommodates hypotheses for initiating and eliciting CI in human populations that involve both environmental chemicals and physical or psychological stressors. Recent studies in this laboratory have demonstrated sensitization in individuals with CI over repeated sessions for dependent variables such as electroencephalographic (EEG) activity and diastolic blood pressure. Psychological distress variables alone do not explain these findings. Individuals with CI and/or vulnerability to sensitization share specific characteristics, for example, female gender, certain genetic background (offspring of alcohol-preferring parents), and personal preference for high sugar carbohydrate intake. Overall, the data suggest that the 15-30% of the general population who report heightened CI are highly sensitizable. Sensitizability may serve an adaptive, sentinel function in threatening environments with poor signal-to-noise ratios. However, as sensitization gradually shifts operating set points of physiological systems out of the normal range in response to allostatic load, this process may contribute to the development of chronic, polysymptomatic health conditions such as multiple chemical sensitivity and/or fibromyalgia. Individual response specificity and stereotypy rather than toxicant properties may determine which types of central, autonomic, and/or peripheral nervous system dysfunctions manifest at subclinical and clinical levels.
query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12000034

(2001) [Connection between changes in the nasal and mouth mucosa with immune status under the effect of environmental factors].

The paper summarizes the results of determination of the cytological status of nasal and oral mucosae in 789 preschool and school children from different cities and towns of the Russian Federation: Moscow, Klimovsk, Yaroslavl. A relationship between the mucosae, immunity, and morbidity, and environmental pollution is shown in the town of Klimovsk as an example.


Physicians qualified in environmentally related disorders due to their participation in special training courses in the Federal State of Schleswig-Holstein (Germany) used a standardised questionnaire to report on their environmental medicine related cases. The course of the illness, if known, has been documented on a separate data sheet. During the period from 1995-1999 916 cases and 508 courses of illness were assessed. The environmental factors/toxicants of exposure most frequently documented by the 85 participating physicians and found to be related to symptoms of illness were biocides (mainly insecticides used indoors for pest control (32%), moulds (27%), dental amalgam (22%), solvents/volatile organic compounds (21%) and formaldehyde (16%), respectively. In 42% of the documented cases an exposure to more than one environmental factor/toxicant was registered. Age distribution, gender, location of exposure as well as the symptoms of illness of the patients were found to be dependent on the type of exposure. Cessation of exposure to harmful substances environments was achieved in 54% of those cases where information regarding the course of the illness was given. In 65% of these cases recovery was reported and 30% recovered partially. In those cases where a cessation of exposure could not be achieved or was not complete, no or only partial recovery was mostly reported. From these results it may be concluded that research work on environmentally related disorders should be enforced in order to prevent unnecessary illness and to lower the public health system expenditure.

The primary health effects of radiation are traditionally believed to result from cellular genetic damage. These effects are believed to result in a statistically detectable increase in the induction of cancer in exposed populations. A significant number of residents of areas affected by the Chernobyl disaster and workers involved in the clean-up ('liquidators') have reported debilitating physical illnesses that cannot be easily explained by a genetic effect. This paper presents results of a literature search that strongly suggests that a previously unrecognized neural pathway may be responsible for the induction of these debilities. In addition, a common link between radiation and chemical sensitivity syndromes may now be identified.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11601868


BACKGROUND: about one fourth of patients with chronic idiopathic urticaria (CIU) experience flares of hives after taking chemically unrelated nonsteroidal anti-inflammatory drugs (NSAID). The reasons for such intolerance are still elusive. OBJECTIVE: this study aimed to investigate NSAID intolerance in patients with CIU in view of the in vivo and in vitro histamine releasing activity of their sera. METHODS: 117 adults (M/F 41/76) with CIU underwent intradermal test with autologous serum, and the ability of their sera to induce histamine release from normal blood donors was evaluated. NSAID intolerance was ascertained by careful interview. RESULTS: overall, 32/117 (27 %) patients reported NSAID intolerance. The prevalence on NSAID intolerance did not differ in the three subgroups: negative on both in vivo and in vitro tests (9/36; 25 %), positive or intradermal test but negative on basophil histamine release assay (16/58; 28 %), or positive on both in vivo and in vitro tests (7/23; 30 %). CONCLUSION: in patients with CIU intolerance to NSAID does not depend on the mechanism of histamine release.

Artinian, LR, Ding, JM and Gillette, MU Journal/Exp Neurol. 171: 293-300.
Within the central nervous system, acetylcholine (ACh) functions as a state-dependent modulator at a range of sites, but its signaling mechanisms are yet unclear. Cholinergic projections from the brain stem and basal forebrain innervate the suprachiasmatic nucleus (SCN), the master circadian clock in mammals, and cholinergic stimuli adjust clock timing. Cholinergic effects on clock state require muscarinic receptor-mediated activation of guanylyl cyclase and cGMP synthesis, although the effect is indirect. Here we evaluate the roles of carbon monoxide (CO) and nitric oxide (NO), major activators of cGMP synthesis. Both heme oxygenase 2 (HO-2) and neuronal nitric oxide synthase (nNOS), enzymes that synthesize CO and NO, respectively, are expressed in rat SCN, with HO-2 localized to the central core of the SCN, whereas nNOS is a punctate plexus. Hemin, an activator of HO-2, but not the NO donor, SNAP, mimicked cholinergic effects on circadian timing. Selective inhibitors of HO fully blocked cholinergic clock resetting, whereas NOS inhibition partially attenuated this effect. Hemoglobin, an extracellular scavenger of both NO and CO, blocked cholinergic stimulation of cGMP synthesis, whereas l-NAME, a specific inhibitor of NOS, had no effect on cholinergic stimulation of cGMP, but decreased the cGMP basal level. We conclude that basal NO production generates cGMP tone that primes the clock for cholinergic signaling, whereas HO/CO transmit muscarinic receptor activation to the cGMP-signaling pathway that modulates clock state. In light of the recently reported inhibitory interaction between HO-2/CO and amyloid-beta, a marker of Alzheimer's disease (AD), we speculate that HO-2/CO signaling may be a defective component of cholinergic neurotransmission in the pathophysiology of AD, whose manifestations include disintegration of circadian timing.


Cockroach allergy has been recognized as an important cause of asthma. Exposure to high levels of cockroach allergens in the home is a major risk factor for symptoms in sensitized individuals. Previously identified allergens from Blatella germanica and Periplaneta americana include Bla g 2 (inactive aspartic proteinase), Bla g 4 (calycin), Bla g 5 (glutathione-S-transferase), Bla g 6 (troponin), the Group 1 cross-reactive allergens Bla g 1 and Per a 1, Per a 3 (arylphorin), and Per a 7 (tropomyosin). The primary site of cockroach allergen accumulation is the kitchen. However, lower levels of allergen can be found in bedding, on the bedroom floor, and in sofa dust. Strategies for decreasing exposure to cockroach have been investigated. The results suggest that a sustained decrease in cockroach allergen levels is difficult to accomplish, even after successful extermination of cockroach populations. The use of recombinant cockroach allergens may lead to the development of new approaches to asthma treatment in the future.
(2001) 1,3-Butadiene: Human health aspects.
This CICAD on 1,3-butadiene was prepared by the Environmental Health Directorate of Health Canada based on documentation prepared concurrently as part of the Priority Substances Program under the Canadian Environmental Protection Act (CEPA). The objective of health assessments on Priority Substances under CEPA is to assess the potential effects of indirect exposure in the general environment on human health. Data identified as of the end of April 1998 were considered in this review. Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Helsinki, Finland, on 26-29 June 2000. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 0017) for 1,3-butadiene, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.
1,3-Butadiene (CAS No. 106-99-0) is a product of incomplete combustion resulting from natural processes and human activity. It is also an industrial chemical used primarily in the production of polymers, including polybutadiene, styrene-butadiene rubbers and lattices, and nitrile-butadiene rubbers. 1,3-Butadiene enters the environment from exhaust emissions from gasoline- and diesel-powered vehicles, from non-transportation fuel combustion, from biomass combustion, and from industrial on-site uses. While 1,3-butadiene is not persistent, it is ubiquitous in the urban environment because of its widespread combustion sources. The highest atmospheric concentrations have been measured in air in cities and close to industrial sources. The general population is exposed to 1,3-butadiene primarily through ambient and indoor air. In comparison, other media, including food and drinking-water, contribute negligibly to exposure to 1,3-butadiene. Tobacco smoke may contribute significant amounts of 1,3-butadiene. Metabolism of 1,3-butadiene appears to be qualitatively similar across species, although there are quantitative differences in the amounts of putatively toxic metabolites formed; mice appear to oxidize 1,3-butadiene to the monoepoxide, and subsequently the diepoxide, metabolite to a greater extent than do rats or humans. However, there may also be interindividual variation in metabolic capability for 1,3-butadiene in humans, related to genetic polymorphism for relevant enzymes. 1,3-Butadiene is of low acute toxicity in experimental animals. However, long-term exposure to 1,3-butadiene was associated with the development of ovarian atrophy at all concentrations tested in mice. Other effects in the ovaries have also been observed in shorter-term studies. Atrophy of the testes was also observed in male mice at concentrations greater than those associated with effects in females. Based on limited available data, there is no conclusive evidence that 1,3-butadiene is teratogenic in experimental animals following maternal or paternal exposure or that it induces significant fetal toxicity at concentrations below those that are maternally toxic.
1,3-Butadiene also induced a variety of effects on the blood and bone marrow of mice; although data are limited, similar effects have not been observed in rats. Inhaled 1,3-butadiene is a potent carcinogen in mice, inducing tumours at multiple sites at all concentrations tested in all identified studies. 1,3-Butadiene was also carcinogenic in rats at all exposure levels in the only relevant study available; although only much higher concentrations were tested in rats than in mice, rats appear to be the less sensitive species, based on comparison of tumour incidence data. The greater sensitivity in mice than in rats to induction of these effects by 1,3-butadiene is likely related to species differences in metabolism to the active epoxide metabolites. 1,3-Butadiene is mutagenic in somatic cells of both mice and rats, although the mutagenic potency was greater in mice than in rats. Similarly, 1,3-butadiene induced other genetic damage in somatic cells of mice, but not in those of rats. 1,3-Butadiene was also consistently genotoxic in germ cells of mice, but not in the single assay in rats identified. However, there were no apparent differences in species sensitivity to genetic effects induced by epoxide metabolites of 1,3-butadiene. There is also limited evidence from occupationally exposed populations that 1,3-butadiene is genotoxic in humans, inducing mutagenic and clastogenic damage in somatic cells. An association between exposure to 1,3-butadiene in the occupational environment and leukaemia fulfils several of the traditional criteria for causality. In the largest and most comprehensive study conducted to date, involving a cohort of workers from multiple plants, mortality due to leukaemia increased with estimated cumulative exposure to 1,3-butadiene in the styrene-butadiene rubber industry; this association remained after controlling for exposure to styrene and benzene and was strongest in those subgroups with highest potential exposure. Similarly, an association between exposure to 1,3-butadiene and leukaemia was observed in an independently conducted case-control study of largely the same population of workers. However, there was no increase in mortality due to leukaemia in butadiene monomer production workers who were not concomitantly exposed to some of the other substances present in the styrene-butadiene rubber industry, although there was some limited evidence of an association with mortality due to lymphosarcoma and reticulosarcoma in some subgroups. The available epidemiological and toxicological data provide evidence that 1,3-butadiene is carcinogenic in humans and may also be genotoxic in humans. The carcinogenic potency (the concentration associated with a 1% increase in mortality due to leukaemia) was determined to be 1.7 mg/m3, based on the results of the largest well conducted epidemiological investigation in exposed workers. This value is similar to the lower end of the range of tumorigenic concentrations determined on the basis of studies in rodents. 1,3-Butadiene also induced reproductive toxicity in experimental animals. As a measure of its potency to induce reproductive effects, a benchmark concentration of 0.57 mg/m3 was derived for ovarian toxicity in mice. Although the health effects associated with exposure to 1,3-butadiene and the mode of action for induction of these effects have been extensively investigated, there continues to be considerable research on this substance in an effort to address some of the uncertainties associated with the database.
(2001) Predicting the kinetics of peptide-antibody interactions using a multivariate experimental design of sequence and chemical space.

A multivariate approach involving modifications in peptide sequence and chemical buffer medium was used as an attempt to predict the kinetics of peptide-antibody interactions. Using a BIACORE system the kinetic parameters of the interaction of Fab 57P with 18 peptide analogues of an epitope of tobacco mosaic virus protein were characterized in 20 buffers of various pH values and containing different chemical additives (NaCl, urea, EDTA, KSCN and DMSO). For multivariate peptide design, three amino acid positions were selected because their modification was known to moderately affect binding, without abolishing it entirely. Predictive mathematical models were developed which related kinetic parameters (k(a) or k(d)) measured in standard buffer to the amino acid sequence of the antigen. ZZ-scales and a helix-forming-tendency (HFT) scale were used as descriptors of the physico-chemical properties of amino acids in the peptide antigen. These mathematical models had good predictive power (Q(2) = 0.49 for k(a), Q(2) = 0.73 for k(d)). For the non-essential residues under study, HFT and charge were found to be the most important factors that influenced the activity. Experiments in 19 buffers were performed to assess the sensitivity of the interactions to buffer composition. The presence of urea, DMSO and NaCl in the buffer influenced binding properties, while change in pH and the presence of EDTA and KSCN had no effect. The chemical sensitivity fingerprints were different for the various peptides. The results indicate that multivariate experimental design and mathematical modeling can be applied to the prediction of interaction kinetics.


We reviewed blink reflexes recorded from 51 railroad workers with long-term occupational exposure to solvents who were diagnosed by others with solvent-induced toxic encephalopathy. No worker fulfilled conventional clinical criteria for dementia or trigeminal mononeuropathy. All workers had normal R1 and R2 blink reflex latencies. R1 latencies correlated significantly with several nerve conduction measures, including F wave latencies, suggesting that some intersubject variability reflected intrinsic conduction properties, not isolated brain-stem function. Although normal, the workers' R1 latencies were significantly prolonged compared with historical control groups, including gender-matched control subjects of similar mean age (11.2 ms vs 9.9 ms; P < 0.0001). Stepwise multiple regression models demonstrated significant associations of R1 latency with age and use of CNS-active prescription medications (P = 0.003), but
duration of occupational solvent exposure did not enter into the models. Paradoxically, workers using CNS-active medications had significantly shorter R1 latencies compared with workers not using such medications (10.9 vs 11.7 ms; \( P = 0.01 \)). Job title, another potential surrogate measure of exposure, was not significantly related to reflex latencies. The geographical site of predominant solvent exposure did influence R1 latency, and workers from one site had longer exposure duration and longer R1 latencies than remaining workers. However, an interaction between age and exposure duration \( (r = 0.39; P = 0.003) \) confounded interpretation of this observation. Disability or work status, mental status findings, or classification of encephalopathy did not influence blink reflex latencies. The overall results do not support, but do not entirely exclude, a possible relationship between subclinical blink reflex abnormalities and occupational exposure to solvents. Nevertheless, it is clear from these results that the small group differences in R1 latency between exposed workers and control subjects are of no diagnostic importance and of uncertain physiologic importance, and they may reflect unrecognized confounders and technical factors.

(2001) [Ecologically-caused diseases in residents of Moscow, connected with anthropogenic load]. Aksenova, OI, Volkova, IF, Kornienko, AP and Li, VG Journal/Gig Sanit. 82-4.


Two up-to-date known paraoxonase 1 (PON1) polymorphisms (Gln--Arg 191 and Leu--Met 54) affect the hydrolysis of toxic oxons and might intensify effects of pollutants, organophosphates and other environmental chemicals in development of Parkinson's disease (PD). We reported previously that PON1 Gln--Arg 191 polymorphism did not influence on the susceptibility to PD. In the present study we have investigated the PON1 Leu--Met 54 polymorphism in 117 patients with sporadic idiopathic PD. A new approach for Leu--Met 54 polymorphism genotyping has been developed. We have showed the frequency of the Met 54 allele of PON1 to be significantly increased in patients with PD compared with the controls \( (\text{chi}(2)=8.63, \text{df}=1, P<0.003) \). The relative risk of PD in the Met 54 allele carriers has been estimated to be 2.3 fold higher than in homozygotes for the L allele. Moreover it appeared to be even 5.15 higher in the subgroup of patients with early-onset PD. We suggest that the Met 54 allele may be considered to be an independent risk factor for PD. This mutation
could probably cause PON1 impaired metabolism of environmental neurotoxins and might be responsible for neurodegeneration.

(2001) Induction of urinary excretion of 3-nitrotyrosine, a marker of oxidative stress, following administration of pyridostigmine bromide, DEET (N,N-diethyl-m-toluamide) and permethrin, alone and in combination in rats. Abu-Qare, AW, Suliman, HB and Abou-Donia, MB Journal/Toxicol Lett. 121: 127-34.

In this study, we determined levels of 3-nitrotyrosine in rat urine following administration of a single oral dose of 13 mg/kg pyridostigmine bromide (PB) (3-dimethylaminocarbonyloxy-N-methylpyridinium bromide), a single dermal dose of 400 mg/kg N,N-diethyl-m-toluamide (DEET) and a single dermal dose of 1.3 mg/kg permethrin, alone and in combination. Urine samples were collected from five treated and five control rats at 4, 8, 16, 24, 48, and 72 h following dosing. Solid-phase extraction coupled with high-performance liquid chromatography with ultraviolet detection at 274 nm was used for the determination of tyrosine and 3-nitrotyrosine. A single oral dose of PB and a single dermal dose of DEET or their combination significantly (P<0.05) increased levels of 3-nitrotyrosine starting 24 h after dosing compared with control urine samples. The maximum increase of 3-nitrotyrosine was detected 48 h after combined administration of PB and DEET. The ratio of 3-nitrotyrosine to tyrosine in urine excreted 48 h after dosing was 0.19+/-0.04, 0.20+-0.05, 0.28+/-0.03, 0.32+/-0.04, 0.19+/-0.05, 0.42+/-0.04, 0.27+/-0.03, 0.36+/-0.04, and 0.48+/-0.04 following administration of water, ethanol, PB, DEET, permethrin, PB+DEET, PB+permethrin, DEET+permethrin, and PB+DEET+permethrin, respectively. The results indicate that an oral dose of PB and a dermal administration of DEET, alone and in combination, could generate free radical species, and thus increase levels of 3-nitrotyrosine in rat urine. Induction of 3-nitrotyrosine, a marker of oxidative stress, following exposure to these compounds could be significant in understanding the proposed enhanced toxicity following combined exposure to these compounds.


This study describes a chromatographic method for the determination of diazepam, an anxiolytic drug that is also used as an antidote against nerve agent seizures, its metabolites N-desmethyldiazepam, and temazepam, the anti-nerve agent drug pyridostigmine bromide (PB; 3-dimethylaminocarbonyloxy-N-methyl pyridinium...
bromide) and its metabolite N-methyl-3-hydroxypyridinium bromide in rat plasma and urine. The compounds were extracted using C18 Sep-Pak Vac 3cc (500 mg) cartridges and separated using isocratic mobile phase of methanol, acetonitrile and water (pH 3.2) (10:40:50) at a flow-rate of 0.5 ml/min in a period of 12 min, and UV detection ranging between 240 and 280 nm. The limits of detection for all analytes ranged between 20 and 50 ng/ml, while limits of quantitation were 100 ng/ml. Average percentage extraction recoveries of five spiked plasma samples were 79.1+/-.7.7, 83.5+-6.4, 83.9+/-5.9, 71.3+/-6.0 and 77.7+/-5.6, and from urine 79.4+/-7.9, 83.1+/-6.9, 73.6+/-7.7, 74.3+/-7.1 and 77.6+/-5.9 for diazepam, N-desmethyldiazepam, temazepam, pyridostigmine bromide, and N-methyl-3-hydroxypyridinium bromide, respectively. The relationship between peak areas and concentration was linear over the range between 100 and 1000 ng/ml. This method was applied to determine the above analytes following a single oral administration in rats as a tool to study the pharmacokinetic profile of each compound, alone and in combination.


A method was developed for the separation and quantification of the insecticide chlorpyrifos (O,O-diethyl-O[3,5,6-trichloro-2-pyridinyl] phosphorothioate), its metabolites chlorpyrifos-oxon (O,O-diethyl-O[3,5,6-trichloro-2-pyridinyl] phosphate) and TCP (3,5,6-trichloro-2-pyridinol), the anti-nerve agent drug pyridostigmine bromide (PB; 3-dimethylaminocarbonyloxy-N-methyl pyridinium bromide), its metabolite N-methyl-3-hydroxypyridinium bromide, the insect repellent DEET (N,N-diethyl-m-toluamide), and its metabolites m-toluamide and m-toluic acid in rat plasma and urine. The method is based on using solid-phase extraction and high-performance liquid chromatography (HPLC) with reversed-phase C18 column, and gradient UV detection ranging between 210 and 280 nm. The compounds were separated using a gradient of 1-85% acetonitrile in water (pH 3.20) at a flow-rate ranging between 1 and 1.7 ml/min over a period of 15 min. The retention times ranged from 5.4 to 13.2 min. The limits of detection ranged between 20 and 150 ng/ml, while the limits of quantitation were between 150 and 200 ng/ml. Average percentage recovery of five spiked plasma samples was 80.2+/-7.9, 74.9+/-8.5, 81.7+/-6.9, 73.1+-7.8, 74.3+/-8.3, 80.8+/-6.6, 81.6+/-7.3 and 81.4+/-6.5, and from urine 79.4+/-6.9, 77.8+/-8.4, 83.3+/-6.6, 72.8+/-9.0, 76.3+/-7.7, 83.4+/-7.9, 81.6+/-7.9 and 81.8+/-6.8 for chlorpyrifos, chlorpyrifos-oxon, TCP, pyridostigmine bromide, N-methyl-3-hydroxypyridinium bromide, DEET, m-toluamide and m-toluic acid, respectively. The relationship between peak areas and concentration was linear over a range between 200 and 2000 ng/ml.

This study reports a simple and rapid high-performance liquid chromatographic (HPLC) method for the determination of the insecticide diazinon (O,O-diethyl-O[2-isopropyl-6-methylpyridimidinyl] phosphorothioate), its metabolites diazoxon (O,O-diethyl-O-2-isopropyl-6-methylpyridimidinyl phosphate) and 2-isopropyl-6-methyl-4-pyrimidinol, the insecticide chlorpyrifos (O,O-diethyl-O[3,5,6-trichloro-2-pyridinyl] phosphorothioate) and its metabolites chlorpyrifos-oxon (O,O-diethyl-O[3,5,6-trichloro-2-pyridinyl] phosphate), and TCP (3,5,6-trichloro-2-pyridinol) in rat plasma and urine samples. The method is based on using C18 Sep-Pak cartridges for solid-phase extraction and HPLC with a reversed-phase C18 column and programmed UV detection ranging between 254 and 280 nm. The compounds are separated using a gradient of 1% to 80% acetonitrile in water (pH 3.0) at a flow rate ranging between 1 and 1.5 mL/min in a period of 16 min. The limits of detection ranged between 50 and 150 ng/mL, and the limits of quantitation were 100 to 200 ng/mL. The average percentage recovery of five spiked plasma samples were 86.3 +/- 8.6, 77.4 +/- 7.0, 82.1 +/- 8.2, 81.8 +/- 8.7, 73.1 +/- 7.4, and 80.3 +/- 8.0 and from urine were 81.8 +/- 7.6, 76.6 +/- 7.1, 81.5 +/- 7.9, 81.8 +/- 7.1, 73.7 +/- 8.6, and 80.7 +/- 7.7 for diazinon, diazoxon, 2-isopropyl-6-methyl-4-pyrimidinol, chlorpyrifos, chlorpyrifos-oxon, and TCP, respectively. The relationship between the peak area and concentration was linear over a range of 200 to 2,000 ng/mL. This method was applied in order to analyze these chemicals and metabolites following dermal administration in rats.


A high-performance liquid chromatographic (HPLC) method was developed for the separation and quantitation of the insecticide chlorpyrifos (O,O-diethyl-O[3,5,6-trichloro-2-pyridinyl] phosphorothioate), its metabolites chlorpyrifos-oxon (O,O-diethyl-O[3,5,6-trichloro-2-pyridinyl] phosphate) and TCP (3,5,6-trichloro-2-pyridinol), the insecticide permethrin (3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylic acid-(3-phenoxyphenyl) methylester), and two of its metabolites, m-phenoxybenzyl alcohol and m-phenoxybenzoic acid, in rat plasma and urine. The method is based on using C18 Sep-Pak cartridges for solid-phase extraction and reversed-phase HPLC. The compounds were separated using a gradient of 1 to 80% acetonitrile in water (pH 3.2)
at a flow rate ranging between 1 and 1.5 mL/min in a period of 17 min and gradient UV
detection ranging between 210 and 280 nm. The retention times ranged from 9.3 to
14.5 min. The limits of detection ranged between 20 and 150 ng/mL, whereas the limits
of quantitation were 150-200 ng/mL. The respective average percentage recoveries of
chipryrifos, chlorpyrifos-oxon, TCP, permethrin, m-phenoxybenzyl alcohol, and
m-phenoxybenzoic were 78.6 +/- 6.4, 72.8 +/- 6.8, 84.8 +/- 8.0, 79.2 +/- 8.4, 80.5 +/-
7.2, and 82.3 +/- 7.1 from five spiked plasma samples and 77.5 +/- 8.1, 72.8 +/- 8.3,
79.9 +/- 6.4, 79.1 +/- 8.9, 80.5 +/- 7.6, and 81.4 +/- 7.8 from urine samples. The
relationship between peak areas and concentration was linear for concentrations
between 200 and 2,000 ng/mL. This method was used to analyze these chemicals and
metabolites following dermal administration in rats.

(2001) Quantification of nicotine, chlorpyrifos and their metabolites in rat plasma
and urine using high-performance liquid chromatography.
Abu-Qare, AW and Abou-Donia, MB Journal/J Chromatogr B Biomed Sci Appl. 757:
295-300.

This study describes a high-performance liquid chromatographic method for the
separation and quantification of nicotine, its metabolites nor nicotine and cotinine, the
insecticide chlorpyrifos (O,O-diethyl-O[3,5,6-trichloro-2-pyridinyl]phosphorothioate),
and its metabolites chlorpyrifos-oxon
(O,O-diethyl-O[3,5,6-trichloro-2-pyridinyl]phosphate), and TCP
(3,5,6-trichloro-2-pyridinol) in rat plasma and urine. The compounds were separated
using gradient mobile phase of methanol, acetonitrile and water (pH 3.20) at a
flow-rate of 0.8 ml/min in a period of 17 min, and gradient UV detection ranging
between 260 and 280 nm. The retention times ranged from 3.4 to 16.7 min. The limits
of detection were ranged between 20 and 150 ng/ml, while limits of quantitation were
50-200 ng/mL. Average percentage recovery of five spiked plasma samples were 84.7+
-8.3, 78.2+/-.7.6, 80.1+/-6.4, 79.0+/-.6.4, 74.0+/-.7.4, 87.6+/-.5.5, and from urine 85.1+
-5.2, 75.9+/-.7.0, 82.1+/-6.1, 79.5+/-.6.1, 71.3+/-.7.4 and 81.3+/-.6.9 for nicotine,
normotone, cotinine chlorpyrifos, chlorpyrifos-oxon and TCP, respectively. Intra-day
accuracy and precision for this method were ranged between 2.2-3.6 and 2.1-2.8%,
respectively. The relationship between peak areas and concentration was linear over
range between 200 and 2000 ng/mL. This method was applied to analyze the above
chemicals and metabolites following combined oral administration in rats.

(2001) Combined exposure to DEET (N,N-diethyl-m-toluamide) and
permethrin-induced release of rat brain mitochondrial cytochrome c.
The release of cytochrome c from the mitochondrial intermembrane space can induce apoptosis. The levels of mitochondrial cytochrome c in rat brain following a single dermal dose of 400 mg/kg of DEET, and of 1.3 mg/kg of permethrin, alone or in combination were determined. Rats were sacrificed at a time interval of 0.5, 1, 2, 4, 8, 16, 24, 48, or 72 h after dosing. Brain mitochondria were isolated and the levels of cytochrome c were measured using reversed-phase high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. Average percentage recovery of cytochrome c spiked with control rat brain mitochondria was 83.2 +/- 8.9%. Limits of detection and quantitation were 1 and 5 ng, respectively. The results showed that a single dermal dose of a combination of DEET and permethrin significantly increased the release of brain mitochondrial cytochrome c starting 24 h after treatment. DEET and permethrin alone did not affect the release of cytochrome c. The results indicate that combined exposure to DEET and permethrin might induce the apoptotic processes in rat brain as seen by the release of cytochrome c.


A simple and reliable method was developed for the quantification of depleted uranium, the anti nerve agent drug pyridostigmine bromide (PB;3-dimethylaminocarbonyloxy-N-methyl pyridinium bromide) and its metabolite N-methyl-3-hydroxypyridinium bromide in rat plasma and urine. The method involved using solid phase extraction and spectrophotometric determination of uranium, and high performance liquid chromatography (HPLC) with reversed phase C(18) column, and UV detection at 280 nm for PB and its metabolite. Uranium was derivatized using dibenzoylmethane (DBM) then the absorbance was measured at 405 nm. PB and its metabolite were separated using a gradient of 1--40% acetonitrile in 0.1% trifluoroacetic acid water solution (pH 3.2) at a flow rate of 0.8 ml/min in a period of 14 min. Limits of detection were 2 ng/ml for uranium and 50 ng/ml for PB and its metabolite. Limits of quantitation were between 10 and 100 ng/ml for uranium and the other two analytes, respectively. Average percentage recovery of five spiked plasma samples were 83.7 +/- 8.6, 76.8 +/- 6.7, 79.1 +/- 7.1, and from urine 82.7 +/- 8.6, 79.3 +/- 9.5 and 78.0 +/- 6.2, for depleted uranium, PB and N-methyl-3-hydroxypyridinium bromide, respectively. The relationship between peak areas and concentration was linear for standards between 100 and 1000 ng/ml for all three analytes. This method was applied to analyze the above chemicals and metabolites following combined administration in rats.
Simultaneous determination of malathion, permethrin, DEET (N,N-diethyl-m-toluamide), and their metabolites in rat plasma and urine using high performance liquid chromatography.
Abu-Qare, AW and Abou-Donia, MB

A method was developed for the separation and quantification of the insecticide malathion (O,O-dimethyl-S-(1,2-carbethoxyethyl) phosphorodithioate), its metabolite malaoxon (O,O-dimethyl-S-(1,2-carbethoxyethyl) phosphorothioate), the insecticide permethrin (3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylic acid(3-phenoxyphenyl)methylester), two of its metabolites m-phenoxybenzyl alcohol and m-phenoxybenzoic acid, the insect repellent N,N-diethyl-m-toluamide (DEET), and its metabolites m-toluamide and m-toluic acid in rat plasma and urine. The method used high performance liquid chromatography (HPLC) with reversed phase C(18) column, and UV detection at 210 nm. The compounds were separated using gradient of 45--99% acetonitrile in water (pH 3.5) at a flow rate ranging between 0.5 and 2 ml min in a period of 15 min. The retention times ranged from 7.4 to 12.3 min. The limits of detection ranged between 20 and 100 ng/ml, while limits of quantitation were 50-150 ng/ml. Average percentage recovery of five spiked plasma samples were 80.1 +/- 4.2, 75.2 +/- 4.6, 84.5 +/- 4.0, 84.3 +/- 3.4, 82.8 +/- 3.9, 83.9 +/- 5.5, 82.2 +/- 6.0, 83.1 +/- 4.3, and 78.8 +/- 3.9, 76.4 +/- 4.9, 82.3 +/- 4.5, 82.5 +/- 3.9, 81.4 +/- 4.0, 83.9 +/- 4.3, 81.5 +/- 5.0, and 84.5 +/- 3.8 for, malathion, malaoxon, DEET, m-toluamide, m-toluic acid, permethrin, m-phenoxybenzyl alcohol, and m-phenoxybenzoic acid, respectively. The method was reproducible and linear over range between 100 and 1000 ng/ml. This method was applied to analyze the above chemicals and metabolites following combined dermal administration in rats.

High-performance liquid chromatographic determination of pyridostigmine bromide, nicotine, and their metabolites in rat plasma and urine.
Abu-Qare, AW and Abou-Donia, MB

This study reports on the development of a rapid and simple method for the determination of the antinerve agent drug pyridostigmine bromide (3-dimethylaminocarbonyloxy-N-methyl pyridinium bromide) (PB), its metabolite N-methyl-3-hydroxypyridinium bromide, nicotine (S-1-methyl-5-(3-pyridyl)-2-pyrrolidine), and its metabolites nornicotine (2-(3-pyridyl)pyrrolidine) and cotinine (S-1-methyl-5-(3-pyridyl)-2-pyrrolidone) in rat plasma and urine. The compounds are extracted and eluted by methanol and acetonitrile using C18 Sep-Pak cartridges and separated using high-performance liquid chromatography by a gradient of methanol, acetonitrile, and water (pH 3.2) at a flow rate of 0.8 mL/min in a period of 14 min. UV detection was at 260 nm for nicotine and its metabolites and at 280 nm for PB and its metabolite. The limits of detection ranged between 20 and 70 ng/mL, and the limits of quantitation were 50-100 ng/mL. The average percent recovery of five spiked plasma samples were 85.7 +/- 7.3%, 80.4 +/- 5.8%, 78.9 +/- 5.4%, 76.7 +/- 6.4%, and 79.7 +/- 4.4%.
5.7% and for urine were 85.9 +/- 5.9%, 75.5 +/- 6.9%, 82.6 +/- 7.9%, 73.6 +/- 5.9%, and 77.7 +/- 6.3% for nicotine, nornicotine, cotinine, PB, and N-methyl-3-hydroxypyridinium bromide, respectively. The calibration curves for standard solutions of the compounds of peak areas and concentration are linear for a range between 100 and 1,000 ng/mL. This method is applied in order to analyze the previously mentioned chemicals and metabolites following their oral administration in rats.

(2001) Inhibition and recovery of maternal and fetal cholinesterase enzyme activity following a single cutaneous dose of methyl parathion and diazinon, alone and in combination, in pregnant rats.
Abu-Qare, AW and Abou-Donia, MB Journal/J Appl Toxicol. 21: 307-16.

Pregnant Sprague-Dawley rats (14-18 days of gestation) were treated with a single cutaneous subclinical dose(s) of 10 mg kg(-1) (15% of LD(50)) of methyl parathion (O,O-dimethyl O-4-nitrophenyl phosphorothioate) and 65 mg kg(-1) (15% of LD(50)) of diazinon (O,O-diethyl O-2-isopropyl-6-methylpyrimidinyl phosphorothioate), and their combination. Animals were sacrificed at 1, 2, 4, 12, 24, 48, 72, and 96 h after dosing. Inhibition of maternal and fetal cholinesterase enzyme activity has been determined. Methyl parathion significantly inhibited maternal and fetal brain acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BuChE) activity within 24 h after dosing. Diazinon and a mixture of methyl parathion and diazinon caused lesser inhibition compared with methyl parathion alone. Recovery of maternal and fetal brain AChE activity was in the order of diazinon > combination of diazinon and methyl parathion > methyl parathion 96 h after dosing. Although fetal plasma BuChE activity recovered to 100% of control within 96 h of application, maternal BuChE activity remained inhibited to 55% and 32% of control 96 h after application of methyl parathion and a mixture of methyl parathion and diazinon, respectively. Following a single dermal dose of methyl parathion, the activity of maternal liver BuChE was 63% of control 2 h after dosing, whereas inhibition of placental AChE or BuChE activity occurred 12 and 1 h following a single dose of methyl parathion, corresponding to activities of 63% and 54% of control, respectively. Diazinon, alone or in combination with methyl parathion, did not inhibit significantly the maternal liver BuChE or placental AChE and BuChE activity. The results suggest that dermal application of a single dose of methyl parathion and diazinon, alone or in combination, has an easy access into maternal and fetal tissues, resulting in inhibition of cholinesterase enzymes. The lower inhibitory effect of the combination of methyl parathion and diazinon might be due to competition of diazinon with methyl parathion for cytochrome P-450 enzymes, resulting in formation of the potent cholinesterase inhibitor methyl paraoxon. The faster recovery of fetal cholinesterase enzymes is attributed to the rapid de novo synthesis of cholinesterase fetal tissues compared with the mother.

A rapid method was developed for the analysis of the insecticide (A) diazinon (O,O-diethyl O-2-isopropyl-6-methylpyridimidinyl) phosphorothioate, its metabolites (B) diazoxon (O,O-diethyl O-2-isopropyl-6-methylpyridimidinyl) phosphate, and (C) 2-isopropyl-6-methyl-4-pyrimidinol, the insecticide (D) permethrin [3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylic acid (3-phenoxyphenyl)methylester], its metabolites (E) m-phenoxybenzyl alcohol, and (F) m-phenoxybenzoic acid, the insect repellent (G) DEET (N,N-diethyl-m-toluamide), and its metabolites (H) m-toluamide and (I) m-toluic acid in rat plasma and urine. The method is based on using C18 Sep-Pak cartridges (Waters Corporation, Milford, Mass., U.S.A.) for solid phase extraction and high performance liquid chromatography with a reversed phase C18 column, and absorbance detection at 230 nm for compounds A, B, and C, and at 210 nm for compounds D-I. The compounds were separated using a gradient from 1% to 99% acetonitrile in water (pH 3.0) at a flow rate ranging between 1 and 1.7 mL/min in a period of 17 min. The limits of detection were ranged between 20 and 100 ng/mL, while limits of quantification were 80-200 ng/mL. The relationship between peak areas and concentration was linear over a range of 100-1000 ng/mL. This method was applied to determine the above insecticides and their metabolites following dermal administration in rats.

Abu-Qare, AW and Abou-Donia, MB Journal/J Toxicol Environ Health B Crit Rev. 4: 313-32.

Biomarkers rely on biochemical, histological, morphological, and physiological changes in whole organisms. Their use is becoming an important tool to examine changes at cellular and molecular levels, especially in nucleic acids and proteins. Biomarkers are used to measure exposure to a toxic agent, to detect severity of any toxic response, and to predict the possible outcome. Information on the mechanisms of action of toxicants can allow the development of potential biomarkers of effect and thus improvement of the risk assessment processes. Use of biomarkers as a tool to predict induction of apoptosis allows identification of biological signs that may indicate increased risk for disease. In cells undergoing apoptosis, the release of cytochrome c from the mitochondria to the cytoplasm and the activation of caspase-3, a key enzyme to execution stage of apoptotic pathway, have been studied as biomarkers of cell death.
(apoptosis). Products of DNA fragmentation that either accumulate in the cellular tissues or are excreted in the urine are useful markers of DNA damage. The induction level of urinary or cellular level of 8-hydroxy-2-deoxyguanosine and 3-nitrotyrosine has been used as a marker to measure extent of DNA oxidative damage. Furthermore, alteration or overexpression of the p53 gene was considered an indication of apoptosis. This article reviews some of the aspects of biomarkers of apoptosis, indicating relevance of their uses to predict apoptosis following exposure to environmental toxicants.

(2001) Combined exposure to sarin and pyridostigmine bromide increased levels of rat urinary 3-nitrotyrosine and 8-hydroxy-2'-deoxyguanosine, biomarkers of oxidative stress.

In this study concentrations of markers of oxidative stress 3-nitrotyrosine and 8-hydroxy-2'-deoxyguanosine (8-OhdG) were determined in rat urine following a single oral dose of pyridostigmine bromide (PB) 13 mg/kg and a single intramuscular dose of sarin 80 microg/kg alone or in combination. Urine samples were collected 16, 24, 48, 72, and 96 h following dosing. Control urine samples of five rats treated with normal saline were also collected at the same time intervals. A combined dose of PB and sarin significantly increased levels of 3-nitrotyrosine and (8-OhdG) starting 48 h after dosing. An increase in the concentration of these markers was not detected following a single dose of PB or sarin alone. Maximal increase in 3-nitrotyrosine and 8-OhdG was detected 48 h after administration of a combination PB and sarin. The results indicate that concurrent exposure to PB and sarin could generate free radical species that may cause oxidative stress in rats. The results may have significant impact if veterans were expose to sarin following an oral dose of PB.


A method was developed for the separation and quantification of the anti-nerve agent pyridostigmine bromide (PB; 3-dimethylaminocarbonyloxy-N-methyl pyridinium bromide), the analgesic drugs acetaminophen and acetylsalicylic acid, and the stimulant caffeine (3,7-dihydro-1,3,7-trimethyl-1-H-purine-2,6-dione) in rat plasma and urine. The compounds were extracted using C(18) Sep-Pak(R) cartridges then analyzed by high performance liquid chromatography (HPLC) with reversed phase C18 column, and UV detection at 280 nm. The compounds were separated using gradient
of 1-85% acetonitrile in water (pH 3.0) at a flow rate ranging between 1 and 1.5 ml/min in a period of 14 min. The retention times ranged from 8.8 to 11.5 min. The limits of detection were ranged between 100 and 200 ng/ml, while limits of quantitation were 150-200 ng/ml. Average percentage recovery of five spiked plasma samples were 70.9+/-9.5, 73.7+/-9.8, 88.6+/-9.3, 83.9+/-7.8, and from urine 69.1+/-8.5, 74.5+/-8.7, 85.9+/-9.8, 83.2+/-9.3, for pyridostigmine bromide, acetaminophen, acetylsalicylic acid and caffeine, respectively. The relationship between peak areas and concentration was linear over range between 100 and 1000 ng/ml. The resulting chromatograms showed no interfering peaks from endogenous plasma or urine components. This method was applied to analyze these compounds following oral administration in rats.

(2001) DEET (N,N-diethyl-m-toluamide) alone and in combination with permethrin increased urinary excretion of 6beta-hydroxycortisol in rats, a marker of hepatic CYP3A induction.
Abu-Qare, AW and Abou-Donia, MB Journal/J Toxicol Environ Health A.  64:  373-84.

In this study, the ratio of 6beta-hydroxycortisol (6beta-OHF) to free cortisol (F) was determined in urine following a single dermal dose of 400 mg/kg of DEET (N,N-diethyl-m-toluamide), and 1.3 mg/kg of permethrin, alone and in combination, in rats. Urine samples were collected at 2, 4, 8, 16, 24, 48, and 72 h after application. Recoveries of 6beta-OHF and cortisol (F) from control urine samples were between 75 and 85%, with limits of detection at 30 and 10 ng/ml for cortisol and 6beta-OHF, respectively. A single dermal dose of DEET alone and in combination with permethrin significantly increased urinary excretion of 6beta-hydroxycortisol 24 h after dosing. Permethrin did not significantly alter the urinary excretion of 6beta-hydroxycortisol. These results indicate that DEET, alone and in combination with permethrin, increased urinary excretion of 6beta-OHF in rats following a single dermal dose application.

(2001) A solid phase extraction reversed-phase HPLC method for the simultaneous determination of methoprene, permethrin and selected metabolites in rat plasma and urine.
Abu-Qare, AW and Abou-Donia, MB Journal/Biomed Chromatogr.  15:  464-70.

A method was validated and applied for the analysis of the insect growth regulator methoprene [Isopropyl (2E,4E)-11-methoxy-3,7,11-trimethyldodeca-2,4-dienoate], its metabolite methoprene acid, the insecticide permethrin [3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylic acid(3-phenoxyphenyl)methylester], and two of its metabolites, m-phenoxybenzyl alcohol and m-phenoxybenzoic acid, in rat plasma and urine using solid-phase extraction and reversed-phase high performance liquid chromatography. The analytes
were separated using gradient of 55-100% acetonitrile in water (pH 4.0) at a flow rate ranging between 0.6 and 1.0 mL/min over a period of 20 min, and UV detection at 210 and 254 nm. The retention times ranged from 7.3 to 18.4 min. The limits of detection ranged between 50 and 100 ng/ml, while limits of quantitation were 100-150 ng/mL. Average percentage recovery of five spiked plasma samples was 83.6 +/- 3.9, 80.1 +/- 5.4, 82.1 +/- 4.4, 83.7 +/- 3.9 and 83.1 +/- 4.7, and from urine 79.3 +/- 4.3, 82.0 +/- 5.4, 80.7 +/- 4.2, 78.9 +/- 5.7 and 83.9 +/- 4.5 for methoprene, methoprene acid, permethrin, m-phenoxybenzyl alcohol and m-phenoxybenzoic acid, respectively. The method was linear and reproducible over the range of 100-1000 ng/mL. This method was applied to analyze the above chemicals and metabolites following their combined administration in rats.

------------------------------------------------------------------------------------------------------------------

Abu-Qare, AW, Abdel-Rahman, AA, Ahmad, H, Kishk, AM and Abou-Donia, MB

Adult hens were given oral daily doses of 2 mg (2 microC(i))/kg/day (14% of oral LD(50) in male rats) of [14C]methyl parathion (O,O-dimethyl O-4-nitrophenyl phosphorothioate) for 10 consecutive days. Five treated hens were sacrificed at 1, 2, 4, 8, 12, 24, and 48 h after the last dose. Methyl parathion was absorbed from the gastrointestinal tract and distributed rapidly. Maximum radioactivity was detected in tissues within 8 h of dosing, (ng methyl parathion equivalent/g fresh tissue or ml plasma): Plasma (189.2), liver (94.7), kidney (146.2), brain (61.4), gastrointestinal tissues (106.7). Methyl parathion was detected in the plasma, kidney and liver, while methyl parathion metabolite p-nitrophenol was detected in the liver and in the kidney. Elimination of methyl parathion from plasma was monophasic with a terminal half-life of 17.5 h, corresponding to an elimination rate constant of 0.039 ng/hr. Most of the absorbed radioactivity was excreted in the combined fecal-urine excreta (98%). Analysis of the metabolites in the excreta revealed that non-conjugated metabolites accounted for 13% of the total excretion. Conjugated metabolites accounted for 87% of the total excretion; of that, 6% as p-nitrophenyl-glucoronide conjugate, 7% as p-nitrophenyl-sulfate conjugate, 23% as bound hot sulfuric acid hydrolyzable residues, and 51% as water soluble metabolites. The presence of majority of radioactivity in the excreta as conjugated metabolites indicates that determining only unbound p-nitrophenol as a biological marker for methyl parathion exposure underestimates total fecal-urine excretion of p-nitrophenol. The slow elimination rate of methyl parathion is significant, since hens are more comparable to humans with respect to their cytochrome P450 activities.

------------------------------------------------------------------------------------------------------------------
Inhibition of cholinesterase enzymes following a single dermal dose of chlorpyrifos and methyl parathion, alone and in combination, in pregnant rats.
Abu-Qare, AW, Abdel-Rahman, A, Brownie, C, Kishk, AM and Abou-Donia, MB

Pregnant Sprague-Dawley rats (14-18 d of gestation) were treated with either a single dermal subclinical dose of 30 mg/kg (15% of dermal LD50) chlorpyrifos (O,O-diethyl-O-[3,5,6-trichloro-2-pyridinyl] phosphorothioate) or a single dermal subclinical dose of 10 mg/kg (15% of dermal LD50) methyl parathion (O,O-dimethyl O-4-nitrophenyl phosphorothioate) or the two in combination. Chlorpyrifos inhibited maternal and fetal brain acetylcholinesterase (AChE) activity within 24 h of dosing, (48% and 67% of control activity, respectively). Following application of methyl parathion, peak inhibition of maternal and fetal brain AChE activity occurred at 48 h and 24 h after dosing (17% and 48% of control activity, respectively). A combination of chlorpyrifos and methyl parathion produced peak inhibition of maternal and fetal brain AChE activity at 24 h postdosing (35% and 73% of control activity, respectively). Maternal and fetal brain AChE activity recovered to various degrees of percentage of control 96 h after dosing. Application of methyl parathion or chlorpyrifos alone or in combination significantly inhibited maternal plasma butyrylcholinesterase (BuChE) activity. No significant inhibition of fetal plasma BuChE activity was detected. Peak inhibition of maternal liver BuChE occurred 24 h after application of methyl parathion or chlorpyrifos alone or in combination (64%, 80%, and 61% of control activity, respectively). Significant inhibition of placental AChE occurred within 24 h after application of methyl parathion or chlorpyrifos alone or in combination. The results suggest that methyl parathion and chlorpyrifos, alone or in combination, were rapidly distributed in maternal and fetal tissues, resulting in rapid inhibition of cholinesterase enzyme activities. The lower inhibitory effect of the combination could be due to competition between chlorpyrifos and methyl parathion for cytochrome P-450 enzymes, resulting in inhibition of the formation of the potent cholinesterase inhibitor oxon forms. The faster recovery of fetal plasma BuChE is attributed to the de novo synthesis of cholinesterase by fetal tissues compared to maternal tissues.

Locomotor and sensorimotor performance deficit in rats following exposure to pyridostigmine bromide, DEET, and permethrin, alone and in combination.

Since their return from Persian Gulf War (PGW), many veterans have complained of symptoms including muscle and joint pain, ataxia, chronic fatigue, headache, and difficulty with concentration. The causes of the symptoms remain unknown. Because these veterans were exposed to a combination of chemicals including pyridostigmine...
bromide (PB), DEET, and permethrin, we investigated the effects of these agents, alone and in combination, on the sensorimotor behavior and central cholinergic system of rats. Male Sprague-Dawley rats (200-250 gm) were treated with DEET (40 mg/kg, dermal) or permethrin (0.13 mg/kg, dermal), alone and in combination with PB (1.3 mg kg, oral, last 15 days only), for 45 days. Sensorimotor ability was assessed by a battery of behavioral tests that included beam-walk score, beam-walk time, incline plane performance, and forepaw grip on days 30 and 45 following the treatment. On day 45 the animals were sacrificed, and plasma and CNS cholinesterase, and brain choline acetyl transferase, muscarinic and nicotinic acetylcholine receptors were evaluated. Animals treated with PB, alone or in combination with DEET and permethrin, showed a significant deficit in beam-walk score as well as beam-walk time as compared with controls. Treatment with either DEET or permethrin, alone or in combination with each other, did not have a significant effect on beam-walk score. All chemicals, alone or in combination, resulted in a significant impairment in incline plane testing on days 30 and 45 following treatment. Treatment with PB, DEET, or permethrin alone did not have any inhibitory effect on plasma or brain cholinesterase activities, except that PB alone caused moderate inhibition in midbrain acetylcholinesterase (AChE) activity. Treatment with permethrin alone caused significant increase in cortical and cerebellar AChE activity. A combination of DEET and permethrin or PB and DEET led to significant decrease in AChE activity in brainstem and midbrain and brainstem, respectively. A significant decrease in brainstem AChE activity was observed following combined exposure to PB and permethrin. Coexposure with PB, DEET, and permethrin resulted in significant inhibition in AChE in brainstem and midbrain. No effect was observed on choline acetyl transferase activity in brainstem or cortex, except combined exposure to PB, DEET, and permethrin caused a slight but significant increase in cortical choline acetyltransferase activity. Treatment with PB, DEET, and permethrin alone caused a significant increase in ligand binding for m2 muscarinic acetylcholine receptor (mAChR) in the cortex. Coexposure to PB, DEET, and permethrin did not have any effect over that of PB-induced increase in ligand binding. There was no significant change in ligand binding for nicotinic acetylcholine receptor (nAChR) associated with treatment with the chemical alone; a combination of PB and DEET or coexposure with PB, DEET, and permethrin caused a significant increase in nAChR ligand binding in the cortex. Thus, these results suggest that exposure to physiologically relevant doses of PB, DEET, and permethrin, alone or in combination, leads to neurobehavioral deficits and region-specific alterations in AChE and acetylcholine receptors.

(2001) Effects of daily dermal application of DEET and epermethrin, alone and in combination, on sensorimotor performance, blood-brain barrier, and blood-testis barrier in rats.
DEET and permethrin were implicated in the development of illnesses in some veterans of the Persian Gulf War. This study was designed to investigate the effects of daily dermal application of these chemicals, alone or in combination, on the permeability of the blood-brain barrier (BBB) and blood-testes barrier (BTB) and on sensorimotor performance in male Sprague-Dawley rats. Groups of five rats were treated with a dermal daily dose of 4, 40, or 400 mg/kg DEET in ethanol or 0.013, 0.13, or 1.3 mg/kg permethrin in ethanol for 60 d. A group of 10 rats received a daily dermal dose of ethanol and served as controls. BBB permeability was assessed by injection of an iv dose of the quaternary ammonium compound [3H]hexamethonium iodide. While permethrin produced no effect on BBB permeability, DEET alone caused a decrease in BBB permeability in brainstem. A combination of DEET and permethrin significantly decreased the BBB permeability in the cortex. BTB permeability was decreased by treatment with DEET alone and in combination with permethrin. The same animals underwent a battery of functional behavior tests 30, 45, and 60 d after exposure to evaluate their sensorimotor abilities. All treatments caused a significant decline in sensorimotor performance in a dose- and time-dependent manner. These results show that daily dermal exposure to DEET, alone or in combination with permethrin, decreased BBB permeability in certain brain regions, and impaired sensorimotor performance.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11289702

(2001) Human sensitivity to 1,3-butadiene: role of microsomal epoxide hydrolase polymorphisms.

1,3-Butadiene (BD) is a major commodity chemical used in the manufacture of synthetic rubber and various plastics and has been shown to be a potent animal carcinogen and a probable human carcinogen. The bioactivation of BD to reactive epoxides, and the balance between activation and detoxication of these reactive metabolites, is thought to play a critical role in the genotoxic and carcinogenic effects of BD. The detoxication of reactive BD metabolites involves enzymatic conjugation with glutathione by glutathione S-transferases (GSTs) and by hydrolysis, a reaction mediated by microsomal epoxide hydrolase (mEH). Since polymorphisms in genes of xenobiotic-metabolizing enzymes such as mEH may influence individual susceptibility to adverse health effects from BD exposure, we tested the hypothesis that the mEH Tyr113His polymorphism increases sensitivity to the genotoxic effects of BD in exposed workers. We used the autoradiographic hprt mutant lymphocyte assay as a biomarker of effect to identify genotoxicity associated with BD exposure in 49 workers from two styrene/butadiene polymer plants in Southeast Texas. Exposure to BD was assessed by collecting breathing zone air samples using passive badge dosimeters for three full 12 h work shifts 25, 20 and 14 days before blood was collected for
genotyping and for the hprt assay. We genotyped the study participants for the Tyr113His polymorphism in the mEH gene and also for deletion polymorphisms in the glutathione S-transferase genes, GSTM1 and GSTT1, as potential biomarkers of susceptibility to BD. Our data indicate that the majority of the study subjects (67%) were exposed to very low levels of BD of <150 parts per billion (p.p.b.) time-weighted average (TWA). In some workers, however, we found levels of BD exposures that exceeded a TWA of 2000 p.p.b. Our data indicate a significant (P < 0.05) 2-fold increase in frequencies of hprt variant (mutant) lymphocytes (Vf) in workers exposed to >150 p.p.b. BD, compared with workers exposed to <150 p.p.b. There was no significant effect from individual GSTM1, GSTT1 or mEH genotypes in workers exposed to <150 p.p.b. BD. In workers exposed to >150 p.p.b., individuals with at least one polymorphic mEH His allele (His/His or His/Tyr genotypes) had a significant (P < 0.001) 3-fold increase in Vf (mean Vf x 10(-6) +/- SE = 13.25 +/- 1.78) compared with individuals with the Tyr/Tyr genotype (mean Vf x 10(-6) +/- SE = 4.02 +/- 0.72). There was no significant effect from individual GSTM1 or GSTT1 polymorphisms, but combined polymorphism analysis showed that the genetic damage was highest in individuals who had at least one mEH His allele and either the GSTM1 and/or GSTT1 null genotypes (hprt Vf = 14.19 +/- 2.30 x10(-6)). In contrast, this response was not observed in individuals exposed to levels of BD < 150 p.p.b. These results indicate that polymorphisms in the mEH gene may play a significant role in human sensitivity to the genotoxic effects of BD exposure, and that the hprt mutant lymphocyte assay can serve as a sensitive biomarker of genotoxicity for monitoring occupational exposure to BD in industrial settings. Additional investigations in larger populations of workers are needed to confirm our results and to characterize the possible role of additional mEH polymorphisms in the induction of genetic damage associated with occupational exposure to butadiene.

(2001) Subchronic dermal application of N,N-diethyl m-toluamide (DEET) and permethrin to adult rats, alone or in combination, causes diffuse neuronal cell death and cytoskeletal abnormalities in the cerebral cortex and the hippocampus, and Purkinje neuron loss in the cerebellum. Abdel-Rahman, A, Shetty, AK and Abou-Donia, MB Journal/Exp Neurol. 172: 153-71.

N,N-Diethyl m-toluamide (DEET) and permethrin have been implicated as potential neurotoxic agents that may have played an important role in the development of illnesses in some veterans of the Persian Gulf War. To determine the effect of subchronic dermal application of these chemicals on the adult brain, we evaluated histopathological alterations in the brain of adult male rats following a daily dermal dose of DEET (40 mg/kg in 70% ethanol) or permethrin (0.13 mg/kg in 70% ethanol) or a combination of the two for 60 days. Control rats received a daily dermal dose of 70% ethanol for 60 days. Animals were perfused and brains were processed for morphological and histopathological analyses following the above regimen. Quantification of the density of healthy (or surviving) neurons in the motor cerebral
cortex, the dentate gyrus, the CA1 and CA3 subfields of the hippocampus, and the cerebellum revealed significant reductions in all three treated groups compared with the control group. Further, animals receiving either DEET or permethrin exhibited a significant number of degenerating (eosinophilic) neurons in the above brain regions. However, degenerating neurons were infrequent in animals receiving both DEET and permethrin, suggesting that neuronal cell death occurs earlier in animals receiving combined DEET and permethrin than in animals receiving either DEET or permethrin alone. The extent of neuron loss in different brain regions was similar among the three treatment groups except the dentate gyrus, where neurodegeneration was significantly greater with exposure to DEET alone. The neuron loss in the motor cerebral cortex and the CA1 subfield of all treated groups was also corroborated by a significant decrease in microtubule associated protein 2-immunoreactive elements (15-52% reduction), with maximal reductions occurring in rats receiving DEET alone; further, the surviving neurons in animals receiving both DEET and permethrin exhibited wavy and beaded dendrites. Analysis of glial fibrillary acidic protein immunoreactivity revealed significant hypertrophy of astrocytes in the hippocampus and the cerebellum of all treated groups (24-106% increase). Thus, subchronic dermal application of DEET and permethrin to adult rats, alone or in combination, leads to a diffuse neuronal cell death in the cerebral cortex, the hippocampal formation, and the cerebellum. Collectively, the above alterations can lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.


OBJECTIVES: Chronically fatiguing illness, defined as fatigue for at least 6 months, has been associated with various physical health conditions. Our objective was to determine whether there is a significant relationship between chronically fatiguing illness and 10 clinical conditions that frequently appear to be associated with fatigue, adjusting for the potentially confounding effects of psychiatric illness. DESIGN: A co-twin control study controlling for genetic and many environmental factors by comparing chronically fatigued twins with their nonfatigued co-twins. SETTING: A nationally distributed volunteer twin registry. PARTICIPANTS: The study included 127 twin pairs in which one member of the pair experienced fatigue of at least 6 months’ duration and the co-twin was healthy and denied chronic fatigue. Fatigued twins were classified into 3 levels using increasingly stringent diagnostic criteria. MEASUREMENTS AND MAIN RESULTS: Twins reported on a history of fibromyalgia, irritable bowel syndrome, multiple chemical sensitivities, temporomandibular disorder, interstitial cystitis, postconcussion syndrome, tension headache, chronic low back pain, chronic pelvic pain (women), and chronic nonbacterial prostatitis (men). The prevalence of these comorbid clinical conditions was significantly higher in the fatigued twins compared to their nonfatigued co-twins. Most notably, compared to their
nonfatigued co-twins, the chronically fatigued twins had higher rates of fibromyalgia (> 70% vs < 10%) and irritable bowel syndrome (> 50% vs < 5%). The strongest associations were observed between chronic fatigue and fibromyalgia (odds ratios > 20), irritable bowel syndrome, chronic pelvic pain, multiple chemical sensitivities, and temporomandibular disorder (all with odds ratios > or = 4). Regression analysis suggested that the number of comorbid clinical conditions associated with chronic fatigue could not be attributed solely to psychiatric illness. CONCLUSIONS: Chronically fatiguing illnesses were associated with high rates of many other clinical conditions. Thus, patients with chronic fatigue may present a complex clinical picture that poses diagnostic and management challenges. Nonetheless, clinicians should assess such patients for the presence of comorbid clinical conditions. Future research should provide a better understanding of the temporal relationship of the onset of fatigue and these conditions, and develop strategies for early intervention.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11251747


PURPOSE: Unexplained clinical conditions share features, including symptoms (fatigue, pain), disability out of proportion to physical examination findings, inconsistent demonstration of laboratory abnormalities, and an association with "stress" and psychosocial factors. This literature review examines the nature and extent of the overlap among these unexplained clinical conditions and the limitations of previous research. DATA SOURCES: English-language articles were identified by a search of the MEDLINE database from 1966 to January 2001 by using individual syndromes and their hallmark symptoms as search terms. STUDY SELECTION: Studies that assessed patients with at least one unexplained clinical condition and that included information on symptoms, overlap with other unexplained clinical conditions, or physiologic markers. Conditions examined were the chronic fatigue syndrome, fibromyalgia, the irritable bowel syndrome, multiple chemical sensitivity, temporomandibular disorder, tension headache, interstitial cystitis, and the postconcussion syndrome. DATA EXTRACTION: Information on authorship, patient and control groups, eligibility criteria, case definitions, study methods, and major findings. DATA SYNTHESIS: Many similarities were apparent in case definition and symptoms, and the proportion of patients with one unexplained clinical condition meeting criteria for a second unexplained condition was striking. Tender points on physical examination and decreased pain threshold and tolerance were the most frequent and consistent objective findings. A major shortcoming of all proposed explanatory models is their inability to account for the occurrence of unexplained clinical conditions in many affected patients. CONCLUSIONS: Overlap between unexplained clinical conditions is
substantial. Most studies are limited by methodologic problems, such as case definition and the selection and recruitment of case-patients and controls.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11346323

Journal/Curr Opin Pulm Med. 7: B29-42.


Journal/Mutat Res. 482: 1-113.

Oxidative stress is implicated in the intracellular signal transduction pathways for nitric oxide synthase (NOS) induction. The electromagnetic field (EMF) is believed to increase the free radical lifespan [S. Roy, Y. Noda, V. Eckert, M.G. Traber, A. Mori, R. Liburdy, L. Packer, The phorbol 12-myristate 13-acetate (PMA)-induced oxidative burst in rat peritoneal neutrophils is increased by a 0.1 mT (60 Hz) magnetic field, FEBS Lett. 376 (1995) 164-6; F.S. Prato, M. Kavaliers, J.J. Carson, Behavioural evidence that magnetic field effects in the land snail, Cepaea nemoralis, might not depend on magnetite or induced electric currents, Bioelectromagnetics 17 (1996) 123-30; A.L. Hulbert, J. Metcalfe, R. Hesketh, Biological response to electromagnetic fields, FASEB J. 12 (1998) 395-420]. We tested the effects of EMF on endotoxin induced nitric oxide (NO) generation in vivo. Male BALB/C mice were injected with lipopolysaccharide (LPS) intraperitoneously (i.p.), followed by the exposure to EMF (0.1 mT, 60 Hz). Five hours and 30 min after the LPS administration, mice were administered with a NO spin trap, ferrous N-methyl-D-glucaminedithiocarbamate (MGD-Fe). Thirty minutes later, mice were sacrificed, and their livers were removed. The results were compared to three control groups: group A (LPS (-) EMF(-)); group B (LPS(-) EMF(+)); group C (LPS(+) EMF(-)). The ESR spectra of obtained livers were examined at room temperature. Three-line spectra of NO adducts were observed in the livers of all groups. In groups A and B very weak signals were observed, but in groups C and D strong spectra were observed. The signal intensity of the NO adducts in Group D was also significantly stronger than that in Group C. EMF itself did not induce NO generation, however, it enhanced LPS induced NO generation in vivo.


Intrathecal administration of alpha(2) adrenergic agonists, such as clonidine, is capable of alleviating neuropathic pain. Recent studies suggest that spinal nitric oxide (NO) mediates the analgesic effect of intrathecal clonidine. Furthermore, compared to nicotinic receptors, spinal muscarinic receptors play a greater role in the analgesic effect of intrathecal clonidine. In the present study, we tested a hypothesis that clonidine-evoked NO release is dependent primarily on muscarinic receptors in the spinal cord after nerve injury. A rat model of neuropathic pain was induced by ligation of the left L(5)/L(6) spinal nerves. Using an in vitro spinal cord perfusion preparation, the effect of muscarinic and nicotinic receptor antagonists on clonidine-evoked nitrite (a stable product of NO) release was determined. Both muscarinic and nicotinic antagonists dose-dependently attenuated clonidine-elicited nitrite release. In spinal cords from the neuropathic rats, the inhibitory effect of muscarinic receptor antagonists (atropine and scopolamine) on clonidine-elicited nitrite release was more potent than that of nicotinic receptor antagonists (mecamylamine and hexamethonium). However,
in spinal cords obtained from sham animals, the inhibitory effect of muscarinic and nicotinic antagonists did not differ significantly. These results indicate that muscarinic, as well as nicotinic, receptors mediate clonidine-induced NO release in the spinal cord. These data also suggest that after nerve injury, the cascade of activation of alpha(2) adrenergic receptors-muscarinic receptors-NO in the spinal cord likely plays a predominant role in the analgesic effect of intrathecal clonidine on neuropathic pain.


In this study we investigated the effects of deltamethrin on the expression of P53, Bax and Bcl-2 in rat brain. Immunohistochemical analysis demonstrated that the immunoreactivity for P53 was markedly increased in the cerebral cortex and hippocampus at 5 h after deltamethrin treatment, and maintained at an increased level at 24 and 48 h, whereas little immunoreactivity for P53 was seen in the same brain regions of control rats. The immunostaining for Bax was also elevated in the same brain regions, showing the same time course of P53 expression after deltamethrin treatment. However, the immunolabeling for Bcl-2 was markedly decreased at 24 h after a transient increase at 5 h following deltamethrin treatment. These results indicate that deltamethrin leads to the persistent increase of P53 and Bax expression and transient elevation of Bcl-2 expression, resulting in an increased ratio of Bax to Bcl-2, which may contribute to apoptotic cell death in rat brain following deltamethrin treatment.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10771154


In the present study we identified the degeneration and apoptotic cell death in rat brain after deltamethrin treatment. By hematoxylin-eosin (H&E) staining, a large number of degenerative cells (pyknosis of nuclei, disruption of eosinophilic cytoplasm) were seen in the hippocampus and cortex at 24 and 48 h after deltamethrin treatment at a dose of 12.5 mg/kg (i.p.) in corn oil. The similar morphological changes of degenerative cells were observed by cresyl violet staining. Numerous apoptotic cells were detected by in situ end labeling (ISEL) and flow cytometric analysis in the hippocampus and cortex at 24 and 48 h following deltamethrin treatment at the same dose, whereas no ISEL-positive cells were seen in the same brain regions of control rats. Moreover, using DNA gel electrophoresis, it was demonstrated that DNA fragmentation was
markedly induced in the hippocampus and cortex at 24, 48 and 72 h after treatment. In addition, the protein synthesis inhibitor cycloheximide inhibited the DNA fragmentation elicited by deltamethrin in rat brain. These results indicate that deltamethrin induces degeneration and apoptotic cell death in rat brain, suggesting an important role played by apoptosis in neurotoxicity of deltamethrin.


Our previous work indicates that deltamethrin induces degeneration and apoptosis in rat brain at 24 and 48 h after treatment. To determine whether molecular characteristics of apoptosis is involved in neurodegeneration in rat brain after deltamethrin treatment, we investigated the effects of deltamethrin on the mRNA expression of p53 and bax and their correlation with deltamethrin-induced apoptotic cell death in rat brain. Hematoxylin-eosin and cresyl violet staining revealed numerous degenerative cells in cortex and hippocampus at 5 and 24 h after deltamethrin treatment. Apoptotic cells were detected in cortex and hippocampus of treated rats at 24 h by in situ end labeling, whereas no apoptotic cells were observed in the same brain regions at 5 h after treatment. By using in situ hybridization, it was demonstrated that the increase of p53 and bax mRNA levels appeared at 5 and also at 24 h after treatment. The alterations in mRNA expression of p53 and bax preceded the occurrence of delayed apoptotic cell death in the same brain regions after deltamethrin treatment. These results indicate that (1) deltamethrin induces delayed apoptotic cell death, which may play an important role in deltamethrin-elicited neurodegeneration; (2) deltamethrin leads to the persistent increase of p53 and bax mRNA levels, which may contribute to delayed apoptosis in rat brain following deltamethrin treatment.


Multiple chemical sensitivities (MCS) syndrome, also known as idiopathic environmental intolerance, is a controversial diagnosis that encompasses a wide range of waxing and waning, subjective symptoms referable to more than one body system and provoked by exposure to low levels of chemicals, foods, or other agents in the environment. Although MCS has been studied extensively, a unifying mechanism explaining the illness remains obscure, and clinicians are divided as to whether such a medical entity exists separately from psychosomatic syndromes. MCS is an adult diagnosis; there is little reference to pediatric cases in the scientific literature. In this case from the Pediatric Environmental Health Subspecialty Unit at Boston's Children's
Hospital, I present the case of a preschool child who had suffered from milk allergy and poor weight gain as an infant, and then later developed asthma, allergic symptoms, sinusitis, headaches, fatigue, and rashes precipitated by an expanding variety of chemicals, foods, and allergens. I review definitions, mechanisms, diagnostic strategies, and management, and discuss some uniquely pediatric features of MCS as illustrated by this case.


(2000) Statistical problems in bioassay and risk assessment. Williams, PL Journal/Crisp Data Base National Institutes of Health. DESCRIPTION: The purpose of this proposal is to address statistical issues related to the design, analysis, and interpretation of animal bioassays for both cancer and developmental toxicity. These types of animal studies play an essential role in the risk assessment process for evaluating potentially hazardous chemical compounds and other environmental agent. Developmental toxicity studies evaluate adverse effects of exposure on the developing fetus. Increased sensitivity to exposure during certain periods of the gestational cycle makes the timing and the duration of exposures particularly important. A major component of the proposed research involves developing statistical methods for incorporating duration and timing of exposure into the risk assessment process for developmental toxicity. In particular the concept of a Benchmark Dose will be extended to account for exposure duration. Improved methods for study design of developmental toxicity experiments which address exposure level, duration, and timing will also be developed. The assessment of developmental effects often relies on multiple endpoints, such as prenatal death or viability, malformations of various types and low birth weight. The statistical analysis of such data must therefore address both correlations among offspring for the same end-point (i.e., the litter effect) and correlations among the multiple endpoints. The proposed research addresses several issues related to the assessment of multiple outcomes in developmental toxicity studies. First, the issue of testing for exposure effects on multiple outcomes will be addressed when not all outcomes can be observed on each offspring, either due to logistical or economic constraints. Secondly, statistical methods for assessing the effect of exposure on multiple ordinal outcomes will be considered. For both cancer and developmental toxicology, much recent interest has focused on incorporating additional biological information into dose-response models for risk assessment. One component of the proposed research concerns the development of statistical methods for assessing non-linearities in dose-response and their relationship with biological and chemical characteristics, such as mutagenicity,
molecular structure, and chemical activity. Flexible dose response models will first be fit to a large existing body of rodent bioassay data. Meta-analysis techniques will be developed to account for the variability in estimated dose-response patterns for a given chemical across differing sex/species combinations and across multiple endpoint (tumor sites or developmental outcomes).


An increased concentration of nitric oxide (NO) in exhaled air (FENO) is now recognized as a critical component of the asthmatic phenotype. When we identified patients with asthma on the basis of a standard case definition alone, we found that they were remarkably heterogeneous with respect to their FENO. However, when we included genotype at a prominent asthma candidate gene (i.e., NOS1) in the case definition, and determined the number of AAT repeats in intron 20, we identified a remarkably homogeneous cohort of patients with respect to FENO. Both mean FENO (p = 0.00008) and variability around the mean (p = 0.000002) were significantly lower in asthmatic individuals with a high number (> or = 12) of AAT repeats at this locus than in those with fewer repeats. These data provide a biologically tenable link between genotype at a candidate gene in a region of linkage, NOS1, and an important component of the asthmatic phenotype, FENO. We show that addition of NOS1 genotype to the case definition of asthma allows the identification of a uniform cohort of patients, with respect to FENO, that would have been indistinguishable by other physiologic criteria. Our isolation of this homogeneous cohort of patients ties together the well-established associations among asthma, increased concentrations of NO in the exhaled air of asthmatic individuals, and variations of trinucleotide repeat sequences as identified in several neurologic conditions.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11112111


The author provides a brief overview of single photon emission computed tomography in the assessment of multiple chemical sensitivities.


From mollusks to mammals the activation of cAMP response element-binding protein (CREB) appears to be an important step in the formation of long-term memory (LTM). Here we show that a 5 min exposure to a novel environment (open field) 1 hr after acquisition of a one-trial inhibitory avoidance training hinders both the formation of LTM for the avoidance task and the increase in the phosphorylation state of hippocampal Ser 133 CREB [phosphorylated CREB (pCREB)] associated with the avoidance training. To determine whether this LTM deficit is attributable to the reduced pCREB level, rats were bilaterally cannulated to deliver Sp-adenosine 3', 5'-cyclic monophosphothioate (Sp-cAMPS), an activator of PKA. Infusion of Sp-Adenosine 3',5'-cyclic monophosphothioate Sp-cAMPS to CA1 region increased hippocampal pCREB levels and restored normal LTM of avoidance learning in rats exposed to novelty. Moreover, a 5 min exposure to the open field 10 min before the avoidance training interferes with the amnesic effect of a second 5 min exposure to the open field 1 hr after avoidance training and restores the hippocampal levels of pCREB. In contrast, the avoidance training-associated activation of extracellular signal-regulated kinases (p42 and p44 mitogen-activated protein kinases) in the hippocampus is not altered by novelty. Together, these findings suggest that novelty regulates LTM formation by modulating the phosphorylation state of CREB in the hippocampus.

Many pesticides are able to block or activate the steroid hormone receptors and/or to affect the levels of sex hormones, thereby potentially affecting the development or expression of the male and female reproductive system or both. This emphasizes the relevance of screening pesticides for a wide range of hormone-mimicking effects. Twenty-two pesticides were tested for their ability to affect CYP19 aromatase activity in human placental microsomes using the classical [(3)H](2)O method. Prochloraz, imazalil, propiconazole, fenarimol, triadimenol, triadimefon (all fungicides), and dicofol (an acaricide) gave rise to a statistically significant inhibition of aromatase activity. The IC(50)s of prochloraz, imazalil, propiconazole fenarimol, triadimenol, and triadimefon were calculated from dose-response curves to be 0.04, 0.34, 6.5, 10, 21 and 32 microM, respectively. The IC(50) of dicofol was greater than 50 microM. The positive control 4-hydroxyandrostenedione (1 microM) caused an inhibition of aromatase activity by 74%. The compounds, which did not affect the aromatase activity, were bromopropylate, chlortetracycline, chlorpromazine, chlorpyrifos, diuron, heptachlor, iprodion, linuron, pentachlorophenol, procymidone, propyzamide, quintozen, tetrachlorvinphos and tetrachlorvinphos. With the purpose of comparing the results for fenarimol obtained with the microsomal system with data from an intact cell system, an aromatase assay based on JEG-3 cells was established. 4-Hydroxyandrostenedione (1 microM) inhibited the aromatase activity in JEG-3 cells by 94%. The IC(50) for fenarimol in this system was 2 microM, slightly lower than that observed in the microsomal system. For the first time, fenarimol has been demonstrated to inhibit aromatase activity in human tissues and, furthermore, propiconazole, triadimefon, and triadimenol were identified as weak aromatase inhibitors. In conclusion, seven out of 22 tested pesticides turned out to be weak to moderate aromatase inhibitors in vitro, indicating the relevance of elucidating the endocrine effects in vivo of these compounds.


In 1985, a WHO Working Group presented diagnostic criteria and a classification for solvent-induced chronic toxic encephalopathy (CTE). In the same year, the "Workshop on neurobehavioral effects of solvents" in Raleigh, N.C., USA introduced a somewhat different classification for CTE. The objective of this review is to study the diagnostic procedures that are used to establish the diagnosis of CTE, and the extent to which the diagnostic criteria and classification of the WHO, and the classification of the Raleigh Working Group, are applied. A systematic search of studies on CTE was performed, and the diagnostic criteria and use of the WHO and Raleigh classifications were listed. We retrieved 30 original articles published in English from 1985 to 1998, in which CTE was diagnosed. Only two articles did not report the duration of solvent exposure. The type of solvent(s) involved was described in detail in four articles, poorly in 17 articles, and not at all in nine articles. Tests of general intelligence were used in 19 articles, and tests of both attention and mental flexibility and of learning and memory were used in 18 articles. Exclusion, by interview, of potentially confounding conditions, such as somatic diseases with central nervous effects and psychiatric diseases, was reported in 21 and 16 articles, respectively. In only six of the articles were both the WHO diagnostic criteria and the WHO or Raleigh classifications used. In the future, parameters of exposure, psychological test results, and use of medication that possibly affects psychological test results should always be described. We list some advantages and disadvantages of the Raleigh and WHO classifications. To aid inter-study comparisons, the diagnosis of CTE should be categorized and reported according to an internationally accepted classification.

(2000) [Hypersensitivity to electricity is not an allergy, what is it?].


Insulin stimulates the tyrosine kinase activity of its receptor resulting in the tyrosine phosphorylation of pp185, which contains insulin receptor substrates IRS-1 and IRS-2. These early steps in insulin action are essential for the metabolic effects of insulin. Feeding animals a high-fructose diet results in insulin resistance. However, the exact molecular mechanism underlying this effect is unknown. In the present study, we determined the levels and phosphorylation status of the insulin receptor and pp185 (IRS-(1/2)) in liver and muscle of rats submitted to a high-fructose diet evaluated by immunoblotting with specific antibodies. Feeding fructose (28 days) induced a discrete
insulin resistance, as demonstrated by the insulin tolerance test. Plasma glucose and serum insulin and cholesterol levels of the two groups of rats, fructose-fed and control, were similar, whereas plasma triacylglycerol concentration was significantly increased in the rats submitted to the fructose diet (P<0.05). There were no changes in insulin receptor concentration in the liver or muscle of either group. However, insulin-stimulated receptor autophosphorylation was reduced to 72 +/- 4% (P<0.05) in the liver of high-fructose rats. The IRS-1 protein levels were similar in both liver and muscle of the two groups of rats. In contrast, there was a significant decrease in insulin-induced pp185 (IRS-(1/2)) phosphorylation, to 83 +/- 5% (P<0.05) in liver and to 77 +/- 4% (P<0.05) in muscle of the high-fructose rats. These data suggest that changes in the early steps of insulin signal transduction may have an important role in the insulin resistance induced by high-fructose feeding.

(2000) Questioning what we call "alternative".

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11865474

(2000) [Multiple chemical sensitivity].
Torii, S Journal/Ryoikibetsu Shokogun Shirizu. 531-4.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11269155


Although it has become an accepted standard to acknowledge the patient as a full partner in health care decisions, replacing traditional authoritative relationships with those based on an emancipatory model, the experiences of persons living with chronic illness confirm that this paradigm shift is not yet apparent in many health care relationships. In this paper, the authors present a qualitative secondary analysis of combined data sets from their research into chronic illness experience with two quite different chronic diseases - Type I Diabetes (a socially legitimized chronic disease) and Environmental Sensitivities (a disease which is currently treated with considerable scepticism). Comparing the experiences of individuals with diseases that are quite
differently socially constructed, it becomes possible to detect common underlying health professional values and attitudes that powerfully influence the experience of living with and negotiating health care for a chronic illness. In the discussion of findings from this study, the authors examine the implications of the spiral of behaviors that fuels mutual alienation in chronic illness care relationships if professionals are unable to value patient expertise.


Parkinson's disease (PD) has been associated with exposure to pesticides and oxidative injury. The involvement of paraoxonase in both pesticide metabolism and lipid peroxidation suggests that it may play a role in the pathogenesis of PD. We examined the frequency of polymorphic alleles of the PON1 and PON2 genes in a sample of caucasian subjects with PD. The frequency distribution of these genotypes did not differ significantly between patients and controls, including those who had reported exposure to pesticides.


Gulf War veterans have reported health problems that they attribute to their military service, but little is understood about the nature or extent of these conditions. To determine whether Kansas Gulf War veterans are affected by excess health problems, a population-based survey of 1,548 veterans who served in the Persian Gulf War (PGW) and 482 veterans who served elsewhere (non-PGW) was conducted in 1998. Gulf War illness, defined as having chronic symptoms in three of six domains, occurred in 34% of PGW veterans, 12% of non-PGW veterans who reported receiving vaccines
during the war, and 4% of non-PGW veterans who did not receive vaccines. The prevalence of Gulf War illness was lowest among PGW veterans who served on board ship (21%) and highest among those who were in Iraq and/or Kuwait (42%). Among PGW veterans who served away from battlefield areas, Gulf War illness was least prevalent among those who departed the region prior to the war (9%) and most prevalent among those who departed in June or July of 1991 (41%). Observed patterns suggest that excess morbidity among Gulf War veterans is associated with characteristics of their wartime service, and that vaccines used during the war may be a contributing factor.


This chapter focuses on the psychotherapy of individuals who suffer distress from functional somatic syndromes; specifically, idiopathic environmental intolerance (IEI). While patients believe environmental intolerances cause their distress, its origin is treated as psychological, mediated through psychophysiological systems and mechanisms associated with the stress response. Factors considered include stress and trauma premorbid to the alleged onset of IEI; somatization and its expression through affective, anxiety, and somatoform disorders; personality disorders and associated psychological defenses; motivation for the sick role; and iatrogenic suggestion and reinforcement of unsubstantiated toxicogenic theories and treatments. Psychotherapies include behavioral desensitization, cognitive-behavioral therapy, cognitive therapy, and psychotropic medications. The greatest challenge in treatment is to overcome the patient's disabling belief in a toxicogenic explanation for his or her symptoms.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10903556


This chapter addresses the diagnostic evaluation and treatment of the patient presenting with idiopathic environmental intolerance (IEI). Clinicians with different views about the pathogenesis of IEI may agree on clinical management programs aimed at improved symptom control and functional ability.

The editor discusses usage of the terms "idiopathic environmental intolerance," "multiple chemical sensitivity," and "environmental illness." Also addressed are prevalence, theories of etiology, evaluation and treatment, and social and political implications.


OBJECTIVE: To evaluate an ambulatory physiological monitoring system during a mountaineering expedition. We hypothesized that the Environmental Symptoms Questionnaire, combined with frequent measurement of oxygen saturation and core temperature, would accurately identify cases of environmental illness. METHODS: Twelve military mountaineers took a daily Environmental Symptoms Questionnaire, monitored fingertip oxygen saturations, and recorded core temperatures while climbing a 4,949-m peak. Illnesses identified by the system were compared with those identified by spontaneous reports. RESULTS: The system correctly identified one case of high-altitude pulmonary edema and two illnesses that were not reported to the physician (one case of acute mountain sickness and one of self-limited symptomatic desaturation). However, it did not identify two illnesses that were severe enough to preclude further climbing (one case of sinus headache and one of generalized fatigue). CONCLUSIONS: Our monitoring system may complement, but cannot replace, on-site medical personnel during mountaineering expeditions.

(2000) Support for Conference Entitled 'The Role of Neural Plasticity in Chemical Intolerance'.
Shaikh, R Journal//u0105. 29.

Chemical Intolerance (CI), including multiple chemical sensitivity, has been an intriguing problem in environmental health, and it has been suspected that CI played a role in Gulf War Syndrome. The uniqueness of the conference was its focus on neuro-biological changes, which has appeared to occur in individuals with CI. The conference provided a forum for the exchange of ideas among leading investigators in an effort to evaluate evidence regarding the role of neural plasticity in the development of CI. Among the topics discussed was a rationale for further research and clinical applications. Other disorders that overlap with CI, such as Gulf War Syndrome, chronic fatigue and fibromyalgia, were also be discussed. The conference was attended by toxicologists, basic neuroscientists, environmental health professionals and clinicians, including general practitioners and psychiatrists.


The School Health Initiative: Environment, Learning, Disease (SHIELD) study is a novel school-based investigation of children's environmental health in economically disadvantaged urban neighborhoods of Minneapolis. This article describes the study design and summarizes lessons learned about recruiting and monitoring this historically understudied population. The SHIELD study focused on measuring children's exposures to multiple environmental stressors (volatile organic chemicals (VOCs), environmental tobacco smoke, allergens, bioaerosols, metals, pesticides, polychlorinated biphenyls (PCB), phthalates) and exploring related effects on respiratory health (e.g., lung function) and learning outcomes (e.g., standardized test scores, academic achievement). It involved intensive exposure monitoring, including environmental measurements inside and outside the children's schools and inside their homes, personal measurements with passive dosimeters worn by the children, and biological marker measurements in blood and urine. The SHIELD participants comprised a stratified random sample of 153 "index" children and 51 of their siblings enrolled in grades 2-5 at two adjacent elementary schools. The Minneapolis Public Schools (MPS) assisted with identifying, contacting, recruiting, and monitoring this population, which traditionally is difficult to study because families/children are highly mobile, speak a diversity of languages, frequently do not have a telephone, endure economic hardships, often do not trust researchers, and have a spectrum of unconventional lifestyles and living arrangements. Using a school-based approach, the overall SHIELD enrollment (response) rate was 56.7%, with a wide disparity between English-speaking (41.7%) and non-English-speaking (71.0%) families/children. Most children remained involved in the study through both monitoring sessions and exhibited an acceptable degree of compliance with study protocols, including providing blood and urine samples. Results indicate that it is both practical and affordable to conduct
probability-based exposure studies in this population, but that it is also important to
improve our understanding of factors (e.g., cultural, economic, psychological, social)
affecting the willingness of families/children to participate in such studies, with special
emphasis on developing cost-effective recruitment methods.

Semple, S, Dick, F, Osborne, A, Cherrie, JW, Soutar, A, Seaton, A and Haites, N

OBJECTIVES: To investigate loss of colour vision related to exposure to solvents and
the role of three enzyme polymorphisms in modifying the risk in exposed workers.
METHODS: A sample was studied of 68 male dockyard workers and 42 male
community controls with and without neuropsychological symptoms from a previous
cross sectional study. Indices of cumulative and intensity based exposure to solvents
were calculated for all subjects. Alcohol, drug, and smoking histories were obtained.
Colour vision was tested by Lanthony D15d colour vision test. Genotype of glutathione
S-transferase M1 and T1 and N-acetyltransferase 2 polymorphisms were determined.
RESULTS: The relation between impairment of colour vision and exposure to solvents
was investigated with multiple regression techniques. Increasing annual exposure to
solvents was significantly associated with reduced colour vision (p=0.029). Impairment
of colour vision was not associated with neuropsychological symptoms as measured by
the Q16 solvent symptom questionnaire. No significant association was found between
acquired impairment of colour vision and genetic polymorphisms when GSTM1,
GSTT1 or NAT2 phenotypes were included in the analyses. CONCLUSIONS:
Exposure to mixed solvents is associated with impairment in colour vision, the risk
increases with increasing exposure. The risk of impairment of colour vision was not
altered in this study by the presence of different GSTM1, GSTT1 or NAT2
polymorphisms.

(2000) Plausibility of homeopathy and conventional chemical therapy: the
systemic memory resonance hypothesis.

The controversy surrounding clinical observations and double-blind studies on
homeopathic treatments is lessened when modern dynamical systems analysis is
applied to high-dilution therapies. The logic of recurrent feedback loops, which applies
to all dynamical network systems, inexorably leads to the systemic memory hypothesis
- that complex patterns of emergent information and energy are stored to various
degrees in physical, chemical, and biological systems. The addition of resonance, a
dynamic pattern recognition process, explains many classic observations using
high-dilution therapies. The systemic memory resonance hypothesis potentially provides a plausible biophysical mechanism for explaining not only how high-dilution therapies contribute to healing, but by extension, how information and energy in low-dilution and chemical therapies contribute to healing as well.

---

(2000) [Perinatal disorders of the central nervous system in children under ecologically unfavorable conditions].
Saichenko, SP, Soloboeva Iu, I, Plotko, EG, Cherednichenko, AM and Seliankina, KP
Journal/Med Tr Prom Ekol. 21-4.

Regular medical and biologic etiologic risk factors of perinatal disorders of central nervous system in children give much less contribution into neurologic diseases development, than they give under ecologically unfavorable conditions when those factors induce most disorders.

---

(2000) How to deal with medically unknown symptoms.

---


The multiple chemical sensitivities syndrome (MCS) and other chronic syndromes causing fatigue, headache and other protean CNS symptoms without observable signs, are proposed to result from hypoxia/hypercapnia (H/H) due to disturbed breathing. The concept is explained in terms of sleep apnea (SA), although H/H could result from causes other than SA. Reasons for considering this etiologic linkage are as follows: 1. MCS symptoms resemble those of SA. 2. The only physical signs associated with MCS (upper airway inflammation and obstruction) can aggravate SA. 3. The only neuropsychiatric finding common among MCS symptomatics, reduced verbal recall, is associated with SA. 4. Many MCS symptomatics attribute onset of their condition to a pesticide or solvent exposure. Solvent neurotoxicity may cause cacosmia, a symptom of MCS and SA. 5. Improved upper airway patency, a first-line therapy in SA, may improve symptoms in some MCS-like conditions. Implications for diagnosis and treatment of MCS are discussed.
Vulnerable periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the temporal and regional emergence of critical developmental processes (i.e., proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Evidence from numerous sources demonstrates that neural development extends from the embryonic period through adolescence. In general, the sequence of events is comparable among species, although the time scales are considerably different. Developmental exposure of animals or humans to numerous agents (e.g., X-ray irradiation, methylazoxymethanol, ethanol, lead, methyl mercury, or chlorpyrifos) demonstrates that interference with one or more of these developmental processes can lead to developmental neurotoxicity. Different behavioral domains (e.g., sensory, motor, and various cognitive functions) are subserved by different brain areas. Although there are important differences between the rodent and human brain, analogous structures can be identified. Moreover, the ontogeny of specific behaviors can be used to draw inferences regarding the maturation of specific brain structures or neural circuits in rodents and primates, including humans. Furthermore, various clinical disorders in humans (e.g., schizophrenia, dyslexia, epilepsy, and autism) may also be the result of interference with normal ontogeny of developmental processes in the nervous system. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function. This concern is compounded by the fact that developmental neurotoxicity that results in small effects can have a profound societal impact when amortized across the entire population and across the life span of humans.

The same classes of pesticides are used all over the world, but conditions of use vary widely, and public perceptions of risk vary more widely still. Within Western Europe pesticide residues in commercially traded foodstuffs are subject to international standards and are closely monitored. Hence risks to consumers from such foods are negligible. The major hazards are poisoning associated with high acute/chronic operator exposures due to occasional pesticide misuse. In addition pesticides provide a convenient means of attempting suicide in agricultural areas. In contrast, public
perception of risks from pesticides centres on low level exposures, and is heightened by several factors. These are: poisonings associated with pesticide misuse; the indirect nature of the benefit to the consumer (cf. medicines or public health uses); and commercially motivated marketing of pesticide-free produce. In press reports pyrethroid insecticides have been linked to "Multiple Chemical Sensitivity" in Germany, and organophosphates to "Chronic Fatigue Syndrome" in the UK. A number of pressure groups are actively campaigning to ban all uses of organophosphorus pesticides. Unfortunately evaluation of the real risks of pesticide exposure is rendered less certain by the lack of any very useful retrospective exposure measures with which biological effects of uncertain aetiology might be correlated. This means that although we can be sure that pesticides pose no gross threat to health in the general population, subtle effects on more highly exposed sub-populations are, as yet, more difficult to rule out.


Dr. Proctor summarizes the current research literature describing Gulf War (GW) veterans' health issues, particularly as they pertain to chemical sensitivity (CS) and multiple chemical sensitivity (MCS) syndrome. In several studies of GW veterans, using differing criteria and varying assessment measures for CS and MCS, the prevalence rates for CS are reported to be 36-86% in Department of Veterans' Affairs patient populations and 0.8-20% in general cohorts of GW veterans. The rates of MCS are 2-6%. Targeted research is needed to adequately evaluate GW veterans' health concerns and MCS.


BACKGROUND: Idiopathic environmental intolerance (IEI) is associated with unexplained physical symptoms, which overlap considerably with those of panic disorder (PD). OBJECTIVE: This study tested the hypothesis that patients with symptoms to suggest IEI exhibit features of PD in response to nonnoxious environmental stimuli. METHODS: A single-blind, case-control 35% carbon dioxide inhalation challenge was conducted at a university-based occupational health unit with the use of standardized psychologic questionnaires involving 36 patients with IEI and
37 healthy control subjects. The main outcome measures included panic attack symptoms and scores on the Anxiety Sensitivity Index, a measure of panic-related anxiety. RESULTS: Patients with IEI scored significantly higher on the Anxiety Sensitivity Index than control subjects did (P < .05). Significantly more patients with IEI (71%) than control subjects (26%) fulfilled panic attack criteria after carbon dioxide (P < .001). Physiologic responses to the challenge were not significantly different between groups. CONCLUSIONS: Results suggest that, similar to patients with PD, patients with IEI display high anxiety sensitivity and in response to carbon dioxide inhalation tend to experience heightened anxiety and panic attacks.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10669859

(2000) Influence of personality traits on neuropsychological test performance in toxic encephalopathy cases and healthy referent subjects.

The relationship between personality traits and cognitive performance was studied in two groups: men with symptoms and neuropsychological test results compatible with toxic encephalopathy (TE) and demographically similar healthy men (N=57 per group). Personality traits were assessed with the Karolinska Scales of Personality (KSP). The neuropsychological examination included 13 tests covering various functional domains. The TE group displayed elevated scores on all three KSP anxiety scales as well as an elevated impulsiveness score. Furthermore, the TE group had a lower score on the socialization scale than did the referent group. Different relationships between personality dispositions and cognitive functioning emerged in the two groups. Within the referent group the highest correlations were observed between KSP anxiety and socialization scale scores and reaction times measures. This pattern did not appear in the TE group; instead, divergent and a few weak relationships emerged. These relationships involved correlations between the KSP monotony avoidance score and some motor speed scores. By dividing the referent group into low anxiety and high anxiety subgroups on the basis of the multi-component anxiety scale score, it was shown that the test scores in the high anxiety subgroup mostly were indistinguishable from the scores in the TE group. In contrast, the low anxiety group had higher test scores than the TE group in 8 of the 13 tests. In conclusion, the expected relationship between anxiety and cognitive vigilance is absent in TE cases. This indicates that the neuropsychological performance decrement in TE cases is not primarily related to elevated mental distress, but is probably dominated by the effects of organic brain impairment. Thus, in TE cases low neuropsychological test scores should not be regarded as a consequence of emotional symptoms. Furthermore, personality traits may be considered as potential confounders even if traditional matching by demographic criteria has been successfully implemented.
Environmental sensitivity is a multi-system disorder characterized by adverse reactions to certain foods, chemicals, and environmental agents. In this study, the impact of environmental sensitivity on the person, environment, and occupation, as well as on occupational performance and time use, was determined. Using qualitative methods, 12 participants with environmental sensitivity were interviewed during a 2-month period. A time-use diary of activities over a 24-hour period was obtained and compared with a survey conducted by Statistics Canada. Textual analysis was conducted by examining and coding data for emerging themes. Finally, the data were interpreted using the Person-Environment-Occupation Model (Law et al., 1996). Findings suggest a multiple-system involvement that leads to changes in type, time, and location of self-care, productive, and leisure occupations. Changes to personal health, environment, and occupations contributed to a decline in occupational performance. Enabling and constraining factors influenced the adaptation to changes in occupational performance. Emerging themes included an initial struggle for legitimacy, societal stigma, isolation, financial strain, and loss of personal expression. Management of environmental sensitivity involved making personal, environmental, and occupational changes. Possible roles for occupational therapists encompass issues of pacing, energy conservation, environmental changes, job modification, and matching occupational interests with personal abilities.

Simultaneous detection of tyrosine hydroxylase-immunoreactivity and vasopressin mRNA in neurons of the human paraventricular and supraoptic nucleus.

Our purpose was to investigate the proportion of tyrosine hydroxylase (TH)-immunoreactive (IR) neurons expressing vasopressin (VP) mRNA in the human paraventricular and supraoptic nuclei by combining in situ hybridization with immunohistochemistry on the same tissue section. A variability in the proportion of TH-IR neurons synthesizing VP mRNA was observed in adults which was usually more than 50%. In neonates almost all the TH-IR neurons appeared to contain VP mRNA.

Allergic fungal sinusitis.

OBJECTIVES: This study determined whether performance in neurobehavioral tests deteriorates during subjectively annoying chemical challenge below known neurotoxic thresholds among persons with toxic encephalopathy with subjective hypersensitivity to chemicals. METHODS: Subjects with symptoms and previous neuropsychological test results compatible with toxic encephalopathy (TE) of either type 2A (N=12) or 2B (N=12) and unexposed referents (N=12) were challenged in an exposure chamber. In a counterbalanced design, the subjects were exposed on 2 occasions to increasing air concentrations of n-butyl acetate and toluene at levels well below the thresholds for neurotoxic effects. Attention and motor speed tests were given (i) in room air outside the chamber before the challenge, (ii) in room air inside the chamber before the exposure, (iii) at 12 ppm (44 or 56 mg/m3), and (iv) at 48 ppm (at 180 or 228 mg/m3).

RESULTS: For both substances the TE groups showed a slight increase (deterioration) in the simple reaction-time task during chemical exposure, but not in the complex reaction-time task or in the digit symbol test of the Wechsler Adult Intelligence Scale. Contrary to reference subjects, the TE subjects did not show any improvement or learning effect in the digit symbol test over the chamber phases. n-Butyl acetate tended to affect cognitive functioning more obviously than toluene did. Suggestion or expectancy effects were not observed in any group in the clean-air baseline conditions.

CONCLUSIONS: The results do not support the notion that men with subjective hypersensitivity to chemicals would be more affected than healthy men regarding cognitive functioning during annoying solvent exposure below thresholds for acute neurotoxic effects.


BACKGROUND: From the viewpoint of the clinical neuropsychologist, it is not evident if the detection of solvent induced toxic encephalopathy (TE) could be optimized by a
modification of the traditional test batteries, adding tests covering new dimensions or monitoring further functional domains. METHODS: To clarify this issue, TE patients were re-examined with (a) the tests traditionally used in screening for TE and (b) some tests hitherto less utilized within neurotoxicology, involving complex attention and frontal lobe functioning. RESULTS: The results do not indicate that tests of the latter category would be more sensitive to TE than the tests traditionally used. Using an optimized core battery, compiled of tests from both categories, the sensitivity and specificity levels reached a maximum of around 0.7 when using as criterion the reproduction of a subnormal test profile (TE type 2B). CONCLUSIONS: A combination of several traditional and a few newer tests is suggested to optimize the detection of TE. Repeated assessments over time are also recommended.

(2000) [Idiopathic environmental intolerance (IEI): Multiple chemical sensitivity (MCS) and related phenomena]. Obiols Quinto, J Journal/Instituto Nacional de Seguridad e Higiene en el Trabajo, Ediciones y Publicaciones, c/Torrelaguna 73, 28027 Madrid, Spain, 2000. 5p. 11 ref. Multiple chemical sensitivity syndrome (MCS) and associated phenomena are increasingly frequent at work. Certain authors suggest that they could affect 2 to 10% of the population. This information note summarizes current understanding of idiopathic environmental intolerance (IEI) and MCS. Contents: definitions; most frequent causal agents; systems or organs affected and most frequent symptoms; possible mechanisms (biological or psychogenic); diagnosis consensus criteria.


Unusual health problems have been reported by Gulf War (GW) veterans, but no single etiology has been linked to these illnesses. This study was conducted to determine the association between self-reported GW deployment stressors and an illness defined by a combination of fatigue, mood-cognition, and musculoskeletal symptoms. A total of 1002 GW veterans from this cross-sectional survey of four Air Force units completed a self-administered questionnaire that asked about symptoms, demographic and military characteristics, and stressors during deployment. Severe and mild-moderate illness was positively associated with self-reports of pyridostigmine bromide use, insect repellent use and belief in a threat from biological or chemical weapons. Injuries requiring medical attention were only associated with severe illness. These results suggest a link between self-reported chemical, emotional, and physical exposures, and GW veterans' illness. Further research is needed to determine
physiological and psychological mechanisms through which such stressors could have contributed to this symptom complex.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10830562

(2000) Self-reported sensitivity to chemical exposures in five clinical populations and healthy controls.

Two hundred and twenty-five subjects, including normal volunteers and patients with previously documented seasonal affective disorder (SAD), chronic fatigue syndrome (CFS), Cushing's syndrome, Addison's disease and obsessive-compulsive disorder (OCD), completed a self-rated inventory of reported sensitivity to various chemical exposures. Patients with CFS, Addison's disease and SAD self-reported more sensitivity to chemical exposures than normal controls. In addition, women reported more sensitivity than men. This report suggests that chemical sensitivity may be a relevant area to explore in certain medical and psychiatric populations. A possible relationship between reported chemical sensitivity and hypothalamic-pituitary-adrenal (HPA)-axis functioning is discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10904124

(2000) Symposium overview: mechanism of action of nicotine on neuronal acetylcholine receptors, from molecule to behavior.

Nicotine has long been known to interact with nicotinic acetylcholine (ACh) receptors since Langley used it extensively to chart sympathetic ganglia a century ago. It has also been used as an effective insecticide. However, it was not until the 1990s that the significance of nicotine was increasingly recognized from the toxicological, pharmacological, and environmental points of view. This is partly because studies of neuronal nicotinic ACh receptors are rapidly emerging from orphan status, fueled by several lines of research. Since Alzheimer's disease is known to be associated with down-regulation of cholinergic activity in the brain, a variety of nicotine derivatives are being tested and developed for treatment of the disease. Public awareness of the adverse effects of nicotine has reached the highest level recently. Since insect resistance to insecticides is one of the most serious issues in the pest-control arena, it is an urgent requirement to develop new insecticides that act on target sites not shared
by the existing insecticides. The neuronal nicotinic ACh receptor is one of them, and
new nicotinoids are being developed. Thus, the time is ripe to discuss the mechanism
of action of nicotine from a variety of angles, including the molecular, physiological,
and behavioral points of view. This Symposium covered a wide area of nicotine
studies: genetic, genomic, and functional aspects of nicotinic ACh receptors were
studied, as related to anthelmintics and insecticides; interactions between ethanol and
nicotine out the ACh receptor were analyzed, in an attempt to explain the well-known
heavy drinker-heavy smoker correlation; the mechanisms that underlie the
desensitization of ACh receptors were studied as related to nicotine action; selective
pharmacological profiles of nicotine, and descriptions of some derivatives were
described; and chronic nicotine infusion effects on memory were examined using
animal models.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11006350

(2000) [Multiple chemical sensitivity syndrome. Review].
Mozhaev, EA and Golubev, IR Journal/Gig Sanit. 48-50.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11327033

Morton, WE Journal/Arch Neurol. 57: 282.

(2000) Occipital lobe meningioma in a patient with multiple chemical
sensitivities.

BACKGROUND: The concurrent diagnosis of meningioma with increased intracranial
pressure has not been reported previously in a patient who meets diagnostic criteria for
multiple chemical sensitivities (MCS). METHODS: A patient who had been evaluated in
an occupational medicine practice, and by several other physicians for sensitivity to
chemical odors was found to have papilledema and a visual field deficit. The patient
met the clinical criteria set forth by Cullen in 1987 for MCS. A magnetic resonance
imaging (MRI) scan was performed. RESULTS: The MRI revealed a large occipital
lobe meningioma, which was surgically resected. Removal of the meningioma had little
effect on the patient's symptoms. She has been unable to return to her job as a custodian. **DISCUSSION:** The etiology of MCS has been disputed and is currently unresolved. Those who evaluate patients with MCS are reminded that meningiomas and other intracranial mass lesions can affect olfaction, and that patients with MCS can have treatable intracranial abnormalities.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10706757

(2000) **Immunologic parameters of multiple chemical sensitivity.**

Immunologic abnormalities have long been advanced as a potential mechanism for multiple chemical sensitivity (MCS). An immunologic mechanism is supported in part by the systemic nature of the symptoms reported, the complex interactions known to exist between the immune system and other systems, and limited experimental evidence. However, there are both theoretical grounds for doubting an immunologic mechanism in MCS and methodological constraints in many of the studies that have been conducted in humans. The authors discuss the structure and function of the immune system as it potentially applies to MCS, the uses and limitations of immunologic testing, and the evidence for immunologic theories of MCS. They describe recent work to validate some of the immunologic tests used in MCS and consider opportunities for further research.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10903557

(2000) **Quality of life and capsaicin sensitivity in patients with sensory airway hyperreactivity.**
Millqvist, E, Lowhagen, O and Bende, M Journal/Allergy. 55: 540-5.

BACKGROUND: A group of patients with asthma-like symptoms and sensitivity to chemical irritants has shown an increased cough sensitivity to inhaled capsaicin compared to patients with asthma and to healthy controls. The condition is called sensory hyperreactivity (SHR), and the patients often feel that they are socially handicapped because of the risk of exposure to chemical irritants in daily life. **METHODS:** Twenty-six patients with asthma-like symptoms after exposure to nonspecific irritating stimuli, but without IgE-mediated allergy or demonstrable bronchial obstruction, were selected for a study of the response to a capsaicin test and measurement of quality of life by a general health profile (the Nottingham Health Profile [NHP]). We also investigated whether there was a correlation between quality of life
and sensitivity to capsaicin. RESULTS: The patients demonstrated a dose-dependent response to the capsaicin provocation, with coughing and respiratory and other symptoms, that significantly differed from 12 healthy controls. The health profile showed that patients with SHR had a significantly reduced quality of life compared to reference values, and there was a significant correlation between the health profile and sensitivity to capsaicin. CONCLUSIONS: Patients with asthma-like symptoms verified by the capsaicin inhalation test for sensory hyperreactivity have a poor quality of life. The correlation between quality of life and sensitivity to capsaicin objectively demonstrates the validity of this general health profile study.


(2000) Cough provocation with capsaicin is an objective way to test sensory hyperreactivity in patients with asthma-like symptoms.


BACKGROUND: A group of patients with asthma-like symptoms and sensitivity to chemical irritants, but without bronchial obstruction, has been found among subjects referred for suspected asthma. They have no well-defined diagnosis, and no objective diagnostic method has previously been available. These patients are more sensitive to inhaled capsaicin than are patients with asthma or healthy controls. The aim was to study cough and other capsaicin-induced symptoms and to test the effect of a drug (lidocaine) that inhibits nerve transmission in sensory nerves. METHODS: Twelve patients were provoked with three different concentrations of inhaled capsaicin solutions in a randomized, double-blind order. They all had asthma-like symptoms and were sensitive to chemical irritants, but had no IgE-mediated allergy or demonstrable bronchial obstruction. Before the provocations, the patients inhaled lidocaine or placebo (saline), also in a double-blind, randomized order. The results were expressed as the number of coughs and scores of various symptoms. RESULTS: The patients reacted in a dose-dependent way with cough, airway, and eye symptoms, which were significantly reduced after preinhalation of lidocaine. CONCLUSIONS: A drug that inhibits transmission in sensory nerves successfully blocked the number of coughs and other symptoms provoked by inhalation of capsaicin. This indicates that the mechanisms underlying chemical sensitivity in these patients may originate in the sensory nervous system, and we call this condition "sensory hyperreactivity".


(2000) Reproducibility of the University of Toronto self-administered questionnaire used to assess environmental sensitivity.
Environmental sensitivity patients report symptoms provoked by low-level exposure to a wide range of substances. Features of published case definitions include nature of onset, chronicity, symptom provocation by multiple substances, symptom provocation by an escalating number of exposures, involvement of multiple body systems including the nervous system, provocation by unrelated substances, and addictive behaviors. This study assessed the reproducibility of a Canadian self-administered questionnaire, the University of Toronto Health Survey, designed to determine the prevalence of the features described in these case definitions. A total of 191 eligible respondents aged 16-70 years who attended several types of medical practices in 1994 were invited to complete a second questionnaire 5-7 months after the first; 134 (70.2%) complied. Total agreement on whether patients satisfied each of seven case definitions ranged from 80% to 90%. After adjustment for chance, major agreement was observed for three of the seven case definitions (kappa = 0.69, 0.68, and 0.78). The survey achieved good reproducibility regarding self-report of symptoms described in published case definitions of environmental sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10905534

(2000) Exposure to a theta-burst patterned magnetic field impairs memory acquisition and consolidation for contextual but not discrete conditioned fear in rats.

Preceding or immediately following fear-conditioning rats were exposed for 30 min to either a sham field, one of two symmetrical (sine-wave 7, 20 Hz) magnetic fields or to one of two complex magnetic fields whose waveforms were modeled after salient electrophysiological patterns within either the hippocampal formation (theta-burst) or the amygdaloid complex (burst-firing). The magnetic fields were presented in successive 2s intervals through each of the three spatial planes and then simultaneously within all three planes. Field strengths ranged between 0.5 and 1 microTesla. Only the group exposed after the conditioning to the theta-burst (hippocampal) magnetic fields displayed evidence of forgetting, as inferred by their marked attenuation of freezing behavior, during contextual extinction 24h later. This powerful treatment explained 75% of the variance in the extinction scores. Behavioral responses to the discrete conditioned stimulus were not affected. These findings are consistent with the involvement of the hippocampus in learned fear to contextual stimuli but not to discrete auditory stimuli and suggest that physiologically relevant stimuli may be delivered to the brain by weak, complex magnetic fields whose intensities are ubiquitous within modern environments.
McCampbell, A Journal/Am Fam Physician. 61: 45.

Researchers who collaborate on clinical research studies from diffuse locations need a convenient, inexpensive, secure way to record and manage data. The Internet, with its World Wide Web, provides a vast network that enables researchers with diverse types of computers and operating systems anywhere in the world to log data through a common interface. Development of a Web site for scientific data collection can be organized into 10 steps, including planning the scientific database, choosing a database management software system, setting up database tables for each collaborator's variables, developing the Web site's screen layout, choosing a middleware software system to tie the database software to the Web site interface, embedding data editing and calculation routines, setting up the database on the central server computer, obtaining a unique Internet address and name for the Web site, applying security measures to the site, and training staff who enter data. Ensuring the security of an Internet database requires limiting the number of people who have access to the server, setting up the server on a stand-alone computer, requiring user-name and password authentication for server and Web site access, installing a firewall computer to prevent break-ins and block bogus information from reaching the server, verifying the identity of the server and client computers with certification from a certificate authority, encrypting information sent between server and client computers to avoid eavesdropping, establishing audit trails to record all accesses into the Web site, and educating Web site users about security techniques. When these measures are carefully undertaken, in our experience, information for scientific studies can be collected and maintained on Internet databases more efficiently and securely than through conventional systems of paper records protected by filing cabinets and locked doors. JAMA. 2000;284:1843-1849.

Smooth lipopolysaccharide (S-LPS) and lipid A of Brucella abortus and Brucella melitensis induced the production of nitric oxide (NO) by rat adherent peritoneal cells, but they induced lower levels of production of NO than Escherichia coli LPS. The participation of the inducible isoform of NO synthase (iNOS) was confirmed by the finding of an increased expression of both iNOS mRNA and iNOS protein. These observations might help to explain (i) the acute outcome of Brucella infection in rodents, (ii) the low frequency of septic shock in human brucellosis, and (iii) the prolonged intracellular survival of Brucella in humans.


---------------------------------------------------------------


Members of the genera Desulfuromonas and Dehalococcoides reductively dechlorinate tetrachloroethene (PCE) and trichloroethene. Two primer pairs specific to hypervariable regions of the 16S rRNA genes of the Dehalococcoides group (comprising Dehalococcoides ethenogenes and Dehalococcoides sp. strain FL2) and the acetate-oxidizing, PCE-dechlorinating Desulfuromonas group (comprising Desulfuromonas sp. strain BB1 and Desulfuromonas chloroethenica) were designed. The detection threshold of a nested PCR approach using universal bacterial primers followed by a second PCR with the Desulfuromonas dechlorinator-targeted primer pair was 1 x 10^3 BB1 cells added per gram (wet weight) of sandy aquifer material. Total community DNA isolated from sediments of three Michigan rivers and six different chloroethene-contaminated aquifer samples was used as template in nested PCR. All river sediment samples yielded positive signals with the BB1- and the Dehalococcoides-targeted primers. Restriction fragment analysis of the amplicons could discriminate strain BB1 from other known Desulfuromonas species. Microcosm studies confirmed the presence of PCE-dechlorinating, acetate-oxidizing Desulfuromonas and hydrogenotrophic Dehalococcoides species in samples yielding positive PCR signals with the specific primers.

---------------------------------------------------------------
Lin, WW, Friedman, MA, Wang, XF and Abou-Donia, MB Journal/Brain Res. 852: 297-304.

Using the rat pheochromocytoma cell line (PC12), we present molecular evidence that the neurotoxicant acrylamide directly induces neurofilament gene expression, and the signaling pathways are initially distinctive from, but eventually merged into, that for nerve growth factor (NGF)-induced neurofilament expression. In PC12 cells, acrylamide increased neurofilament protein levels and synthesis. Acrylamide had no effect on the stability of neurofilament mRNAs suggesting that it directly increased neurofilament mRNA synthesis. K252a, a selective inhibitor for NGF receptor gp140trk, had no effect on acrylamide induction, but completely inhibited NGF-induced neurofilament protein synthesis. Therefore, the initial step for acrylamide signaling was distinctive from NGF. Dexamethasone reversed the effects of both NGF and acrylamide on neurofilament protein levels and synthesis indicated that there is a dexamethasone-sensitive signaling step upon which NGF and acrylamide merge, suggesting involvement of transcription-activating proteins like AP-1. These results, taken together with previous studies of transgenic mice that overexpress neurofilament genes, may partially explain the mechanisms of neurofilament accumulation in distal parts of large axons, a pathognomonic feature of acrylamide neurotoxicity in animals.


Particulate matter (PM) emissions from stationary combustion sources burning coal, fuel oil, biomass, and waste, and PM from internal combustion (IC) engines burning gasoline and diesel, are a significant source of primary particles smaller than 2.5 microns (PM2.5) in urban areas. Combustion-generated particles are generally smaller than geologically produced dust and have unique chemical composition and morphology. The fundamental processes affecting formation of combustion PM and the emission characteristics of important applications are reviewed. Particles containing transition metals, ultrafine particles, and soot are emphasized because these types of particles have been studied extensively, and their emissions are controlled by the fuel composition and the oxidant-temperature-mixing history from the flame to the stack. There is a need for better integration of the combustion, air pollution control, atmospheric chemistry, and inhalation health research communities. Epidemiology has demonstrated that susceptible individuals are being harmed by ambient PM. Particle surface area, number of ultrafine particles, bioavailable transition metals, polycyclic aromatic hydrocarbons (PAH), and other particle-bound organic
compounds are suspected to be more important than particle mass in determining the effects of air pollution. Time- and size-resolved PM measurements are needed for testing mechanistic toxicological hypotheses, for characterizing the relationship between combustion operating conditions and transient emissions, and for source apportionment studies to develop air quality plans. Citations are provided to more specialized reviews, and the concluding comments make suggestions for further research.


It has been postulated that psychophysiologic mechanisms may account for symptom generation in IEI. In this review, the similarity of IEI and panic disorder symptoms are noted. The results of various challenge studies, both with known panicogenic substances and self-identified triggers, are examined. Available data are consistent with the premise that IEI symptoms have a psychophysiologic basis.


Occupational and environmental medicine evolved out of concern for the effect of work hazards on health. The experienced gained in considering such hazards has been extended to understanding general risks in the environment. As we look toward the future, classical occupational and environmental hazards such as over exposure to lead, asbestos and mercury are waning and being replaced by concerns around sustainable development, toxicology testing and exposure information for high production volume chemicals, development of better approaches for setting workplace and community exposure limits, environmental justice and many others. The opportunities for the future exist in overcoming these new challenges.


(2000) **Food and chemical toxicology.**

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11056264

(2000) **Chlorpyrifos: an unwelcome pesticide in our homes.**

Chlorpyrifos is an extensively used organophosphate insecticide having many urban and agricultural crop pest control uses. Studies conducted in indoor environments after termiticide, crack-and-crevice, broadcast, or fogger applications have shown that chlorpyrifos exposure can occur via inhalation of residual air concentrations, dermal or oral exposure from residues on floors and carpets, children toys, food, and dust. Not long ago the weight of scientific evidence supported safe indoor use, but recent studies support the possibility that when pregnant female rats are given the pesticide, chlorpyrifos causes brain damage in fetal rats. Moreover, the exposure of young rats to chlorpyrifos impairs early nervous system development. After finding that chlorpyrifos is an exposure risk especially to children, in June 2000 the United States Environmental Protection Agency and manufacturers agreed to voluntary measures that will reduce the exposure of children to chlorpyrifos-containing products. This action implies a search for less harmful new products to replace it and/or safer ways to control pests through basic hygiene. Whichever pest control method is selected, one should keep in mind that preventing environmental pesticide exposure in children is always better than treating the resulting disease.

(2000) **Differential activation of nitric oxide synthase through muscarinic acetylcholine receptors in rat salivary glands.**

Muscarinic receptors play an important role in secretory and vasodilator responses in rat salivary glands. Nitric oxide synthase (NOS) appears to be one of the multiple effectors coupled to muscarinic receptors in both submandibular and sublingual glands.
although some differences have been found depending on the gland studied. First, submandibular glands had a lower basal activity of nitric oxide synthase than sublingual glands and the concentration-response curve for carbachol was bell-shaped in the former but not in sublingual glands. Second, cGMP levels displayed a similar profile to that observed for NOS activity in both glands. Third, protein kinase C also coupled to muscarinic receptor activation in the glands might have a regulatory effect on nitric oxide production since its activity was higher in basal conditions in submandibular than sublingual glands and it also increased in the presence of the agonist at a concentration that inhibited NOS activity in submandibular glands. The effects appear to be partly related to the expression of a minor population of M(1) receptors in submandibular glands absent in sublingual as determined in binding and signaling experiments with the muscarinic receptor antagonist pirenzepine.


The concentration of nitric oxide (NO) in exhaled air is increased in patients with asthma, suggesting that measuring fractional exhaled NO concentration (FE(NO)) may be used to monitor asthmatic airway inflammation. However, increased FE(NO) is not specific for asthma, as other inflammatory lung diseases may also increase FE(NO). To augment the specificity of FE(NO) measurement, we tested a novel theoretical modelling of pulmonary NO dynamics that allows the approximation of alveolar NO concentration and bronchial NO flux separately by measuring FE(NO) at several exhalation flow rates. We measured FE(NO) at four exhalation flow rates in 10 steroid-naive asthmatics, 5 patients with extrinsic allergic alveolitis, and in 10 healthy controls. Both the asthmatics and the patients with alveolitis had significantly higher FE(NO) than the healthy controls. The increased NO concentration originated from the bronchial level in the asthmatics and from the alveolar level in the patients with alveolitis. In the second part of the study we assessed the repeatability of FE(NO) test, within-day and day-to-day (during two weeks) variation in FE(NO), and the effects of mouth pressure and cigarette smoking on FE(NO) in healthy volunteers. Repeatability of 10 subsequent measurements was high (coefficient of variation (CV) 4.6% +/- 0.4%), and no diurnal variation was found. The day-to-day variation during a 2-week period gave a CV of 10.6% +/- 1.0%. The magnitude of mouth pressure (5-20 cmH2O in adults, 5-40 cmH2O in children) during measurement had no effect on FE(NO). Smoking a cigarette caused a small and transient but statistically significant increase in FE(NO) at 1 and 5 min after smoking. In conclusion, FE(NO) measurement is highly repeatable with low day-to-day variation among healthy subjects. Our results also suggest that the present novel method of measuring FE(NO) at several exhalation flow rates can be used to approximate alveolar and bronchial contributions to FE(NO) separately and thus increase the clinical value of this test.
Multiple chemical sensitivity (MCS) is a term used to describe a disorder characterized by a vast array of somatic, cognitive, and affective symptoms, the cause of which is attributed to exposure to extremely low levels of a variety of chemicals. Upon examination of the patient with a diagnosis of MCS, objective physical findings and consistent laboratory abnormalities are typically nonexistent. The concept of MCS has ignited considerable controversy in the fields of toxicology, immunology, allergy, psychology, and neuropsychology. Central to the controversy is the disagreement over the extent to which the manifestation of MCS is mediated by psychological factors. Because of the large number of neuropsychological symptoms associated with a diagnosis of MCS, neuropsychologists are increasingly receiving referrals for the assessment of these patients. It is important, therefore, that neuropsychologists become aware of the variety of clinical issues that must be taken into account when assessing an individual with a diagnosis of MCS. The theoretical and research literature on individuals with a diagnosis of MCS is reviewed here.

Microsomal and cytosolic phenacetin deacetylase activities were examined in human liver and kidneys. Kinetic properties of the activities were also studied in human liver microsomes. Phenacetin deacetylase activity was predominantly localized in the liver microsomal fraction. The specific activities of phenacetin deacetylation in liver cytosol and in kidney microsomes and cytosol were all less than 5% of that in liver microsomes. In human liver microsomes, Eadie-Hofstee plots for phenacetin deacetylation were monophasic, indicating a single-enzyme catalytic reaction. The Michaelis-Menten parameters, $K(m)$ and $V(max)$, for the deacetylation were 4.7 mM and 5.54 nmol/min/mg of protein, respectively. The intrinsic clearance, calculated as $V(max)/K(m)$, was 1.18 microl/min/mg of protein. Although the organophosphate bis(4-nitrophenyl)phosphoric acid markedly inhibited the reaction in human liver
microsomes, the activity has a tolerance to the treatment of phenylmethylsulfonyl fluoride, a serine hydrolase inhibitor. Prazosin, a peripheral alpha(1)-adrenergic antagonist, noncompetitively inhibited the phenacetin deacetylation with a K(i) value of 19.0 microM. Flutamide, a nonsteroidal androgen receptor antagonist, stimulated the activity by up to 349%. This increase was accompanied by a decrease in the K(m) value and no change in the V(max) value, resulting in an increase in the intrinsic clearance by up to 700% of the control. These results suggest that the phenacetin deacetylase localized in human liver microsomes has not only a catalytic site but also a negative and/or positive modulation site or sites.


Case definitions of the same phenomenon may be different for different purposes. Case definitions usually become more specific over time as more information about the condition becomes available. Idiopathic environmental intolerance is one of many labels for a heterogeneous group of conditions in which subjects describe multiple symptoms that are attributed to exposure to extremely low doses of common chemicals. Dr. Kreutzer presents issues in case definition for clinical purposes and for population-based studies, and makes recommendations for the clinician and for the public health investigator.


Previous research has demonstrated electroencephalogram (EEG) changes in response to low-odor concentrations, resulting in near-chance detection. Such findings have been taken as evidence for olfaction without awareness. We replicated and extended previous work by examining EEG responses to water-water control, 0.0001, 0.001, 0.01, and 1 ppm isoamyl acetate (IAA) in water paired with water only. Detection was above chance (>50%) for.001 and above, and alpha decreased only to those concentrations, suggesting that EEG changes corresponded to IAA awareness. However, when correct trial EEGs were compared to incorrect trial EEGs during.001 ppm, right posterior/central alpha decreased during incorrect trials and alpha decreased more globally (including frontal sites) during correct trials. These data may not reflect awareness or unawareness per se. Instead, results are discussed regarding
activation of perceptual systems in the posterior region during incorrect trials and the activation of frontal action systems during a subset of correct trials.


A 37-year-old heating, ventilation, and air-conditioning mechanic developed respiratory, musculoskeletal, and central nervous system symptoms associated with a variety of odorous environmental chemicals. Organic disease was not evident, but the patient was distressed by these symptoms and was at risk for becoming disabled by them. His symptoms fit broadly into the condition recognized as multiple chemical sensitivity. Multiple chemical sensitivity is a diagnostic term for a group of symptoms without demonstrated organic basis. The symptoms are characteristic of dysfunction in multiple organ systems, they increase and decrease according to exposure to low levels of chemical agents in the patient's environment, and they sometimes occur after a distinct environmental change or insult such as an industrial accident or remodeling. Although traditional medical organizations have not agreed on a definition for this syndrome, it is being increasingly recognized and makes up an increasing percentage of the caseload at occupational and environmental medicine clinics. Although there is often dispute about whether the symptoms have a functional or organic basis, an informed approach to evaluation, diagnosis, and management and a careful assessment of impairment, disability, and work relatedness are necessary. Careful exclusion of organic causes is critical, and this should be followed by a judicious approach to coping with symptoms.


To determine whether residents exposed to PCBs and thermolysis products had impaired neurobehavioral functions, the performance of 98 exposed adults was compared with 58 unexposed regional referents (all volunteers). Visual field performance, color confusion index, balance as sway speed, blink reflex latency R-1, hearing, grip strength, simple and choice visual reaction times problem solving for Culture Fair and digit symbol, recall memory, peg placement, trail making A and B for attention and dexterity and long-term memory were tested. A profile of mood states (POMS) and questionnaires for chemical exposures, medical histories and the frequency of 35 symptoms were completed. Only statistically significant differences are
described. Exposed subjects had slower simple and choice reaction times and faster sway speeds with eyes closed and open. Color discrimination and visual performance scores were lower and visual fields were often constricted. Scores on Culture Fair, digit symbol, vocabulary and verbal recall were lower. Placement of pegs in a slotted pegboard was slower and trail making A and B took longer. Even embedded memory test scores including vocabulary were lower. POMS scores were elevated. There were no competing chemical exposures, confounding factors or other explanations for the findings. Long residential exposure to PCBs was associated with visual defects and impaired neurophysiologic and neuropsychologic functions.

(2000) A paradigm for environmental epidemiology: why are effects of environmental exposures different from occupational effects?

(2000) Chlorine-induced damage documented by neurophysiological, neuropsychological, and pulmonary testing.

Chlorine causes acute pulmonary edema and damages airways, thus producing obliterative bronchiolitis. In the case series in this study, its adverse effects were extended to visual and central nervous system impairment. Twenty-two patients exposed briefly to undiluted chlorine at home or work were evaluated with a battery of neurobehavioral and visual tests. Their test scores, expressed as percentage predicted, were compared with those of unexposed subjects. Chlorine-exposed subjects had impaired balance (with eyes open and eyes closed), delayed simple and choice reaction times, impaired color discrimination, impaired visual field performance, decreased hearing, and decreased grip strength. Blink reflex latency was delayed on the right. Cognitive performance (i.e., digit symbol and vocabulary), peg placement, trail making A and B, and verbal recall were significantly below predicted levels. Well-learned memory functions were not impaired. Adverse mood states scores were elevated as were the frequencies of 28 of 35 common symptoms. Forced vital capacities were reduced. The duration of chlorine exposures was from a breath or two to several hours, and exposures were associated with impaired neurophysiologic and neuropsychologic functions. Impairments appeared insidiously, were noted 1 to 48 mo after exposure, and persisted. Such functional losses must be prevented. Additional chlorine-exposed patients should be evaluated for neurological and pulmonary damage.
(2000) [Causes of occupational allergy in dental nurses. An analysis based on the material collected at The Institute of Occupational Medicine in Lodz].

The causes of occupational dermatosis were analysed in 27 dental nurses examined at The Nofer Institute of Occupational Medicine during the years 1995-99. Contact sensitisation (at least one positive epidermal test) was found in 18 subjects (66.7%). Occupational allergic dermatitis was induced most frequently by: glutaraldehyde (7 positive patch tests), nickel (7), benzalkonium (4), formaldehyde (4), fragrances (4), chromium compounds (3), glyoxal (3), and thiuram (3). In the authors’ opinion, dental nurses are nowadays sensitised to other chemical compounds than it used to be in the past. The present components of disinfectants (aldehydes, quaternary ammonium bases), metals and rubber are the major etiologic agents that induce occupational allergy.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10971928

-------------------------------------------------------------------------------


Attention Deficit/Hyperactivity Disorder (ADHD) is the most common behavioral disorder in children. ADHD is characterized by attention deficit, impulsivity, and sometimes overactivity ("hyperactivity"). The diagnosis is empirical, with no objective confirmation available to date from laboratory measures. ADHD begins in childhood and often persists into adulthood. The exact etiology is unknown; genetics plays a role, but major etiologic contributors also include adverse responses to food additives, intolerances to foods, sensitivities to environmental chemicals, molds, and fungi, and exposures to neurodevelopmental toxins such as heavy metals and organohalide pollutants. Thyroid hypofunction may be a common denominator linking toxic insults with ADHD symptomatologies. Abnormalities in the frontostriatal brain circuitry and possible hypofunctioning of dopaminergic pathways are apparent in ADHD, and are consistent with the benefits obtained in some instances by the use of methylphenidate (Ritalin) and other potent psychostimulants. Mounting controversy over the widespread use of methylphenidate and possible life-threatening effects from its long-term use make it imperative that alternative modalities be implemented for ADHD management. Nutrient deficiencies are common in ADHD; supplementation with minerals, the B vitamins (added in singly), omega-3 and omega-6 essential fatty acids, flavonoids, and the essential phospholipid phosphatidylserine (PS) can ameliorate ADHD symptoms. When individually managed with supplementation, dietary modification, detoxification, correction of intestinal dysbiosis, and other features of a wholistic/integrative program of management, the ADHD subject can lead a normal and productive life.
(2000) Acute sarin exposure causes differential regulation of choline acetyltransferase, acetylcholinesterase, and acetylcholine receptors in the central nervous system of the rat.


Acute neurotoxic effects of sarin (O:-isopropylmethylphosphonofluoridate) in male Sprague-Dawley rats were studied. The animals were treated with intramuscular (im) injections of either 1 x LD(50) (100 microg/kg), and sacrificed at 0.5, 1, 3, 6, 15, or 20 h after treatment, or with im injections of either 0.01, 0.1, 0.5, or 1 x LD(50) and sacrificed 15 h after treatment. Plasma butyrylcholinesterase (BChE) and brain regional acetylcholinesterase (AChE) were inhibited (45-55%) by 30 min after the LD(50) dose. BChE in the plasma and AChE in cortex, brainstem, midbrain, and cerebellum remained inhibited for up to 20 h following a single LD(50) treatment. No inhibition in plasma BChE activity was observed 20 h after treatment with doses lower than the LD(50) dose. Midbrain and brainstem seem to be most responsive to sarin treatment at lower doses, as these regions exhibited inhibition (approximately 49% and 10%, respectively) in AChE activity following 0.1 x LD(50) treatment, after 20 h. Choline acetyltransferase (ChAT) activity was increased in cortex, brainstem, and midbrain 6 h after LD(50) treatment, and the elevated enzyme activity persisted up to 20 h after treatment. Cortex ChAT activity was significantly increased following a 0.1 x LD(50) dose, whereas brainstem and midbrain did not show any effect at lower doses. Treatment with an LD(50) dose caused a biphasic response in cortical nicotinic acetylcholine receptor (nAChR) and muscarinic acetylcholine receptor (m2-mAChR) ligand binding, using [(3)H]cytisine and [(3)H]AFDX-384 as ligands for nAChR and mAChR, respectively. Decreases at 1 and 3 h and consistent increases at 6, 15, and 20 h in nAChR and m2-mAChR were observed following a single LD(50) dose. The increase in nAChR ligand binding densities was much more pronounced than in mAChR. These results suggest that a single exposure of sarin, ranging from 0.1 to 1 x LD(50), modulates the cholinergic pathways differently and thereby causes dysregulation in excitatory neurotransmission.


Stress management was studied in male patients with solvent-induced chronic toxic encephalopathy (TE) of types 2A (TE 2A, n = 31) and 2B (TE 2B, n = 26). The patients
were compared with a healthy reference group (n = 57). Self-reported symptoms (90-item Symptoms Checklist [SCL-90]), sense of coherence, coping strategies, and level of mastery were measured. As expected, both TE groups reported highly deviating symptoms on most SCL-90 scales. The TE 2B patients, who had objectified cognitive dysfunction, reported more use of passive, less situationally adequate coping strategies; a weaker sense of coherence; and a lower degree of mastery. In contrast, the TE 2A cases showed only minor deviations from the reference group in these respects. The results suggest that having a strong sense of coherence, a sense of mastery, and flexible resources for stress management could be dependent on intact brain functions.


The new questionnaire Euroquest was designed to study effects from exposure to organic solvents, and it covers the most commonly reported symptoms associated with long-term solvent exposure. Its convergence and criterion validity were evaluated by means of comparison with the two well-established generic symptom questionnaires Symptom Checklist (SCL-90) and General Health Questionnaire (GHQ-30). Men with long-term exposure to organic solvents and symptoms common in toxic encephalopathy (TE) classified as TE type 2A (n=29) or 2B (n=28) according to their neuropsychological test performance, and a comparable group of non-exposed healthy referents (N=57), were included. The six Euroquest factors obtained by a factor analysis were labeled: 'emotional lability' 'cognitive disturbances' 'peripheral neurology' 'sleepiness' 'fatigue' and 'sleep disturbances'. These factors correlated well with most SCL-90 scales and with the GHQ-30 total score in the combined TE groups. The combined TE groups were correctly classified to a similar degree by the Euroquest factors 'cognitive disturbances' and 'peripheral neurology' (TE 82.5% and referents 93%) and the SCL-90 scales 'somatization, 'interpersonal sensitivity', 'obsessive-compulsive symptoms' and 'hostility' (TE 84.2% and referents 93.0%), but not as well by GHQ-30 (TE 61.4% and referents 79%). In comparison with the separate TE groups most referents, and a considerably higher percentage of 2B than 2A subjects, could be correctly classified with both Euroquest and SCL-90. With GHQ-30, only a few 2A cases and fewer than half of the 2B cases were correctly classified. In conclusion, the Euroquest factors converged with both SCL-90 scales and GHQ-30 score. With both the Euroquest and SCL-90 questionnaires a similar percentage of the TE subjects were discriminated from the referents, most conspicuously regarding TE 2B subjects, who had an objectified cognitive dysfunction. In a choice between Euroquest and SCL-90, the Euroquest may have the advantage of higher face validity, for TE subjects.

The insect juvenile hormone specific esterases (JHEs), related to acetylcholinesterases but exhibiting substrate specificity for juvenile hormone (JH), are essential enzymes for normal insect development, making them attractive targets for biorationally designed, environmentally safe pesticides. We examine here a new enzyme, JHER, related to, but yet structurally, biochemically, and kinetically distinct from, the classical JHE. Both classical JHE and baculovirus-expressed JHER hydrolyze JH show disproportionately higher catalytic rates at higher substrate concentrations (in contrast to substrate inhibition reported for acetylcholinesterase) and are similarly inhibited by an organophosphate. However, JHER, which possesses an unusual cysteine residue at +1 to the catalytic serine, is less sensitive to trifluoromethyl ketone transition state analogs designed around the structure of JH. We propose a model in which JHER is expressed just prior to metamorphosis for hydrolysis of a JH-like substrate with hydrophobic backbone, a proximal ester, and a terminal epoxide or related substitution.


BACKGROUND AND METHODS: Mass psychogenic illness may be difficult to differentiate from illness caused by bioterrorism, rapidly spreading infection, or toxic substances. We investigated symptoms attributed to exposure to toxic gas at a high school in Tennessee. In November 1998, a teacher noticed a 'gasoline-like' smell in her classroom, and soon thereafter she had a headache, nausea, shortness of breath, and dizziness. The school was evacuated, and 80 students and 19 staff members went to the emergency room at the local hospital; 38 persons were hospitalized overnight. Five days later, after the school had reopened, another 71 persons went to the emergency room. An extensive investigation was performed by several government agencies. RESULTS: We were unable to find a medical or environmental explanation for the reported illnesses. The persons who reported symptoms on the first day came from 36 classrooms scattered throughout the school. The most frequent symptoms (in this group and the group of people who reported symptoms five days later) were headache, dizziness, nausea, and drowsiness. Blood and urine specimens showed no evidence of carbon monoxide, volatile organic compounds, pesticides, polychlorinated biphenyls, paraquat, or mercury. There was no evidence of toxic compounds in the environment. A questionnaire administered a month later showed that the reported symptoms were significantly associated with female sex, seeing another ill person,
knowing that a classmate was ill, and reporting an unusual odor at the school. CONCLUSIONS: The illness attributed to toxic exposure had features of mass psychogenic illness - notably, widespread subjective symptoms thought to be associated with environmental exposure to a toxic substance in the absence of objective evidence of an environmental cause. Alleviation of the anxiety surrounding an episode of mass psychogenic illness requires prompt recognition and a detailed investigation.


Subchronic neurotoxic effects of sarin (O-isopropyl methylphosphonofluoridate) treatment at various doses in male Sprague Dawley rats were studied. The animals were treated with a single intramuscular (im) injection of 0.01, 0.1, 0.5, or 1 x LD50 (100 microg/kg). The animals were maintained for 90 d thereafter. [3H]Hexamethonium iodide was used to monitor the changes in blood-brain barrier (BBB) permeability in cortex, brainstem, midbrain, and cerebellum. Brainstem exhibited a significant decrease (approximately 58% of control) in uptake of [3H]hexamethonium iodide at 1 x LD50 dose. No significant changes were observed in BBB permeability in cortex, midbrain, and cerebellum at any dose. Plasma butyrylcholinesterase (BChE) activity remained unchanged, reflecting recovery of the enzyme activity from the initial inhibition following single exposure of 1 x LD50 sarin. Acetylcholinesterase (AChE) activity in the cortex remained inhibited (approximately 29%), whereas in the brainstem there was an increase (approximately 20%) at 1 x LD50 dose of sarin. The m2-selective muscarinic acetylcholine receptor (m2-mAChR) ligand binding was inhibited significantly at 1 x LD50 in the cortex, whereas brainstem showed significantly increased (approximately 45%) ligand binding at 1 x LD50 dose. Nicotinic acetylcholine receptor (nAChR), on the other hand, showed a biphasic response in ligand binding in the cortex with a decrease (approximately 30%) at 0.01 x LD50 but an increase (approximately 40%) at 1 x LD50. Brainstem did not show any significant change in nAChR ligand binding. These results suggest that single exposure of sarin could lead to changes that may play an important role in neuropathological abnormalities in the central nervous system.


OBJECTIVE: The aim of this study was to determine illness comorbidity rates for individuals with chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivities (MCS). An additional objective was to identify characteristics related to the severity of fatigue, disability, and psychiatric comorbidity in each of these illness groups. METHODS: A random sample of 18,675 residents in Chicago, Illinois, was first interviewed by telephone. A control group and a group of individuals with chronic fatigue accompanied by at least four minor symptoms associated with CFS received medical and psychiatric examinations. RESULTS: Of the 32 individuals with CFS, 40.6% met criteria for MCS and 15.6% met criteria for FM. Individuals with MCS or more than one diagnosis reported more physical fatigue than those with no diagnosis. Individuals with more than one diagnosis also reported greater mental fatigue and were less likely to be working than those with no diagnosis. Individuals with CFS, MCS, FM, or more than one diagnosis reported greater disability than those with no diagnosis. CONCLUSIONS: Rates of coexisting disorders were lower than those reported in prior studies. Discrepancies may be in part attributable to differences in sampling procedures. People with CFS, MCS, or FM endure significant disability in terms of physical, occupational, and social functioning, and those with more than one of these diagnoses also report greater severity of physical and mental fatigue. The findings illustrate differences among the illness groups in the range of functional impairment experienced.


Izquierdo, I and McGaugh, JL Journal/Behav Pharmacol. 11: 517-34.

Recent findings have significantly advanced our understanding the mechanisms of memory formation. Most of these advances stemmed from behavioural pharmacology research involving, particularly, the localized infusion of drugs with specific molecular actions into specific brain regions. This approach has revealed brain structures involved in different memory types and the main neurotransmitter systems and sequence of metabolic cascades that participate in memory consolidation. Biochemical studies and, in several cases, studies of genetically manipulated animals, in which receptors or enzymes affected by the various drugs were absent or overexpressed,
have complemented the pharmacological research. Although most studies have concentrated on the involvement of the hippocampus, many have also investigated the entorhinal cortex, other regions of the cortex, and the amygdala. Behavioural pharmacology has been of crucial importance in establishing the major neurohumoral and hormonal systems involved in the modulation of memory formation. These systems act on specific steps of memory formation in the hippocampus and in the entorhinal, parietal, and cingulate cortex. A specialized system mediated by the basolateral amygdaloid nucleus, and involving several neuromodulatory systems, is activated by emotional arousal and serves to regulate memory formation in other brain regions. The core mechanisms involved in the formation of explicit (declarative) memory are in many respects similar to those of long-term potentiation (LTP), particularly in the hippocampus. However, there are also important differences between memory formation and LTP. Memory formation involves numerous modulatory influences, the co-participation of various brain regions other than the hippocampus, and some properties that are specific to memory and absent in LTP (i.e. flexibility of response). We discuss the implications of these similarities and differences for understanding the neural bases of memory.


-------------------------------------------------------------------------------------------------------------------------------


-------------------------------------------------------------------------------------------------------------------------------


Geographic exposure indicators (GEIs) use point estimates of ambient air pollutant concentrations to characterize the exposure of populations residing within a specified area. Both zone- and proximity-type GEIs have been widely employed in epidemiological studies and other applications to identify regions or populations at high risk. Their use requires a number of assumptions, for example, pollutant concentrations should be homogeneous within the area, and concentrations should differ between areas in a predictable manner. These assumptions have not been rigorously examined. This paper evaluates the most common types of GEIs as surrogate measures of ambient air pollutant exposures. Statistical measures proposed to evaluate GEIs include accuracy, homogeneity, misclassification and statistical power. GEIs and statistical measures are evaluated in two case studies that use different air pollution sources and an air quality dispersion model. The case studies
show that pollutant levels may vary substantially within a small area, and significant errors and exposure misclassification may result if the GEI represents a large geographic area. GEIs based on residential proximity to a pollution source should not be used for elevated emission sources, and the use of proximity measures is discouraged for ground level sources. A systematic evaluation is suggested to evaluate and improve the accuracy of the GEIs used in epidemiological and other applications.


Dr. Hodgson summarizes what is known about human symptoms and discomfort in the built environment, and formulates several critical hypotheses that show striking parallels to the questions arising from discussions of the IEI/MCS syndrome.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10903551

(2000) Mast cell disorder to be ruled out in MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11005435


This study compared psychological defensive strategies in two groups of patients with multiple chemical sensitivity (n = 10) and conversion disorder (n = 10) by means of the projective perceptual Defense Mechanism Test. We attempted to create a model for personality assessment based on the test data of prior patients, in which new patients
could successively be tested. The overall results indicated that it was possible to separate the clinical groups significantly from a control group and from each other. In comparison to the controls, the clinical groups were characterized by patterns that were more nonemotionally adapted as well by a lateness of perception, but the ways in which the clinical groups maintained this difference were not the same. The multiple chemical sensitivity group was characterized above all by blocking maneuvers, while the main defensive strategy of the conversion disorder group was distortion of content.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11153853

Haxhiu, MA, Chavez, JC, Pichiule, P, Erokwu, B and Dreshaj, IA Journal/Brain Res. 883: 77-86.

In six decerebrated and in eight alpha-chloralose anesthetized, paralyzed and mechanically ventilated beagle dogs, we have studied involvement of glutamate and glutamate receptors in transmission of excitatory inputs from the airway sensory receptors to the nucleus tractus solitarius and from this site to airway-related vagal preganglionic cells that regulate the tracheal circulation and the submucosal gland secretion. Stimulation of airway sensory fibers by lung deflation-induced reflex increase in tracheal blood flow and submucosal gland secretion. These responses were diminished by prior administration of AMPA/kainate receptor antagonist CNQX into the fourth ventricle (n=6). Furthermore, topical application or microinjection of AMPA kainate receptor blockers, into the region of the ventrolateral medulla, where airway-related vagal preganglionic neurons are located, abolished the reflex changes in tracheal submucosal gland secretion (n=8); in these dogs mucosal blood flow was not measured). These findings indicate that reflex increase in tracheal blood flow and submucosal gland secretions are mediated mainly via release of glutamate and activation of the AMPA/kainate subtype of glutamate receptors.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11063990


PURPOSE: To test for neuronal brain damage in the basal ganglia and brainstem in Gulf War veterans by using magnetic resonance (MR) spectroscopy. MATERIALS
AND METHODS: Twenty-two Gulf War veterans with one of three factor analysis-derived syndromes (case patients); 18 well veterans matched for age, sex, and education level (control subjects); and six Gulf War veterans with syndrome 2 from a different population (replication sample) underwent long echo time (272 msec) proton (hydrogen 1) MR spectroscopy on a 4 x 2 x 2-cm voxel in the basal ganglia bilaterally and a 2 x 2 x 2-cm voxel in the pons. Syndromes 1-3 are described as "impaired cognition," "confusion-ataxia," and "central pain," respectively. RESULTS: The N-acetylaspartate-to-creatine (NAA/Cr) ratio, which reflects functional neuronal mass, was significantly lower in the basal ganglia and brainstem of Gulf War veterans with the three syndromes than in those structures of the control subjects (P = .007). The finding was corroborated in the replication sample (P = .002). Veterans with syndrome 2 (the most severe clinically) had evidence of decreased NAA/Cr in both the basal ganglia and the brainstem; those with syndrome 1, in the basal ganglia only; and those with syndrome 3, in the brainstem only. CONCLUSION: Veterans with different Gulf War syndromes have biochemical evidence of neuronal damage in different distributions in the basal ganglia and brainstem.

Haley, RW, Fleckenstein, JL, Marshall, WW, McDonald, GG, Kramer, GL and Petty, F
Journal/Arch Neurol. 57: 1280-5.

BACKGROUND: Many complaints of Gulf War veterans are compatible with a neurologic illness involving the basal ganglia. METHODS: In 12 veterans with Haley Gulf War syndrome 2 and in 15 healthy control veterans of similar age, sex, and educational level, we assessed functioning neuronal mass in both basal ganglia by measuring the ratio of N-acetyl-aspartate to creatine with proton magnetic resonance spectroscopy. Central dopamine activity was assessed by measuring the ratio of plasma homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenlyglycol (MHPG). RESULTS: The logarithm of the age-standardized HVA/MHPG ratio was inversely associated with functioning neuronal mass in the left basal ganglia (R(2) = 0.56; F(1,27) = 33.82; P<.001) but not with that in the right (R(2) = 0.04; F(1,26) = 1.09; P = .30). Controlling for age, renal clearances of creatinine and weak organic anions, handedness, and smoking did not substantially alter the associations. CONCLUSIONS: The reduction in functioning neuronal mass in the left basal ganglia of these veterans with Gulf War syndrome seems to have altered central dopamine production in a lateralized pattern. This finding supports the theory that Gulf War syndrome is a neurologic illness, in part related to injury to dopaminergic neurons in the basal ganglia.


(2000) Will we solve the Gulf War syndrome puzzle by population surveys or clinical research.

(2000) C-fos mRNA induction in the central and peripheral nervous systems of diisopropyl phosphorofluoridate (DFP)-treated hens.
Gupta, RP, Damodaran, TV and Abou-Donia, MB Journal/Neurochem Res. 25: 327-34.

A single dose of diisopropyl phosphorofluoridate (DFP), an organophosphorus ester, produces delayed neurotoxicity (OPIDN) in hen. DFP produces mild ataxia in hens in 7-14 days, which develops into severe ataxia or paralysis as the disease progresses. Since, OPIDN is associated with alteration in the expression of several proteins (e.g., Ca2+/calmodulin-dependent protein kinase II (CaM kinase II) alpha-subunit, tau, tubulin, neurofilament (NF) protein, vimentin, GFAP) as well as their mRNAs (e.g., NF, CaM kinase II alpha-subunit), we determined the effect of a single dose of DFP on the expression of one of the best known immediate-early gene (IEG), c-fos. C-fos expression was measured by Northern hybridization in cerebrum, cerebellum, brainstem, midbrain, spinal cord, and the sciatic nerves of hens at 0.5 hr, 1 hr, 2 hr, 1 day, 5 days, 10 days, and 20 days after a single 1.7 mg/kg, sc. injection of DFP. All the
tissues (cerebrum, 52%; cerebellum, 55%; brainstem, 49%; midbrain, 23%; spinal
cord, 80%; sciatic nerve, 157%) showed significant increase in c-fos expression in 30
min and this elevated level persisted at least up to 2 hr. Expressions of beta-actin
mRNA and 18S RNA were used as internal controls. The significant increase in c-fos
expression in DFP-treated hens suggests that c-fos may be one of the IEGs involved in
the development of OPIDN.

phosphorofluoridate-treated hen spinal cord and their presence in axonal
aggregations.
Gupta, RP, Abdel-Rahman, A, Jensen, KF and Abou-Donia, MB Journal/Brain Res.
878: 32-47.

Diisopropyl phosphorofluoridate (DFP) is an organophosphorus ester, which produces
organophosphorus ester-induced delayed neuropathy (OPIDN) in hen and other
sensitive species. A single dose of DFP (1.7 mg/kg, sc.) produces mild ataxia in 7-14
days in hens, which develops into severe ataxia or paralysis with the progression of
disease. OPIDN is associated with axonal swellings and degeneration of axons. This
study was carried out to investigate the expression of neurofilament (NF) subunits in
the spinal cord of DFP-treated hens. Hens were treated with a single dose of DFP and
sacrificed 1, 5, 10, and 20 days post-treatment. Western blot analysis showed
increased expression of middle molecular weight neurofilament protein (NF-M), and
decreased expression of high molecular weight (NF-H) and low molecular weight
(NF-L) neurofilament proteins in the 2 M urea extracts of spinal cord particulate
fraction. These changes were observed within 24 h of DFP administration and
persisted for 10-20 days. Thus, there was increase in the stoichiometry of NF-M:NF-L
in the spinal cord of DFP-treated hens. Immunoprecipitation, cross-linking, and
two-dimensional polyacrylamide gel electrophoresis showed the presence of
heterodimers, but not heterotetramers, in the hen spinal cord extract.
Immunohistochemical staining revealed the presence of all three NF subunits in the
cytoskeletal inclusions in DFP-treated hen spinal cord cross-sections. The results
suggested that each NF subunit might be accumulated by a different mechanism in the
axonal aggregations of DFP-treated hen.

Graves, CG, Matanoski, GM and Tardiff, RG Journal/Regul Toxicol Pharmacol. 32:
99-117.

Carbonless copy paper (CCP), introduced in 1954, is ubiquitous in the U.S.
marketplace, and because of this, many workers come into contact with it. Its safety to
workers who handle large amounts of CCP has been addressed in numerous studies and reports; and the National Institute for Occupational Safety and Health (NIOSH) on two occasions has sought to determine what, if any, hazards to health CCP might pose. This review encompasses the world's literature on CCP and provides a weight-of-evidence analysis of the safety of CCP to workers in the United States. CCP is systematically studied on large groups of humans using repeat insult patch tests. Consistently, CCP in U.S. commerce since 1987 (the focus of this review) has produced neither primary skin irritation nor skin sensitization under exaggerated test conditions, demonstrating that no irritation or sensitization is expected on contact with CCP under normal conditions of manufacture and use. Years after the introduction of CCP, the first case reports appeared in 1974 suggesting an association between CCP use and various generic symptoms. Most of the earliest reports occurred in Sweden in response to negative publicity concerning the product, and to date approximately half of all published articles originate in Scandinavia. Many early reports were questionnaire interview studies which suffered from suggestive questions, biases, and lack of control for confounding factors. Few studies included a comparison group (i.e., people not exposed to CCP) making it impossible to estimate risk values. Later, sick building syndrome studies, accounting for many relevant factors in the office environment, found no association between CCP exposure and symptoms unexplained by other factors. Animal studies showed that compounds used to manufacture CCP do not have acute toxic potential and are not genotoxic. Finally, very few published complaints have come from the manufacturing sector where the closest and most voluminous contact occurs. A few reports of symptoms have emanated from printing facilities (with a multiplicity of other chemical exposures), but generally most symptoms are reported in the office setting where the exposure is lower than in the manufacturing or printing settings. Based on the weight of the evidence, CCP currently in commerce in the United States is shown not to be the causative agent for the reported general symptoms sometimes associated with it over the years. Recently NIOSH evaluated the literature as to possible hazards to health posed by CCP, and NIOSH is anticipated to conclude that CCP is not a hazard to workers and has only a small possibility of producing mild and transient skin irritation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11029273


(2000) **Chronic fatigue syndrome and depression.**

(2000) **Protein kinase C signaling and oxidative stress.**

Oxidative stress is involved in the pathogenesis of various degenerative diseases including cancer. It is now recognized that low levels of oxidants can modify cell-signaling proteins and that these modifications have functional consequences. Identifying the target proteins for redox modification is key to understanding how oxidants mediate pathological processes such as tumor promotion. These proteins are also likely to be important targets for chemopreventive antioxidants, which are known to block signaling induced by oxidants and to induce their own actions. Various antioxidant preventive agents also inhibit PKC-dependent cellular responses. Therefore, PKC is a logical candidate for redox modification by oxidants and antioxidants that may in part determine their cancer-promoting and anticancer activities, respectively. PKCs contain unique structural features that are susceptible to oxidative modification. The N-terminal regulatory domain contains zinc-binding, cysteine-rich motifs that are readily oxidized by peroxide. When oxidized, the autoinhibitory function of the regulatory domain is compromised and, consequently, cellular PKC activity is stimulated. The C-terminal catalytic domain contains several reactive cysteines that are targets for various chemopreventive antioxidants such as selenocompounds, polyphenolic agents such as curcumin, and vitamin E analogues. Modification of these cysteines decreases cellular PKC activity. Thus the two domains of PKC respond differently to two different type of agents: oxidants selectively react with the regulatory domain, stimulate cellular PKC, and signal for tumor promotion and cell growth. In contrast, antioxidant chemopreventive agents react with the catalytic domain, inhibit cellular PKC activity, and thus interfere with the action of tumor promoters.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10924854

(2000) **Behavioral conditioning and idiopathic environmental intolerance.**
Idiopathic environmental intolerance (IEI) is a poorly understood condition that may involve disturbances in immunologic, neurologic, endocrine, behavioral, emotional, and cognitive processes. This chapter reviews theories and evidence that behavioral conditioning processes, including pharmacologic sensitization, conditioned immunomodulation, and conditioned odor and taste aversions, may play a role in the development and maintenance of IEI. It also reviews the psychophysiologic concepts of individual response specificity and situational response stereotypy as potential explanations for the individual differences observed in specific responses to environmental stimuli in patients with IEI. Finally, the treatment implications of a conditioning account of IEI are discussed as part of a more comprehensive treatment approach that incorporates other behavioral and nonbehavioral strategies.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10903547

---------------------------------------------------------------

Frank, AL Journal/Prim Care. 27: 877-94.

This article reviews the importance of the occupational and environmental history, and the approach to a patient with a disease suspected to be of occupational or environmental origin. There is a detailed review of obtaining special aspects of the medical history related to work and environmental exposures as well as illustrative case studies. Sources of additional information are also cited.

---------------------------------------------------------------

(2000) Stressors, personality traits, and coping of Gulf War veterans with chronic fatigue.

OBJECTIVES: preliminary surveys of Persian Gulf veterans revealed a significant prevalence of self-reported symptoms consistent with chronic fatigue syndrome (CFS). The purpose of this study was to compare self-reported life stressors, combat, and chemical exposures, personality and coping between Gulf War veterans with CFS and healthy veterans. METHODS: following a complete physical, psychiatric, and neuropsychological evaluation, 45 healthy veterans, 35 veterans with CFS and co-morbid psychiatric disorder, and 23 veterans with CFS and no co-morbid psychiatric disorder completed questionnaires assessing war and non-war-related life stressors, self-reports of environmental exposure (e.g. oil well fires, pesticides), personality, and coping. RESULTS: measures of personality, self-reported combat and chemical exposures, and negative coping strategies significantly differentiated healthy veterans
from those with CFS. CONCLUSION: a biopsychosocial model of veterans' illness was supported by the fact that personality, negative coping strategies, life stress after the war, and environmental exposures during the war were significant predictors of veterans' current physical function.


Parasympathetic activation of ileal motility is essential for intestinal physiology. We have previously demonstrated that carbachol activates muscarinic acetylcholine receptors (mAChR) of rat intestine and stimulates ileal motility via phospholipase C. This activation induces phosphoinositide turnover and intracellular calcium mobilization. We show here that carbachol stimulation of rat ileal motility is potentiated by the nitric oxide synthase (NOS) inhibitor N(G)-monomethyl arginine. Thus, we confirm that carbachol increases, in a dose-dependent manner, the activity of a NOS isoform that depends on calcium-calmodulin binding. Its product, nitric oxide (NO), activates not only guanylyl cyclase, inducing cGMP synthesis, but also cyclo-oxygenase, producing prostaglandin E(2). The prostanoid probably cooperates with NO to induce ileal smooth muscle relaxation.


The purpose of this project was to investigate the psychological and physical effects of training of body awareness and slow stretching on persons with chronic toxic encephalopathy (CTE). In the present study, a method of self-regulation, a body-mind training, is presented. The body-mind training used was a guided relaxation technique combined with meditative stretching. The techniques are introduced and the psychological and physiological effects of the training is presented. Eight subjects with CTE, 48.5 years, were trained for 8 weeks. Outcome measures were percentage alpha brain waves (alpha%), electromyography (EMG) on the frontalis muscle, state-trait anxiety (STAI), creativity (RAT), and mood measured as anxiousness, humour and mental fatigue. The mean alpha% increased 52% during the training period (P < 0.01), and the EMG decreased 31% (P < 0.001. State anxiety decreased 22% during the training period (P < 0.01), but no changes were observed in trait anxiety and in the creativity score. The level of anxiousness and fatigue before a training session decreased during the training period. In conclusion, the body-mind training resulted in
an improved ability for physical and mental relaxation as indicated from the lower EMG, the higher alpha% and the decrease in state anxiety.

Dunn, JD Journal/Tex Med. 96: 10-1.

Dryson, EW and Ogden, JA Journal/Neurotoxicology. 21: 659-65.

AIMS: to determine extent and nature of recovery of solvent induced chronic toxic encephalopathy (CTE). METHOD: 21 confirmed cases had repeat neuropsychological and clinical assessments 6-42 (mean 27) months after ceasing exposure. An exposure score was calculated for each. RESULTS: less than half (42.8%) showed evidence of improvement, which showed no association with time away from solvents or exposure score. The more severely affected at first diagnosis were nearly four times more likely to improve (RR 3.85 (95%CI 1.03, 14.38), p = 0.03). Those with no subjective improvement were five times more likely to have been on antidepressants (RR 5.25 (95%CI 0.83, 33.2), p=0.02). CONCLUSIONS: The largely irreversible nature of Type 2 CTE is confirmed. The study results suggest that severity of effect and partial recovery are not dose related but multifactorial, with individual susceptibility probably important. Concomitant depression may also adversely influence recovery.


Treating patients with multiple allergies to cosmetic products is a difficult proposition. Many of these patients may simply be experiencing irritant contact dermatitis. Others may have defective barrier function caused by a dermatitis that requires treatment. And some patients with sensitive skin need to exercise care in choosing which products they use on their skin. For many of these patients, products with the fewest ingredients work best because they contain the least or no sensitizers, irritants, or cutaneous sensory stimulants.


Subjects with asthma have higher concentrations of exhaled nitric oxide (NO) than normal individuals. It has been demonstrated that in asthmatics, repeated FVC maneuvers reduce NO. Although the cause of this phenomenon is not known, it has been hypothesized that deep breaths associated with FVC maneuvers reduce exhaled NO by affecting neural sources of NO, possibly via a mechanism related to the pathobiology of asthma. To establish whether FVC maneuvers influence NO concentrations in normal individuals, we measured exhaled NO at baseline values and after FVC maneuvers performed every 15 min for 1 h in subjects without asthma. To investigate the role of deep breaths in reducing exhaled NO, we compared these results with concentrations of exhaled NO after plethysmography. Repeated FVC maneuvers over 60 min produced a decrease in NO concentrations in mixed expired gas (F(E)NO; 24.6 +/- 5.1% decrease for F(E)NO, p < 0.01 versus baseline). In contrast to the results after spirometry, repeated specific airway conductance (sGaw) maneuvers do not have a significant effect on F(E)NO (p = 0.16). These results, which demonstrate that in nonasthmatic subjects FVC maneuvers-but not panting maneuvers-produce a fall in NO, suggest that the mechanism responsible for the reduction in exhaled NO after FVC maneuvers is related to volume history of the lung rather than the pathobiology of asthma.

(2000) Exhaled nitric oxide following leukotriene E(4) and methacholine inhalation in patients with asthma.
Nitric oxide (NO) is a molecular gas that can be recovered in higher levels from the exhaled gas of subjects with asthma than from subjects without asthma. However, the precise mechanisms responsible of promoting increased fraction of expired nitric oxide (FE(NO)) in asthma are unknown. As leukotriene antagonism has been shown to reduce FE(NO) in patients with asthma, we hypothesized that leukotrienes mediate the increased FE(NO) encountered in this condition. Furthermore, because leukotriene antagonism stabilizes serum eosinophil markers during reductions in inhaled corticosteroid doses, and FE(NO) has been shown to correlate with sputum eosinophils in asthma, we reasoned that the effect of leukotrienes on FE(NO) might be mediated by eosinophils recruited to the airway by leukotrienes. To test this hypothesis, we performed methacholine and leukotriene (LT) E(4) bronchoprovocation challenges in 16 subjects with atopic asthma and measured FE(NO) and sputum differential counts before and after bronchoprovocation. We then compared FE(NO) in the seven subjects who developed increased sputum eosinophils following LTE(4) inhalation with values measured after methacholine inhalation in these seven subjects. Following LTE(4) inhalation, eosinophils rose from 4.01 +/- 0.89% pre-LTE(4) to 8.33 +/- 1.52% post-LTE(4). The mean change in sputum eosinophils from baseline after LTE(4) inhalation was larger than that after methacholine inhalation (+4.31 +/- 1.25% versus -1.14 +/- 0.93%). After LTE(4) inhalation, FE(NO) levels did not differ from prechallenge baseline or from levels following methacholine inhalation (ANOVA p > 0.05). These data indicate that neither LTE(4) nor recruitment of eosinophils into the airway by LTE(4) is a sufficient stimulus to acutely increase FE(NO) in subjects with asthma.


---------------------------------------------------------------


OBJECTIVE: Somatic symptoms that occur in response to odors can be acquired in a pavlovian conditioning paradigm. The present study investigated 1) whether learned symptoms can generalize to new odors, 2) whether the generalization gradient is linked to the affective or irritant quality of the new odors, and 3) whether the delay between acquisition and testing modulates generalization. METHODS: Conditional odor stimuli (CS) were (diluted) ammonia and niaouli. One odor was mixed with 7.4% CO2-enriched air (unconditional stimulus) during 2-minute breathing trials (CS+ trial), and the other odor was presented with air (CS- trial). Three CS+ and three CS- trials were conducted in a semirandomized order (acquisition phase). The test phase involved one CS+ only (CS+ without CO2) and one CS- test trial, followed by three trials using new odors (butyric acid, acetic acid, and citric aroma). Half of the subjects
(N = 28) were tested immediately, and the other half were tested after 1 week. Ventilatory responses were measured during and somatic symptoms were measured after each trial. RESULTS: Participants had more symptoms in response to CS+-only exposures, but only when ammonia was used as the CS+. Also, generalization occurred: More symptoms were reported in response to butyric and acetic acid than to citric aroma and only in participants who had been conditioned. Both the selective conditioning and the generalization effect were mediated by negative affectivity of the participants. The delay between the acquisition and test phases had no effect. CONCLUSIONS: Symptoms that occur in response to odorous substances can be learned and generalize to new substances, especially in persons with high negative affectivity. The findings further support the plausibility of a pavlovian perspective of multiple chemical sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11138993


It has been suggested that the most critical missing link between science and policy is causality; that is, the establishment of a definite cause-effect relationship between exposure and adverse health effects. As has been clearly demonstrated by the decades-long tobacco debate, causality is extremely difficult to establish with absolute certainty, particularly in the minds of scientists. Because of this, it has been suggested that a "weight of evidence" approach based on biologic plausibility should be used as a surrogate for causality when translating science into policy and public health practice. In the case of neurodevelopmental effects, the case for biologic plausibility is supported by scientific findings from three broad areas consisting of wildlife biology, toxicology, and epidemiology. A striking example of this is provided by research findings from the Great Lakes Basin, an area which has been the focus of significant scientific research for the last thirty years in these three broad areas. In this paper, we examine relevant findings from the Great Lakes Basin and elsewhere as they relate to establishing and supporting the biologic plausibility of neurodevelopmental effects associated with environmental exposures to persistent toxic substances.

When abnormal psychologic/psychiatric symptom data are obtained on personality tests or psychiatric interviews administered to patients who report symptoms of Multiple Chemical Sensitivities Syndrome, investigators typically attribute these to either psychiatric traits or to psychogenic origins of illness. The primary purpose of these studies was the evaluation of the plausibility of nonpsychiatric explanations of psychologic/psychiatric symptom data. In Study 1, patients with Multiple Chemical Sensitivities Syndrome used the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) to describe which items had changed after they developed the condition. In Study 2, three diverse groups of professionals predicted which items on the MMPI-2 might change after a mentally healthy person developed the Syndrome or a condition resembling it. In Study 3, a second sample of Multiple Chemical Sensitivities Syndrome patients completed the MMPI-2 and other questionnaires by mail, which allowed the authors to ascertain whether these patients showed more or different psychopathology than was described by patients and hypothesized by professionals. Data from Study 1 patient informants indicated that developing the syndrome might result in a psychopathological MMPI-2 profile, characterized by abnormal Hypochondriasis and Hysteria scale scores. Professionals in Study 2 showed a consensus about hypothesized MMPI-2 changes following the development of the syndrome. These changes likely elevated the Hypochondriasis, Hysteria, Psychasthenia, Depression, and Schizophrenia scale scores. In Study 3, the patients taking the MMPI-2 showed elevations on the Hypochondriasis, Hysteria, Depression (women only), and Schizophrenia scales. Abnormal scores were associated closely with greater severity of illness and greater adjustment to illness. The strategy of administering psychometric tests to ill populations for the purposes of evaluating psychiatric illness or traits, and/or psychogenic origins of illness was shown to be potentially misleading.


Diisopropyl phosphorofluoridate (DFP) produces organophosphorus-ester induced delayed neurotoxicity (OPIDN) in the hen, human and other sensitive species. We studied the effect of a single dose of DFP (1.7 mg/kg/sc) on the expression of c-jun, which is one of the heterodimerizing ITFs (Inducible Transcriptional Factors) of the AP-1 family. The hens were sacrificed at different time points ie 0.25, .0.50, 1 and 2 hrs. Total RNA was extracted from the following brain regions: cerebrum, cerebellum, brainstem, midbrain and as well as spinal cord. Northern blots prepared using standard protocols were hybridized with c-jun as well as b-actin and 18S RNA cDNA (control) probes. The results indicate differential regulation of c-jun levels which may be due to the activation of both cholinergic and non-cholinergic pathways of CNS, besides
changing roles of c-jun (as mediator of degeneration or regeneration) depending on heterodimerization with other ITFs. In the highly susceptible tissues like brainstem and spinal cord c-jun transcript levels increased at 15 minutes and continued to increase gradually till it reached the maximum at 2 hrs. Overall spinal cord showed the maximum levels of c-jun induction (207%) at 2 hrs time point of all the CNS tissues. The enhancement of cholinergic transmisson by the inhibition of cholinesterase may be responsible for the gradual increase mediated by neural and vascular factors. In contrast, less susceptible tissue, cerebellum showed almost immediate induction to high level of (179%) at 15 minutes and the levels stayed more or less the same until it peaked to 185% at 2 hrs. Relatively low abundance of cholinergic neurons and high number of sensitized specialized cell types like Bergman glia and Purkinje cells may be responsible for the immediate higher induction. Non-susceptible tissue cerebrum did not show any changes in the c-jun levels. In midbrain the induction pattern was very similar to that of brainstem. This differential induction pattern of c-jun encompassing the differences in the quantity and time course was directly proportionate to the degree of susceptibility and cellular heterogeneity of different regions of CNS. The significant increase in c-jun levels along with our earlier observation on the increased c-fos levels indicate that AP-1 family of genes may be one of the IEGs involved in the long term changes which eventually lead to OPIDN.

---

(2000) Alterations in levels of mRNAs coding for glial fibrillary acidic protein (GFAP) and vimentin genes in the central nervous system of hens treated with diisopropyl phosphorofluoridate (DFP).
Damodaran, TV and Abou-Donia, MB Journal/Neurochem Res. 25: 809-16.

Diisopropyl phophorofluoridate (DFP) produces organophosphorus-ester induced delayed neurotoxicity (OPIDN) in the hen, human and other sensitive species. We studied the effect of DFP administration (1.7 mg/kg/s.c.) on the expression of Intermediate Filament (IF) proteins: Glial Fibrillary Acidic Protein (GFAP) and vimentin which are known indicators of neurotoxicity and astroglial pathology. The hens were sacrificed at different time points i.e. 1,2,5,10 and 20 days. Total RNA was extracted from the following brain regions: cerebrum, cerebellum, and brainstem as well as spinal cord. Northern blots prepared using standard protocols were hybridized with GFAP and vimentin as well as beta-actin and 18S RNA cDNA (controls) probes. The results indicate a differential/spatial/temporal regulation of GFAP and vimentin levels which may be due to the result of disruption of glial-neuronal network. The GFAP transcript levels reached near control levels (88% and 95%) at 20 days post DFP treatment after an initial down-regulation (60% and 73%) in highly susceptible tissues like spinal cord and brainstem respectively. However vimentin transcript levels remained down-regulated (61% and 53%) at 20 days after an early reduced levels(47% and 55%) for spinal cord and brainstem respectively. This may be due to the astroglial pathology resulting in neuronal alterations or vice-versa. In cerebellum (less susceptible tissue) GFAP levels were moderately down-regulated at 1,2 and 5 days and reached
near control values at 10 and 20 days. Vimentin was rapidly reinduced (128%) in cerebellum at 5 days and remained at the same level at 10 days and then returned to control values at 20 days after an initial down-regulation at 1 and 2 days. Thus these alterations were less drastic in cerebellum as indicated by initial susceptibility followed by rapid recovery. On the other hand both GFAP and vimentin levels were upregulated from 2 days onwards in the non-susceptible tissue cerebrum, implying protective mechanisms from the beginning. Hence the DFP induced astroglial pathology as indicated by the complex expression profile of GFAP and vimentin mRNA levels may be playing an important role in the delayed degeneration of axons or is the result of progressive degeneration of axons in OPIDN.

---------------------------------------------------------------------

(2000) Environmental risk factors (outdoor air pollution and climatic changes) and increased trend of respiratory allergy.

A wealth of evidence suggests that allergic respiratory diseases such as rhinosinusitis and bronchial asthma have become more common worldwide in recent years and a great deal of etiological and pathogenic research has been carried out to evaluate the possible causes of this increasing trend. There is also some evidence that increased atmospheric concentrations of pollutants such as ozone (O3), nitric oxides (NOx), respirable particulate (PM10) and volatile organic chemicals (VOC5), which result from increased use of liquid petroleum gas or kerosene, may be linked to the increased prevalence of allergic diseases which develop more frequently in urban areas of developed countries. Since bronchial asthma is a syndrome which can be aggravated by inhaled compounds, the effects of air pollutants on health have been the focus of attention. In fact, various studies have demonstrated that inhalation of air pollutants such as O3, nitrogen dioxide (NO2) and sulfur dioxide (SO2), either individually or in combination, can enhance the airway response to inhaled allergens in atopic subjects, thus inducing asthma exacerbations. Moreover, experimental studies have shown that diesel exhaust particulate causes respiratory symptoms and is able also to modulate the immune response by increasing IgE synthesis in predisposed animals and humans. There is also some evidence that air pollutants can interact with aeroallergens in the atmosphere and/or on human airways, potentiating their effects. In fact, by inducing airway inflammation which increases epithelial permeability, some pollutants overcome the mucosal barrier and lead to allergen-induced responses. However, air pollution and climatic changes should also have an indirect effect on allergic response by influencing quantitatively and qualitatively the pollen production by allergenic plants.

---------------------------------------------------------------------

This chapter reviews the current literature on the possible role of olfactory and trigeminal chemosensory function in idiopathic environmental intolerances (IEI). Two general points emerge from the review. First, studies of chemosensory function in IEI patients indicate that, despite their self-reported "heightened sensitivity" and enhanced responsivity to environmental odors, when compared to healthy controls they generally are found to be equally or even less sensitive to odors as measured by objective psychophysical and electrophysiological measures of olfactory function. These studies point towards alterations in the cognitive processing of olfactory information as the major characteristic of IEI. Second, studies of the role of sensitivity and bias in olfactory and trigeminal chemosensory functioning indicate that nonsensory factors (e.g., attention, bias, personality) can dramatically alter the self-reported impact of exposure to volatile chemicals. Together, these general points suggest a perspective on IEI that views many symptoms of the disorder to primarily reflect the influence of nonsensory, cognitive processes on responses to environmental odors.


Although the use of pesticides has doubled every ten years since 1945, pest damage to crops is more prevalent now than it was then. Many pests are now pesticide resistant due to the ubiquitous presence of pesticides in our environment. Chlorinated pesticide residues are present in the air, soil, and water, with a concomitant presence in humans. Organophosphate and carbamate pesticides - the compounds comprising the bulk of current pesticide use - are carried around the globe on air currents. Municipalities, schools, churches, business offices, apartment buildings, grocery stores, and homeowners use pesticides on a regular basis. Pesticides are neurotoxins that can cause acute symptoms as well as chronic effects from repeated low-dose exposure. These compounds can also adversely affect the immune system, causing cell-mediated immune deficiency, allergy, and autoimmune states. Certain cancers are also associated with pesticide exposure. Multiple endocrine effects, which can alter reproduction and stress-handling capacity, can also be found. Limited testing is available to assess the toxic overload of these compounds, including serum pesticide levels and immune system parameters. Treatment for acute or chronic effects of these toxins includes avoidance, supplementation, and possibly cleansing.
Among the sanitary effects of environmental chemicals, 3 examples illustrate the complexity of the issues to be solved: 1. endocrine disrupters, xenobiotics which interfere with hormonal systems, could increase the risk of reproductive and developmental disturbances and explain the rising incidence of hormone-dependent cancers; 2. multiple chemical sensitivity due to odorous chemicals has severe social consequences and warrants further research; 3. the reappearance of well-known poisoning cases and the emergent new toxic diseases due to substitutive products for solvents, cooling agents and spray propellants banned for ecological purpose, demonstrate the need for surveillance programmes of industrial and household products.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10748669

Clustering of health events in or around industrial facilities sometimes leads to worker and community concerns that plant management or local health professionals must address. We provide an eight-step process to deal with these concerns systematically. We emphasize the use of good scientific practices with managerial oversight for effective worker and community communication. This process is directed to plant management and the local health professional and emphasizes the practical aspects of the investigation.

Propionic acidemia is an inherited disorder caused by a defect of propionyl CoA carboxylase. Untreated, propionic acidemia leads to metabolic decompensation and toxic encephalopathy. We report on the magnetic resonance imaging (MRI) and
magnetic resonance spectroscopy (MRS) findings in five children who were properly treated by protein restriction and carnitine supplementation, during a phase of clinically and metabolically stable conditions. The examinations were performed on a whole-body 1.5 T scanner. During the observation period, from 1992 to 1996 we employed long echo time single-voxel spectroscopy and chemical shift imaging in addition to a conventional MRI protocol. The two children with the longest delay before onset of therapy showed cerebral atrophy. MRS yielded elevated lactate peaks in four of the children. These results indicate that MRS can detect metabolic alterations in the brains of children with propionic acidemia during metabolically stable conditions. The presence of lactate could be caused by hampered aerobic oxidation within the citrate cycle due to intracellular elevated propionic metabolites.

---------------------------------------------------------------------------------------------------------------------------------


Early after the development of aspirin, almost 150 years ago, its auditory toxicity has been associated with high doses employed in the treatment of chronic inflammatory diseases. Tinnitus, loss of absolute acoustic sensitivity and alterations of perceived sounds are the three auditory alterations described by human subjects after ingestion of large doses of salicylate. They develop over the initials days of treatment but may then level off, fluctuate or decrease, and are reversible within a few days of cessation of treatment. They may also occur within hours of ingestion of an extremely large dose. Individual subjects vary notably as to their susceptibility to salicylate-induced auditory toxicity. Tinnitus may be the first subjective symptom, and is often described as a continuous high pitch sound of mild loudness. The hearing loss is slight to moderate, bilaterally symmetrical and affects all frequencies with often a predominance at the high frequencies. Alterations of perceived sounds include broadening of frequency filtering, alterations in temporal detection, deterioration of speech understanding and hypersensitivity to noise. Behavioral conditioning of animals provides evidence for mild and reversible hearing loss and tinnitus, similar to those observed in humans. Anatomical examinations revealed significant alterations only at outer hair cell lateral membrane. Electrophysiological investigations showed no change in endocochlear resting potential, and small changes in the compound sensory potentials, cochlear microphonic and summatating potential, at low acoustic levels. Measures of cochlear mechanical responses to sounds indicated a clear loss of absolute sensitivity and an associated broadening of frequency filtering, both of a magnitude similar to audiometric alterations in humans, but at extremely high salicylate levels. Otoacoustic emissions demonstrated changes in the mechano-sensory functioning of the cochlea in the form of decrease of spontaneous emissions and reduced nonlinearities. In vitro measures of isolated outer hair cells showed reduction of their fast motile responses which are thought to be at the origin of cochlear absolute sensitivity and associated fine filtering. Acoustically evoked neural responses from the eighth nerve to the auditory cortex showed reversible and mild losses of absolute sensitivity and associated broadening of
frequency filtering. There is no evidence of a direct alteration of cochlear efferent innervation. Evidence was obtained for decreases in cochlear blood supply under control of autonomous innervation. Spontaneous neural activity of the auditory nerve revealed increases in firings and/or in underlying temporal synchronies. Similar effects were found at the inferior colliculus, mostly at the external nucleus, and at the cortex, mostly at the anterior and less at the secondary auditory cortex but not at the primary auditory cortex. These changes in spontaneous activity might underlie tinnitus as they affect mostly neural elements coding high frequencies, can occur without a loss of sensitivity, are dose dependent, develop progressively, and are reversible. Biochemical cochlear alterations are poorly known. Modifications of oxydative phosphorylation does not seem to occur, involvement of inhibition of prostaglandin synthesis appears controversial but could underlie changes in blood supply. Other biochemical alterations certainly also occur at outer hair cells and at afferent nerve fibers but remain unknown.


Patients with multiple chemical sensitivities (MCS) often report heightened sensitivity to odors. Odor detection thresholds to phenyl ethyl alcohol (PEA) and pyridine (PYR) were evaluated as a measure of odor sensitivity for 33 MCS subjects, 13 chronic fatigue syndrome subjects, 16 asthmatic subjects, and 27 healthy controls. Odor identification ability (based on University of Pennsylvania Smell Identification Test results) and ratings in response to four suprathreshold levels of PEA and PYR were also assessed. Odor detection thresholds for PEA and PYR and odor identification ability were equivalent for all groups; however, when exposed to suprathreshold concentrations of PEA, MCS subjects reported significantly more trigeminal symptoms and lower esthetic ratings of PEA. No group differences were found in response to suprathreshold concentrations of PYR. In summary, MCS subjects did not demonstrate lower olfactory threshold sensitivity or enhanced ability to identify odors accurately. Furthermore, they were differentiated from the other groups in their symptomatic and esthetic ratings of PEA, but not PYR.
Byrne, E Journal/J Clin Neurosci. 7: 9-12.

(2000) [Psychiatric and somatic morbidity of patients with suspected multiple chemical sensitivity syndrome (MCS)].

Multiple chemical sensitivity (MCS) or idiopathic environmental intolerance (IEI) is understood as an acquired disorder with multiple recurrent symptoms that cannot be traced to any well-known medical or psychiatric condition and is associated with diverse environmental influences that are well tolerated by the majority of people. In a prospective study, we investigated 120 consecutive patients admitted a university-based outpatient department for environmental medicine during 1 year. Apart from routine medical examination and special toxicological diagnostic procedures, a structured clinical interview for DSM-IV psychiatric disorders was performed with every patient. At least one psychiatric diagnosis was found in 100 patients. The diagnostic criteria for somatoform disorders were filled by 53 patients. We found lifetime or current affective disorders in 39 patients, anxiety disorders in 29, and substance dependency or abuse in 25. In 16 patients, personality disorders were diagnosed. Nine suffered from psychotic disorders. This is the largest prospective study with standardized psychiatric diagnostic methods concerning psychiatric morbidity and MCS. The data show that many patients with environmental health problems obviously suffer from somatoform disorders but also from other, well-known psychiatric conditions.

(2000) Use of neuropsychological testing in idiopathic environmental testing.
Individuals with idiopathic environmental intolerance (IEI) report fatigue, headaches, weakness, malaise, decreased attention/concentration, memory loss, disorientation, confusion, and psychological disturbances. These neurobehavioral symptoms may be a sign of possible alterations in the central nervous system (CNS). The evaluation of neurobehavioral functioning using standardized testing provides a surrogate measure of integrity of the CNS. However, the interpretation of neuropsychological test results must be made cautiously since this technique is extremely sensitive, but not specific. Abnormal test results could be due to a neurological disorder, a medical disorder, or a neuropsychiatric disorder. Therefore, when evaluating patients who present with symptoms of IEI, abnormal neurobehavioral results should not be attributed routinely to environmental chemical exposure until other causes are systematically ruled out.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10903555


Black, DW, Okiishi, C and Schlosser, S Journal/Psychosomatics. 41: 253-61.

The authors assessed self-reported health status and clinical symptoms in people reporting multiple chemical sensitivities (MCS) at a 9-year follow-up interview using structured and semistructured instruments and self-report questionnaires. Of the original sample, 18 people (69%) consented to an interview. By use of the best estimate diagnostic method, 15 subjects (83%) met DSM-IV criteria for a lifetime mood disorder, 10 (56%) for a lifetime anxiety disorder, and 10 (56%) for a lifetime somatoform disorder. None of the subjects met the criteria for a substance use disorder (current or lifetime). The Illness Behavior Questionnaire and the Symptom Check-list-90-Revised results showed little change from 1988 and remained significantly different from the control group on many subscales. The authors conclude that the subjects remain strongly committed to the diagnosis of MCS, and although improved since their original interview, many remain symptomatic and continue to report ongoing lifestyle changes.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10849458
Subject: Multiple chemical sensitivity syndrome: symptom prevalence and risk factors in a military population.

Objective: To assess the prevalence of and risk factors for self-reported symptoms suggestive of multiple chemical sensitivities/idiopathic environmental intolerance (MCS/IEI) in Persian Gulf War (PGW) veterans from Iowa and a comparison group of PGW-era military personnel.

Methods: A population-based sample of Iowa military personnel was surveyed using a cross-sectional telephone interview. Study participants were randomly drawn from 1 of 4 domains: PGW active duty, PGW National Guard Reserve, non-PGW active duty, and non-PGW National Guard/Reserve. A complex sample survey design was used selecting participants from the following substrata: age, sex, race, rank, and military branch. The criteria for MCS/IEI were developed using expert consensus and the medical literature.

Results: A total of 3695 study participants (76% of those eligible) completed the telephone survey. The prevalence of symptoms suggestive of MCS/IEI in all participants was 3.4%. Veterans of the PGW reported a significantly higher prevalence of symptoms suggestive of MCS/IEI than did non-PGW military personnel (5.4% vs 2.6%); greater sensitivity to organic chemicals, vehicle exhaust, cosmetics, and smog; and more lifestyle changes. The following risk factors for MCS/IEI were identified with univariate analysis: deployment to the Persian Gulf, age (>25 years), female sex, receiving a physician diagnosis of MCS, previous professional psychiatric treatment, previous psychotropic medication use, current psychiatric illness, and a low level of preparedness. Multiple logistic regression analysis identified several independent risk factors for MCS/IEI, including deployment to the Persian Gulf, age, sex, rank, branch of service, previous professional psychiatric treatment, and current mental illness.

Conclusions: Self-reported symptoms suggestive of MCS/IEI are relatively frequent in a military population and are more common among PGW veterans than comparable controls. Reported chemical sensitivities and accompanying behavioral changes were also frequent. After adjusting for age, sex, and training preparedness, previous professional psychiatric treatment and previous psychotropic medication use (before deployment) showed a robust association with symptoms suggestive of MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10789611

Subject: The relationship of mental disorders and idiopathic environmental intolerance.

Objective: To explore the relationship between mental disorders and idiopathic environmental intolerance.

Methods: A survey was conducted among military personnel in Iowa.

Results: A total of 3695 participants completed the survey. The prevalence of symptoms suggestive of MCS/IEI was 3.4%. Veterans of the PGW reported a significantly higher prevalence of symptoms suggestive of MCS/IEI than did non-PGW military personnel (5.4% vs 2.6%).

Conclusions: Self-reported symptoms suggestive of MCS/IEI are relatively frequent in a military population and are more common among PGW veterans than comparable controls. Reported chemical sensitivities and accompanying behavioral changes were also frequent. After adjusting for age, sex, and training preparedness, previous professional psychiatric treatment and previous psychotropic medication use (before deployment) showed a robust association with symptoms suggestive of MCS.
Idiopathic environmental intolerance (IEI) is an acquired condition with multiple symptoms associated with diverse environmental factors tolerated by most persons, not explained by known medical or psychiatric disorders. Data from clinical and epidemiologic samples show a robust association between IEI and lifetime psychiatric disorder, particularly mood, anxiety, somatoform, and personality disorders. IEI has not been associated with lifetime substance use disorders or psychotic disorders. The relationship of IEI and psychiatric disorder is important to acknowledge because it alerts clinicians to the fact that many persons diagnosed with IEI suffer treatable emotional illnesses, and because it suggests that some persons with mental illness are being misdiagnosed when their symptoms are misinterpreted as evidence of IEI.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10903550

(2000) **Is allergy a preventable disease?**

(2000) **The special and unique vulnerability of children to environmental hazards.**
Bearer, CF Journal/Neurotoxicology. 21: 925-34.

There are several factors that alter an individual's risk for an environmentally related illness. A major determinant is the developmental stage of the individual. The environment can be divided into three spheres: physical, biological and social. The components of each sphere are dependent on developmental stage. This presentation will discuss the components of each of these spheres and their variability with age. The discussion will be illustrated with known examples of environmentally related disease.


Physicians qualified in environmental medicine due to their participation in special training courses in the federal state Schleswig-Holstein (Germany) may use a standardized questionnaire to report on their environmental medicine-related cases. The course of the illness and recovery, respectively, if known, is to be documented on a separate data sheet. During a three year period from 1995 to 1997 716 cases and 216 courses of illness and recovery, respectively, have been reported. The relevant
environmental factors/toxicants of exposure most frequently documented by these physicians and found to be related to symptoms of illness were biocides (mainly insecticides used indoors for pest control, 31%), molds (30%), dental amalgam (28%), solvents or volatile organic compounds (VOC, 23%) and formaldehyde (17%), respectively. In 47% of the documented cases an exposure to more than one environmental factor/toxicant was registered. Age distribution as well as the symptoms of illness of the patients were found to be dependent on the type of exposure. After the physicians diagnosis of an environmental medicine-related illness the exposure was stopped completely in 57% of those cases of whom the course of the illness was known. Recovery was reported in 62% of these patients, and additional 30% had improved but had not recovered completely at the time of data-assessment. From these results it may be concluded that research work in the field of environmental medicine should be enforced in order to prevent unnecessary illness and to lower the costs of the public health system.


The question of when it would be appropriate to conclude that the associations between particulate pollution and various outcomes (including mortality) should be judged as causal in nature has been difficult and controversial. Although such a judgment must be subject to revision, the volume of new information and new experimental findings has been so great that such a reevaluation is required at frequent intervals. The useful summary by Gamble [PM(2.5) and Mortality in Long-Term Prospective Cohort Studies: Cause-Effect or Statistical Associations? Environ Health Perspect 106:535-554 (1998)] of the reasons why a causal inference was, in his opinion, not justified provides a basis for reevaluation in the light of new data. Such a reexamination indicates that the associative evidence is now stronger and that the biologic basis for a number of adverse effects has now been demonstrated. All of the useful guideline criteria customarily applied to such questions seem to have been met, although there is still much to be learned about interactive effects and the possibility of statistical thresholds.

Ashford, NA and Zwetsloot, G Journal/J Hazard Mater. 78: 123-44.

It is now generally recognized that in order to make significant advances in accident prevention, the focus of industrial firms must shift from assessing the risks of existing
production and manufacturing systems to discovering technological alternatives, i.e. from the identification of problems to the identification of solutions. Encouraging the industrial firm to perform (1) an inherent safety opportunity audit (ISOA) to identify where inherently safer technology (IST) is needed, and (2) a technology options analysis (TOA) and to identify specific inherently safer options that will advance the adoption of primary prevention strategies that will alter production systems so that there are less inherent safety risks. Experience gained from a methodology to encourage inherently safer production (ISP) in industrial firms in the Netherlands and Greece is discussed. Successful approaches require both technological and managerial changes. Firms must have the willingness, opportunity, and the capability to change. Implications for the EU Seveso, IPPC, and EMAS Directives are also discussed.


One hundred ninety-five 6- to 7-year-old children who lived in the municipality of Siena (Tuscany, Italy), underwent biologic monitoring to evaluate urinary excretion of several alkylphosphates that are metabolites of organophosphorus pesticides. We evaluated dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP). We obtained urine samples taken in the children's schools, and each sample was accompanied by a questionnaire about lifestyle and dietary habits. We found DMP and DMTP in detectable concentrations in the greatest number of samples (96 and 94%, respectively). The DMP values were geometric mean (GM) 116.7, [geometric standard deviation (GSD) 2.5], and a range of 7.4-1,471.5 nmol/g creatinine. The corresponding DMTP values were GM 104.3 (GSD 2.8) and a range of 4.0-1,526.0 nmol/g creatinine. DMDTP, DEP, DETP, and DEDTP concentrations were GM 14.1, (GSD 3.0), and a range of 3.3-754.6 nmol/g creatinine in 34% of the children; GM 33.2, (GSD 2.4), and a range of 5.1-360.1 nmol/g creatinine in 75% of the children; GM 16.0, (GSD 2.9), and a range of 3.1-284.7 in 48% of the children; and GM 7.7, (GSD 2.1), and a range of 2.3-140.1 in 12% of the children, respectively. The significant variable for urinary excretion of these metabolites in children was pest control operations performed inside or outside the house in the preceding month; however, the presence of a vegetable garden near the house rarely emerged. The urinary excretion of alkylphosphates in children was significantly higher than in a group of the adult population resident in the same province.
(2000) **Multiple chemical sensitivity.**

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10741329

(2000) **Multiple chemical sensitivity (MCS)--differential diagnosis in clinical neurotoxicology: a German perspective.**

The multiple chemical sensitivity syndrome (MCS) is a new cluster of environmental symptoms which have been described and commented on for more than 15 years now in the USA. In the meantime it has also been observed in European countries. The main features of this syndrome are: multiple symptoms in multiple organ systems, precipitated by a variety of chemical substances with relapses and exacerbation under certain conditions when exposed to very low levels which do not affect the population at large. There are no lab markers or specific investigative findings. In our view, MCS is not a separate clinical syndrome but a collective term. A very small part of the patients in question may actually exhibit a somatic or psychosomatic response to low levels of a variety of chemicals in the environment. For another part, even if the MCS symptoms are induced by chemical substances in the environment, the basic hypersensitivity is a psychological stress reaction. In the third and largest group, the patients have been misdiagnosed, i.e. a somatic or psychiatric disease has been overlooked. There is a fourth group of patients in whom there is no evidence of any exposure at all but instead a belief system installed by certain physicians, the media and other groups in society. This paper tries to describe the neurological and neurotoxic aspects of MCS problems and to illustrate it with examples of an alleged outbreak of chronic neurotoxic disease caused by pyrethroids in Germany. Research strategy should establish clearly determined diagnostic criteria, agreement on the use of specific questionnaires as well as clinical and technical diagnostic procedures, prospective clinical studies of MCS patients and comparative groups as well as experimental approaches.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11022866

(2000) **Neurologic evaluation of workers previously diagnosed with solvent-induced toxic encephalopathy.**
We examined 52 railroad workers with long-term occupational solvent exposures (average 22 years duration) who had been previously diagnosed by others as having solvent-induced toxic encephalopathy. All described episodes of transient intoxication associated with occupational solvent exposure. Persistent symptoms developed, an average, 16 years after exposure onset and included impaired memory (38), altered mood (21), imbalance (18), and headache (17). Thirteen workers had mild mental status abnormalities, but none fulfilled conventional clinical criteria for encephalopathy or dementia. None had abnormal blink reflex (51) or abnormal electroencephalographic (39) studies. Eight of 47 magnetic resonance imaging studies showed evidence of scattered ischemic lesions among workers with known diabetes mellitus (2), elevated blood pressure (4), or peripheral vascular disease (2). One magnetic resonance imaging scan showed mild cortical atrophy. In stepwise multiple linear and logistic regression models, no statistically significant (P < 0.05) dose-response relationships were found between exposure duration and symptoms or signs that were suggestive of encephalopathy. However, the number of symptoms (P < 0.001) and the number of signs (P = 0.05) were associated with current use of central nervous system-active medications. Further, lower Mini-Mental Status Examination scores were associated with a history of alcohol abuse (P = 0.01) and lower educational level (P = 0.03). The number of chief symptoms involving memory, mood, balance, or headache differed significantly among workers in different geographic sites (F(3.48) = 2.94, P = 0.04), a finding that was not explained by job title or exposure duration. There also was a significant (P = 0.0001) inverse relationship between initial exposure year (r2 = 0.60) or total years of exposure through 1987 (r2 = 0.56) and interval to major neurologic symptom onset, suggesting that factors other than solvent exposure account in part for worker complaints. We found no objective neurologic evidence supportive of toxic encephalopathy or any other uniform syndrome among these individuals, and most complaints were explained by neuropsychological factors or conditions unrelated to occupational solvent exposure.

(2000) [Focus on skin and environment].

Abu-Qare, AW, Brownie, CF and Abou-Donia, MB Journal/Arch Toxicol. 74: 388-96.

The pharmacokinetics and placental transfer of a single oral dose of 100 mg/kg (10 microCi/kg, 16% of acute oral LD50) of uniformly phenyl-labeled [14C]p-nitrophenol were investigated in pregnant Sprague-Dawley rats at 14-18 days of gestation. Three
animals were killed on gestation day 18, at 0.5, 1, 2, 4, 12, 24, and 48 h after dosing. Radioactivity was rapidly absorbed and distributed throughout the maternal and fetal tissues. The gastrointestinal tract contents retained 20% and 2% of the dose at 0.5 h and 4 h after dosing. The peak maternal plasma concentration of radioactivity (microg p-nitrophenol equivalent/ml) was 7.17 compared with 0.37 for fetal plasma at 0.5 h. Maximum concentration of radioactivity (microg p-nitrophenol equivalent/g fresh tissue) was detected in most tissues 0.5 h after dosing and was in descending order: kidney 23.27, liver 12.37, placenta 3.56, fetus 2.17, and brain 1.99. Radioactivity was eliminated from plasma and all tissues beixponentially. The half-lives of elimination of 14C were 34.65 h and 69.30 h for maternal and fetal plasma, respectively. p-Nitrophenol, detected by HPLC, was the major compound identified in plasma and tissues. While p-nitrophenol disappeared biphasically from maternal plasma and kidney, it was eliminated monophasically from brain, placenta, and liver. p-Nitrocatechol and p-aminophenol were detected in the liver with peak concentrations at 0.5 h of 1.13 and 1.00 microg/g fresh tissue, respectively. While the change in the concentration of p-nitrocatechol with time was monophasic, that of p-aminophenol showed a biphasic pattern with elimination half-lives of 1.93 h and 4.95 h, respectively. Radioactivity was rapidly excreted in the urine mostly as polar metabolites, while only 3% of the dose was recovered in the feces. Radioactive materials excreted in the urine comprised: glucuronides 4%, sulfates 8%, hot-acid hydrolysates 11%, nonconjugated compounds 16%, and water-soluble metabolites 61%. This study demonstrated that although orally administered p-nitrophenol is a rapidly absorbed and excreted compound, it is transported to the maternal brain and the fetus and may pose a health risk following exposure to toxic doses during pregnancy.

Abu-Qare, AW and Abou-Donia, MB Journal/Toxicology. 150: 119-27.

The identification and kinetics of urinary excretion of metabolites of uniformly phenyl-labeled O,O-dimethyl O-4-nitrophenyl phosphorothioate ([14C]methyl parathion) were carried out following a single dermal dose of 10.0 mg (10 microCi)/kg in pregnant Sprague-Dawley rats at 14-18 days of gestation. Urine was collected at each time interval of 1, 2, 4, 12, 24, 48, 72, and 96 h after dosing. Total p-nitrophenol in the conjugated and non-conjugated metabolites was measured as a marker of methyl parathion exposure. Elimination of radioactivity in the urine was rapid. Of the total 14C urinary excretion, 30% of the dose was excreted within 4 h, while 50 and 90% of the dose were recovered in the urine by 24 and 96 h, respectively. Excretion rate of total radioactivity was 60 microgram methyl parathion equivalent/h (1.4 mg/day). By the end of the 96-h experiment, conjugated and non-conjugated metabolites accounted for 78.1 and 21.9%, respectively. Of the non-conjugated metabolites, p-nitrophenol and O,O-dimethyl O-4-nitrophenyl phosphate (methyl paraoxon) were identified by high performance liquid chromatography (HPLC) that accounted for 20%, and 1.9% of total...
Appearance and disappearance rate constants of p-nitrophenol in urine were 0.12 and 0.048 microgram/h, respectively. Conjugated metabolites were classified as: glucuronides 12% of urinary excretion, sulfates 3%, hot sulfuric acid hydrolysable residues 47% and 16.1% remained as unidentified water soluble metabolites. Direct hot acid hydrolysis of urine yielded 49% of extractable 14C-radioactivity compared to 62% when hot acid hydrolysis followed the enzymatic hydrolysis. The presence of the conjugated metabolites as the major class of metabolites of the total excretion indicates that determining only unbound p-nitrophenol as a biological marker for methyl parathion exposure underestimates total urinary excretion of p-nitrophenol. Sequential enzymatic and acid hydrolyses of urine prior solvent extraction are necessary for complete recovery of p-nitrophenol. The results indicate that the present method would show that the pregnant field worker or a housewife being at a greater risk than previously thought.


A rapid and simple method was developed for the separation and quantification of the anti nerve agent drug pyridostigmine bromide (PB; 3-dimethylaminocarbonyloxy-N-methyl pyridinium bromide) its metabolite N-methyl-3-hydroxypyridinium bromide, the insect repellent DEET (N,N-diethyl-m-toluamide), its metabolites m-toluamide and m-toluic acid, the insecticide permethrin (3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylic acid(3-phenoxyphenyl)methylester), and two of its metabolites m-phenoxybenzyl alcohol, and m-phenoxybenzoic acid in rat plasma and urine. The method is based on using C18 Sep-Pak cartridges for solid-phase extraction (SPE) and high-performance liquid chromatography (HPLC) with reversed-phase C18 column, and gradient UV detection ranging between 208 and 230 nm. The compounds were separated using gradient of 1 to 99% acetonitrile in water (pH 3.20) at a flow-rate ranging between 0.5 and 1.7 ml/min in a period of 17 min. The retention times ranged from 5.7 to 14.5 min. The limits of detection were ranged between 20 and 100 ng/ml, while limits of quantitation were 150-200 ng/ml. Average percentage recovery of five spiked plasma samples were 51.4+/-10.6, 71.1+/-11.0, 82.3+/-6.7, 60.4+/-11.8, 63.6+/-10.1, 69.3+/-8.5, 68.3+/-12.0, 82.6+/-8.1, and from urine 55.9+/-9.8, 60.3+/-7.4, 77.9+/-9.1, 61.7+/-13.5, 68.6+/-8.9, 62.0+/-9.5, 72.9+/-9.1, and 72.1+/-8.0, for pyridostigmine bromide, DEET, permethrin, N-methyl-3-hydroxypyridinium bromide, m-toluamide, m-toluic acid, m-phenoxybenzyl alcohol and m-phenoxybenzoic acid, respectively. The relationship between peak areas and concentration was linear over the range between 100 and 5000 ng/ml. This method was applied to analyze the above chemicals and metabolites following their administration in rats.
Abu-Qare, AW, Abdel-Rahman, AA, Kishk, AM and Abou-Donia, MB Journal/Toxicol Sci. 53: 5-12.

The pharmacokinetics and placental transfer of a single dermal 10.0 mg (10microCi)/kg dose of uniformly phenyl-labeled [14C] methyl parathion (0,0-dimethyl 0-4-nitrophenyl phosphorothioate) were investigated in pregnant Sprague-Dawley rats at 14-18 days of gestation. Three rats were killed at each time interval: 1, 2, 4, 12, 24, 48, 72, and 96 h after dosing. Radioactivity disappeared biexponentially from the administration sites, which retained 50% and 3% of the dose after 1 h and 96 h, respectively. Most of the absorbed radioactivity was excreted in the urine (91%). Only 3% of the 14C was recovered in the feces. One h after the administration, radioactivity was detected in all tissues, including fetal tissue. The peak maternal plasma concentration of radioactivity (ng methyl parathion equivalent/ml) was 1005 at 2 h, compared to 318 ng for fetal plasma at 12 h. The maximum concentrations of radioactivity (ng methyl parathion equivalent/g), detected in most tissues within 12 h of dosing, were, in descending order: adipose tissue (67,532), kidney (1,571), spleen (1,256), spinal cord (1,004), heart (729), liver (706), brain (546), placenta (389), and fetus (256). The metabolism studies showed that methyl parathion, detected by HPLC, was the major compound identified in plasma and tissues. The maximum concentration detected was in plasma, at 513 ng/ml, and in the following tissues (ng/g fresh tissue): kidney (819), fetus (668), placenta (394), liver (375), and brain (282). The metabolite methyl paraoxon was detected in maternal brain and liver at maximum concentrations (ng/g fresh tissue) of 135 and 64 after 12 h and 4 h respectively, while p-nitrophenol was only detected in liver at a maximum concentration of 21 ng/g 72 h after dosing. Pharmacokinetic studies showed that methyl parathion disappeared monoexponentially from plasma and tissues. The half-life of elimination of methyl parathion from plasma was 11 h corresponding to a constant rate value of 0.06 h(-1). The results indicate that skin and placenta are poor barriers against methyl parathion permeability, resulting in a rapid and extensive dermal absorption of this insecticide and extensive placental transfer. This is indicated by the relative residence (R(R)) of methyl parathion in the plasma, which was largest in the placenta followed by the fetus. This study suggests that pregnant women and fetuses may be at risk of cholinergic toxicity following dermal exposure to methyl parathion.

(2000) Increased 8-hydroxy-2'-deoxyguanosine, a biomarker of oxidative DNA damage in rat urine following a single dermal dose of DEET (N, N-diethyl-m-toluamide), and permethrin, alone and in combination.
Abu-Qare, A and Abou-Donia, M Journal/Toxicol Lett. 117: 151-60.

Levels of the biomarker of DNA oxidative damage 8-hydroxy-2'-deoxyguanosine (8-OHdG) in rat urine following dermal exposure to DEET (N,N-diethyl-m-toluamide) and permethrin, alone and in combination have been determined. A group of five rats for each time point were treated with a single dermal dose of 400 mg/kg of DEET, 1.3 mg/kg of permethrin or their combination. Urine samples were collected 2, 4, 8, 16, 24, 48, and 72 h following application. Control urine samples of rats treated with ethanol were also collected at the same time intervals. Solid phase extraction coupled with high performance liquid chromatography (HPLC) with UV detection at 254 nm was used for determination of 2'-deoxyguanosine, and (8-OHdG). The limits of detection (LOD) were 0.5 ng of both 2'-deoxyguanosine and 8-OHdG. Their average percentage recoveries from urine samples were between 70-85%. A single dermal dose of DEET or in combination with permethrin significantly induced levels of (8-OHdG) that are excreted in the urine over the time course of the study compared to control urine samples. Permethrin did not cause significant increase in the amount of 8-OHdG in the urine. Levels of 8-OHdG in urine excreted at 24 h were 1009+/−342, 1701+/−321, 1140+/−316, and 1897+/−231 ng following treatment with ethanol, DEET, permethrin, and DEET+permethrin, respectively. The results indicate that dermal administration of DEET could generate free radical species hence cause DNA oxidative damage in rats.


Ethyl methacrylate (ethyl 2-methyl-2-propenoate, EMA) has been implicated in the development of neurologic impairment following occupational exposure. The potential of EMA to produce neurotoxicity was investigated in adult male Sprague-Dawley rats in two experiments. In the first experiment, animals were administered 100, 200, 400, or 800 mg/kg by daily intraperitoneal (i.p.) injections for 60 d. Control rats received daily i.p. injections of 1 ml saline/kg. Clinical observations, spontaneous motor activity, and performance in the Morris water maze were assessed. Alterations in clinical parameters in the higher dose groups included lethargy, impaired breathing, decreased weight gain, and increased mortality. Alterations in motor activity were observed at 100 mg/kg, a dose that did not cause alterations in clinical parameters, body weight gain, or mortality. There was also a dose-dependent impairment in performance in the Morris water maze. In the second experiment, animals were administered EMA in drinking water at concentrations of 0.1, 0.2, or 0.5% for 60 d. Control rats were administered tap water. Animals were perfused at the termination of exposure and samples of brain, spinal cord, and sciatic nerve were prepared for histological examination. Spongiform alterations were observed in fiber tracts of the forebrain, brainstem, and spinal cord. Clusters of axonal swellings were scattered throughout the dorsal, ventral, and lateral
columns of the spinal cord, and typically involved internodal segments of two or three neighboring axons. Shrunken axons with separated myelin lamellae and large axons with thinner than normal myelin sheaths were apparent in the sciatic nerve. The patterns of alterations in the white matter of the spinal cord and the sciatic nerve are consistent with myelinopathy, but additional experiments are necessary to confirm whether oligodendroglia and Schwann cells are the primary sites of injury. In addition to the alterations associated with myelin, there was a decrease in the density of neurons in the ventral horn of the spinal cord. While the observed effects of EMA on the nervous system of rats are consistent with neurologic symptoms of workers exposed to EMA, additional experiments are necessary to determine if the level and route of exposures associated with occupational use produce these impairments in experimental animals.

(2000) Heavy metals in Egyptian spices and medicinal plants and the effect of processing on their levels.

To determine the contamination of Egyptian spices and medicinal plants with heavy metals, a total of 303 samples, which represent 20 different types of spices and medicinal plants that were collected from areas of exportation in Egypt, were analyzed for heavy metals. Some of them have different growing seasons, and each has its own agricultural practices and several shipments. The results revealed that heavy metal contents in spice and medicinal plants depend on the plant species. The maximum levels of heavy metals in the analyzed samples were 14.4, 2.44, 33.75, 2.85, 0.10, 68.80, 343.0, 11.40, and 1046.25 microg/g for Pb, Cd, Cr, Ni, Sn, Zn, Mn, Cu, and Fe, respectively. Cobalt was not detected in any of the various samples under investigation. The levels of heavy metals determined in the analyzed samples were found to exceed the maximum allowable levels of Zentrale Erfassungs und Bewertungsstelle fur Umweltchemikalien. The investigated medicinal plants were also processed by two different methods to determine the behavior of their metal contents during processing. It has been found that boiling the plant in water leads to the extraction of higher amounts of the metal from the plant than immersing it in the hot water. The achieved results were tabulated.

Aaron, LA, Burke, MM and Buchwald, D Journal/Arch Intern Med. 160: 221-7.

BACKGROUND: Patients with chronic fatigue syndrome (CFS), fibromyalgia (FM), and temporomandibular disorder (TMD) share many clinical illness features such as
myalgia, fatigue, sleep disturbances, and impairment in ability to perform activities of daily living as a consequence of these symptoms. A growing literature suggests that a variety of comorbid illnesses also may commonly coexist in these patients, including irritable bowel syndrome, chronic tension-type headache, and interstitial cystitis.

OBJECTIVE: To describe the frequency of 10 clinical conditions among patients with CFS, FM, and TMD compared with healthy controls with respect to past diagnoses, degree to which they manifested symptoms for each condition as determined by expert-based criteria, and published diagnostic criteria. METHODS: Patients diagnosed as having CFS, FM, and TMD by their physicians were recruited from hospital-based clinics. Healthy control subjects from a dermatology clinic were enrolled as a comparison group. All subjects completed a 138-item symptom checklist and underwent a brief physical examination performed by the project physicians.

RESULTS: With little exception, patients reported few past diagnoses of the 10 clinical conditions beyond their referring diagnosis of CFS, FM, or TMD. In contrast, patients were more likely than controls to meet lifetime symptom and diagnostic criteria for many of the conditions, including CFS, FM, irritable bowel syndrome, multiple chemical sensitivities, and headache. Lifetime rates of irritable bowel syndrome were particularly striking in the patient groups (CFS, 92%; FM, 77%; TMD, 64%) compared with controls (18%) (P<.001). Individual symptom analysis revealed that patients with CFS, FM, and TMD share common symptoms, including generalized pain sensitivity, sleep and concentration difficulties, bowel complaints, and headache. However, several symptoms also distinguished the patient groups. CONCLUSIONS: This study provides preliminary evidence that patients with CFS, FM, and TMD share key symptoms. It also is apparent that other localized and systemic conditions may frequently co-occur with CFS, FM, and TMD. Future research that seeks to identify the temporal relationships and other pathophysiologic mechanism(s) linking CFS, FM, and TMD will likely advance our understanding and treatment of these chronic, recurrent conditions.
(1999) **Understanding patients with multiple chemical sensitivity.**
Ziem, G Journal/Am Fam Physician. 59: 2101, 2104; author reply 2112, 2115.

(1999) **[Allergology: quo vadis?].**

The discovery of the immunoglobulin E 30 years ago, and the subsequent availability of serological techniques for in vitro allergy tests, have given fresh impetus to allergy diagnosis in clinical practice. Independently of the more refined allergy diagnosis, there has been a continuous increase in allergic diseases in recent decades. Various factors, summed by the term "Western lifestyle", have produced this increase. As well as individual measures (primary, secondary and tertiary allergy prevention), intensive interdisciplinary cooperation is necessary to arrive at a broad and successful prevention concept. Governments and the political community should accord higher priority than hitherto to fighting allergies, which are now the primary environmental diseases. Parallel to progress in fundamental immunology and the introduction of effective drugs for symptomatic treatment of the various atopic manifestations, a problem facing us today is the growing popularity among the public of "alternative medicine" for the treatment of allergies, even though many of these unconventional diagnostic and therapeutic methods are judged pseudoscientific and their efficacy is unproven. The allergy patient is increasingly caught in the tug-of-war between allopathic and "alternative" medicine, pharmacists, so-called "natural healers", patient and consumer organisations and the mass media. Expectations of successful results from "natural", "soft", "Chinese" or "Tibetan" medicine are high, along with the corresponding marked placebo effect and scepticism about allopathic medicine. This "nocebo" effect thrives on psychosocial territory and is fostered by public opinion. Evidence of this is the rise of new environment-related forms of disease for which there is no proof of a toxic or immunologic origin ("idiopathic environment-related intolerances", according to the new WHO terminology). Allopathic and complementary medicine are often consumed together, thus increasing treatment costs. At the same time, fewer and fewer allergy patients are treated by allergen immunotherapy, the only treatment which can affect the natural course of allergic disease and which may also prevent the development of asthma in patients which allergic rhinitis.

(1999) **Effects of deltamethrin on nitric oxide synthase and poly(ADP-ribose) polymerase in rat brain.**

The effects of deltamethrin on the activities of nitric oxide synthase (NOS) and poly(ADP-ribose) polymerase (PARP) and the protein expression of neuronal NOS (nNOS) and PARP in rat brain were investigated in the present study. The activity of NOS was significantly increased in cortex and hippocampus at 5 h after deltamethrin treatment, and maintained at an increased level at 24 h. The activity of PARP was also elevated at the same time points in the same brain regions of treated rats. By immunohistochemical analysis, it was demonstrated that the nNOS-immunoreactive cells were markedly increased at 24 h after treatment in the cortex and hippocampus, whereas few nNOS-immunoreactive cells were observed in the same brain regions of control and treated rats at 5 h after treatment. The immunoreactivity for PARP was also increased in the same brain regions, showing the similar time course of the induction of nNOS by deltamethrin. These results indicate that deltamethrin increases the activities of NOS and PARP and initiates the protein expression of nNOS and PARP, suggesting that NOS and PARP might play important roles in neurotoxicity of deltamethrin.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10629771


BACKGROUND OF STUDY: Three hundred and sixty three subjects from various civil service organisations were administered the SCOPE-i (Stress, Coping and Personality Inventory) as part of the Institute of Mental Health's efforts to promote mental health in the workplace. AIM OF STUDY: This study examines the relationship between stress-related factors and absenteeism. Absenteeism is measured by the number of days of medical leave taken (MC) and self-report of minor illnesses (MI) which are not severe enough to warrant the coverage of a medical certificate. RESULTS: In this study, we are interested in the differences between MI and MC, and their respective relationships with stress-related factors. We hypothesised that MI, rather than MC, is more related to poor workplace conditions. The findings of this study support this hypothesis. Thus if workplace environment is stressful, people are still likely to come to work despite their illness. An interesting observation in this study is the different ways in which environmental stressors and psychosocial aspects of the workplace environment affect the MC variable. Individuals are more likely to take MC when the environmental stressors are high (i.e., poor lighting, uncomfortable temperatures, etc) as compared to poor psychosocial environmental conditions (e.g., work overload, high organisational tension, career limitations and high personal constraints). On the other hand, when faced with poor psychosocial environmental conditions, MI increases instead of MC. CONCLUSION: These findings have implications on the types of changes in a workplace which employers should make in order to decrease MC and
improve physical well-being. In addition, the study shows the usefulness of MI in future studies as a dependent variable.

(1999) **Fragrances: friend or foe?**
Wolff, P Journal/Beginnings. 19: 4-5.

(1999) **1st Aachen Symposium "Environment and psyche".**

(1999) **Interferon-induced proteins are elevated in blood samples of patients with chemically or virally induced chronic fatigue syndrome.**

Overlapping symptomatologies between Chronic Fatigue Syndrome (CFS) and Chemical Sensitivity have been observed by different investigators. Therefore, it is of great importance to develop biomarker(s) for possible differentiation between viral induced CFS (without sensitivity to chemicals) versus chemically induced CFS. Since interferon induced proteins 2-5A Synthetase and Protein Kinase RNA (PKR) have been implicated in the viral induction of CFS, the objective of this study was to utilize 2-5A and PKR activity for differentiation between CFS induced by either viruses or chemicals. Based on the CDC definition and criteria, twenty CFS patients who were positive for viral genome(s) (mainly HHV6; HTLVII, EBV, and CMV) and did not have any history of exposure to toxic chemicals were included in this study. As a comparison, the second group of patients consisted of twenty individuals from the same geographical area who were negative for viral genomes but had been exposed to methyl tertiary-butyl ether concentration of up to 70 ppb and benzene concentration up to 14 ppb. All patients complained of fatigue and other symptoms overlapping between the two groups. From all 40 patients, blood was drawn, leukocyte extract was prepared and assayed for 2-5A Synthetase and PKR activity. Clinical specimens which were positive for viral genomes showed from 2.2-38.7 fold increase in 2-5A activity and 1.3-13.5 fold increase in PKR activities over the background of the healthy controls. Similarly, the second group (negative for viral genomes, but exposed to chemicals) showed a 1.1-29.2 fold increase for 2-5A Synthetase and a 1.3-11.6 fold increase for PKR when they were compared to healthy subjects. To elucidate mechanisms involved
in viral versus chemical induction of 2-5A Synthetase and PKR, MDBK cell lines were cultered either in the presence or absence of HHV6, MTBE, or Benzene, heat shock proteins and interferon-beta. 2-5A and PKR activities were measured in all the above conditions. A clear induction of 2-5A and PKR was observed when MDBK cells were exposed to HHV6, MTBE, and Benzene. This induction was more significant with HSP90, HSP70, and IFN-beta indicating their involvement in the mechanism of action. However, when MDBK cells were incubated either with MTBE + Benzene or HHV6 in the presence or absence of anti IFN-beta or anti-HSP-70, the activities of both 2-5A and PKR in HHV6 infected cells were inhibited by more than 90% due to addition of anti IFN-beta, and only 20% by addition of anti-HSP70. While in MTBE + Benzene exposed cells anti IFN-beta reduced the activity of these enzymes by 40% and anti-HSP70 by more than 90%. This variation in the induction of 2-5A and PKR by anti-HSP70 or IFN-beta indicates involvement of IFN-beta in viral induction 2-5A and PKR, and HSP involvement in chemical induction of these enzymes. We conclude that 2-5A and PKR are not only biomarkers for viral induction of CFS, but biomarkers to other stressors that include MTBE and Benzene.


BACKGROUND: Nitric oxide (NO) production catalyzed by iNOS (inducible NO synthase) is thought to take place mainly in macrophages after activation by inflammatory mediators. NO is subsequently oxidized to nitrite and nitrate, which are excreted in urine. The concentration of inflammatory mediators in small bowel biopsy specimens from patients with coeliac disease is increased. The latter could induce increased NO production by stimulation of intestinal macrophage iNOS, resulting in high levels of urinary NO oxidation products, nitrite and nitrate (NOx). AIM: In the present study we evaluated the urinary NOx/creatinine ratios in children with active coeliac disease (n = 22), coeliac disease patients on a gluten-free diet (n = 9), healthy (n = 11) and sick control children (n = 18). METHODS: The Griess reagent method was used for measuring urinary NOx. RESULTS: Median NOx/creatinine ratios of active coeliac disease patients, coeliac disease patients on a gluten-free diet, healthy and sick control children were 1.21, 0.19, 0.10 and 0.13 mmol/mmol, respectively. All active coeliac disease patients showed increased NOx/ creatinine ratios. Urinary NOx creatinine ratios of the active coeliac disease patients were significantly higher than those of healthy controls (p < 0.0001), sick controls (p < 0.0001) and coeliac disease patients on a gluten-free diet (p < 0.0001). CONCLUSION: The urinary NOx/creatinine ratio is increased in patients with active coeliac disease and reverts to normal on a gluten-free diet.
Free radicals and their metabolites, also called reactive oxygen species (ROS), have been implicated in the pathogenesis of many diseases. Because of its continuous exposure to toxic pollutants in the ambient air, such as cigarette smoke, air pollution, and mineral dusts, the lung is very vulnerable to ROS-induced injury. In this review, the role of ROS in the pathogenesis of obstructive lung diseases is reviewed. A central theme in this review is the pivotal role of transition metals such as iron, vanadium, and nickel in ROS-induced cell damage, not only in exposure to mineral dusts but also in cigarette smoke and air pollution.


OBJECTIVES: Multiple chemical sensitivity is a poorly understood syndrome in which various symptoms are triggered by chemically unrelated, but often odorous substances, at doses below those known to be harmful. This study focuses on the process of pavlovian acquisition and extinction of somatic symptoms triggered by odours. METHODS: Diluted ammonia and butyric acid were odorous conditioned stimuli (CS). The unconditioned stimulus (US) was 7.4% CO2 enriched air. One odour (CS+) was presented together with the US for 2 minutes (CS+ trial), and the other odour (CS-) was presented with air (CS-trial). Three CS+ and three CS-exposures were run in a semi-randomised order; this as the acquisition (conditioning) phase. To test the effect of the conditioning, each subject then had one CS+ only--that is, CS+ without CO2--and one CS- test exposure. Next, half the subjects (n = 32) received five additional CS+ only exposures (extinction group), while the other half received five exposures to breathing air (wait group). Finally, all subjects got one CS+ only test exposure to test the effect of the extinction. Ventilatory responses were measured during and somatic symptoms after each exposure. RESULTS: More symptoms were reported upon exposure to CS+ only than to CS-odours, regardless of the odour type. Altered respiratory rate was only found when ammonia was CS+. Five extinction trials were sufficient to reduce the level of acquired symptoms. CONCLUSION: Subjects can acquire somatic symptoms and altered respiratory behaviour in response to harmless, but odorous chemical substances, if these odours have been associated with a
physiological challenge that originally had caused these symptoms. The conditioned symptoms can subsequently be reduced in an extinction procedure. The study further supports the plausibility of a pavlovian conditioning hypothesis to explain the pathogenesis of MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10472302

(1999) Solutions needed to control environmental illness.


OBJECTIVE: To describe the risks associated with use of an unproven technique, provocation/neutralization, in diagnosis and treatment of a putative "food allergy" in a patient with systemic mastocytosis. METHODS: A case report of a 68-year-old woman with mastocytosis is reported. The patient was interviewed, examined, and all medical records were reviewed. Photos were taken, and skin and colonic biopsies were performed. RESULTS: The patient was previously diagnosed with urticaria pigmentosa but also had significant diarrhea that was well-controlled by oral cromolyn sodium. She saw a physician who practiced provocation/neutralization and was told that food allergies were the cause of her gastrointestinal symptoms. She was placed on "neutralizing" injections of milk and wheat, but experienced flushing, palpitations, and lightheadedness upon injections into her thigh, which is a skin area highly involved by visible lesions of cutaneous mastocytosis. Later evaluation revealed increased numbers of mast cells in her colonic mucosa as well as confirmation of cutaneous mastocytosis. CONCLUSIONS: The patient's previous history of urticaria pigmentosa, orally communicated by the patient, documented in medical records, and easily visible on physical examination, was discounted by a practitioner of an alternative and unproven medical treatment, provocation/neutralization. She subsequently had potentially life-threatening reactions to "provocative" skin testing and "neutralizing" injections. Patients with systemic mastocytosis are at risk for significant mast cell mediator release during immunotherapy, conventional or alternative.
The association of energy intake bias with psychological scores of women.

Taren, DL, Tobar, M, Hill, A, Howell, W, Shisslak, C, Bell, I and Ritenbaugh, C

OBJECTIVE: Assess the association between reporting bias of dietary energy intake and the behavioral and psychological profiles in women. DESIGN: At baseline a series of questionnaires were administered to 37 women, (the Marlowe-Crowne Social Desirability Scale, Weinberger Adjustment Inventory (WAI), the Eating Disorder Inventory (EDI), the Restraint Scale and Sorensen-Stunkard’s silhouettes). Subjects received training on how to record dietary records. Subjects recorded three days of dietary records to measure energy intake (EI) during a study to determine total energy expenditure (TEE) using doubly labeled water. Reporting accuracy (RA = EI/TEE x 100) was determined for each subject. Statistical analysis of the data used a mixed effects model accounting for within subject variability to determine if the psychological scores were associated with reporting accuracy. SETTING AND SUBJECT: Women were recruited with local advertisements in Tucson, Arizona. The women had a mean ( +/- 1 s.d.) age of 43.6 +/- 9.3 yrs, body mass index (BMI) of 28.7 +/- 8.5 kg/m2 and total body fat (%TBF) of 31.9 +/- 7.3%. RESULTS: Age and %TBF were significantly and inversely associated with RA. Furthermore, Social Desirability was negatively associated with RA. Body dissatisfaction and associating a smaller body size than one’s own as being more healthy were also associated with a lower RA. CONCLUSIONS: These results suggest that Social Desirability and self image of body shape are associated with RA. Modifications in subject training may reduce the effect of these factors on RA.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10452412

Prevention of glucose toxicity in HIT-T15 cells and Zucker diabetic fatty rats by antioxidants.

Tanaka, Y, Gleason, CE, Tran, PO, Harmon, JS and Robertson, RP

Chronic exposure of pancreatic islets to supraphysiologic concentrations of glucose causes adverse alterations in beta cell function, a phenomenon termed glucose toxicity and one that may play a secondary pathogenic role in type 2 diabetes. However, no mechanism of action has been definitively identified for glucose toxicity in beta cells. To ascertain whether chronic oxidative stress might play a role, we chronically cultured the beta cell line, HIT-T15, in medium containing 11.1 mM glucose with and without the antioxidants, N-acetyl-L-cysteine (NAC) or aminoguanidine (AG). Addition of NAC or AG to the culture medium at least partially prevented decreases in insulin mRNA, insulin gene promoter activity, DNA binding of two important insulin promoter transcription factors (PDX-1/STF-1 and RIPE-3b1 activator), insulin content, and
glucose-induced insulin secretion. These findings suggested that one mechanism of glucose toxicity in the beta cell may be chronic exposure to reactive oxygen species, i.e., chronic oxidative stress. To ascertain the effects of these drugs on diabetes, NAC or AG was given to Zucker diabetic fatty rats, a laboratory model of type 2 diabetes, from 6 through 12 weeks of age. Both drugs prevented a rise in blood oxidative stress markers (8-hydroxy-2'-deoxyguanosine and malondialdehyde + 4-hydroxy-2-nonenal), and partially prevented hyperglycemia, glucose intolerance, defective insulin secretion as well as decrements in beta cell insulin content, insulin gene expression, and PDX-1 (STF-1) binding to the insulin gene promoter. We conclude that chronic oxidative stress may play a role in glucose toxicity, which in turn may worsen the severity of type 2 diabetes.


Many patients attribute their health problems to amalgam and other dental metals. In genetically susceptible individuals, mercury and gold may function as haptens and elicit allergic and autoimmune reactions. The frequency of metal-induced lymphocyte responses was examined in 3,162 patients in three European laboratories using MELISA(R), an optimized lymphocyte proliferation test. The patients suffered from local and systemic symptoms attributed to dental restorations. The effect of dental metal removal was studied in 111 patients with metal hypersensitivity and symptoms resembling Chronic Fatigue Syndrome (CFS). After consultation with a dentist the patients decided to replace their metal restorations with non-metallic materials. The changes in health and in vitro lymphocyte reactivity were studied by inquiries and follow-up MELISA(R). Lymphocyte reactivity was also analyzed in 116 healthy subjects with no complaints of metal allergy. A significant number of patients had metal-specific lymphocytes in the blood. Nickel was the most common sensitizer, followed by inorganic mercury, gold, phenylmercury, cadmium and palladium. As compared to lymphocyte responses in healthy subjects, the CFS group had significantly increased responses to several metals, especially to inorganic mercury, phenylmercury and gold. Following dental metal removal, 83 patients (76%) reported long-term health improvement. Twenty-four patients (22%) reported unchanged health and two (2%) reported worsening of symptoms. Following dental metal replacement, the lymphocyte reactivity to metals decreased as well. We propose that an inflammatory process induced by metals may modulate the hypothalamic-pituitary-adrenal axis (HPA axis) and trigger multiple non-specific symptoms characterizing CFS and other chronic conditions like myalgic encephalitis (ME) and multiple chemical sensitivity (MCS).

Two field studies in two cities in Northrhine-Westfalia were carried out in order to characterize the degree of association between environmental odour-exposure, annoyance, and somatic symptoms. In both studies, odour effects were assessed through personal interviews by means of standardised questionnaires. In the first study, the odour source was a fertilizer plant for mushroom cultivation with particularly offensive odour emissions. The distance from the source was taken to characterize the intensity of odour exposure. 250 subjects were interviewed at close, medium or remote distance from the plant. Apart from an extremely high degree of annoyance, an increasing frequency of somatic symptoms was found with increasing proximity to the odour source. Somatic symptoms were directly linked to odour exposure and additionally mediated by annoyance. In the second study (n = 322), the odour source was a pig rearing facility, and the degree of odour exposure was assessed by measuring the frequency of odour-events by means of systematic field observations. Results showed that the degree of odour-annoyance as well as the frequency of somatic symptoms increased significantly with increasing odour-exposure, although their frequency was reduced relative to the first study, and mediated by annoyance. In both studies, perceived negative health was associated with increased symptom reports, however, results for old age were inconsistent. Response tendencies and biases were controlled. Environmental odours have been shown to be associated with somatic symptoms and, may, thus, be considered as a risk factor for health and wellbeing of exposed populations, especially for vulnerable subjects with perceived negative health.

---------------------------------------------------------------


A middle-aged woman with a 10-year history of disability attributed to chemical sensitivities complained that exposure to specific fragrances immediately elicited seizures. Video-EEG monitoring was performed in a hospital neurodiagnostic laboratory during provocative challenge studies employing fragrances identified by the patient as reliably inducing symptoms. The baseline clinical EEG was normal. Immediately after each provocation with air deodorant and perfume, she consistently showed both generalized tonic/clonic and multifocal myoclonic jerking, at times was nonresponsive, spoke with slurred speech, and complained of right-sided paralysis and lethargy. None of these events were associated with any EEG abnormalities. Psychological assessment (MMPI-2, MCMI-II) revealed personality traits that predisposed her to somatization and beliefs about environmental sensitivities. The convulsions were a manifestation of psychogenic pseudoseizures that had been iatrogenically reinforced.

Multiple chemical sensitivity (MCS) is a phenomenon whereby individuals report increased sensitivity to chemicals in the environment, and attribute their sensitivities to prior exposure to the same or often structurally unrelated chemicals. A leading hypothesis suggests that MCS is akin to behavioral sensitization observed in rodents after repeated exposure to drugs of abuse or environmental stressors. Sensitization occurring within limbic circuitry of the central nervous system (CNS) may explain the multisymptom complaints in individuals with MCS. The present studies represent the continuing development of an animal model for MCS, the basis of which is the CNS sensitization hypothesis. Three behaviors were assessed in rats repeatedly exposed to formaldehyde (Form) inhalation. In the first series of experiments, rats were given high-dose Form exposure (11 parts per million [ppm]; 1 h/day x 7 days) or low-dose Form exposure (1 ppm; either 1 h/day x 7 days or 1 h/day x 5 days/week x 4 weeks). Within a few days after discontinuing daily Form, cocaine-induced locomotor activity was elevated after high-dose Form or 20 days of low-dose Form inhalation. Approximately 1 month later, cocaine-induced locomotor activity remained significantly elevated in the 20-day Form-exposed rats. The second experiment assessed whether prior exposure to Form (20 days, as above) would alter the ability to condition to an odor (orange oil) paired with footshock. The results suggested a tendency to increase the conditioned fear response to the odor but not the context of the footshock box, and a decreased tendency to extinguish the conditioned fear response to odor. The third experiment examined whether CNS sensitization to daily cocaine or stress would alter subsequent avoidance responding to odor (Form). Daily cocaine significantly elevated approach responses to Form, while daily stress pretreatment produced a trend in the opposite direction, producing greater avoidance of Form. Preliminary studies indicated that repeated daily Form inhalation (20 days, as above) produced a greater avoidance to subsequent Form presentation, suggesting that daily Form inhalation may serve as a stressor. The results support the hypothesis that repeated chemical exposure in rats may produce CNS plasticity manifest as greater sensitivity to dopaminergic drugs, enhanced fear conditioning to odor paired with an aversive event, and greater avoidance of odors. Some of these behavioral changes observed in rats may provide a link with symptoms in a subset of individuals with MCS.
An emerging issue in environmental health is the phenomenon of multiple chemical sensitivity (MCS). Multiple chemical sensitivity is a controversial disorder characterized by multiorgan symptoms in response to low-level chemical exposures that are considered safe for the general population. The onset of MCS is often attributed to prior repeated chemical exposures in the home and/or workplace, and, once initiated, symptoms are triggered by extremely low levels of many chemicals/foods. No single case definition exists for MCS due to several issues that call into question its validity as a distinct illness induced by prior chemical exposure. Hypotheses regarding the etiological basis for MCS range from direct toxicological effects of chemicals to the notion that MCS is purely a psychological "belief system". One leading hypothesis suggests that MCS represents a neural sensitization phenomenon, wherein susceptible individuals demonstrate extreme sensitivity to chemicals and odor intolerance due to central nervous system (CNS) sensitization processes. The recent development of an animal model for MCS provides some support for the sensitization hypothesis and may offer evidence for behavioral changes observed in at least a subset of those reporting MCS.


Pavlovian conditioning may contribute to some cases of multiple chemical sensitivity (MCS). On the basis of the conditioning analysis, environmental stimuli (especially olfactory cues) present at the time of a toxicant overdose become associated with the toxicant and elicit aversive conditional responses. Similar associations have been reported in patients receiving chemotherapy, and the literature on such 'pretreatment nausea' in cancer patients is relevant to understanding the role of conditioning in MCS. Evaluation of the contribution of conditioning to MCS has been complicated by confounding interpretations that emphasize conditional responses with interpretations which emphasize the psychiatric status of the patient. Appreciation of the contribution of Pavlovian conditioning to MCS will lead to a better understanding of this complex disorder.

(1999) **Commonality and specificity of personality disorder profiles in subjects with trauma histories.**

Recently, attention has been drawn to a range of disturbances in personality functioning that commonly characterize individuals with a history of severe or prolonged trauma. Many of these features overlap with criteria for some of the Axis II personality disorders. The current study investigated the similarity of personality disorder features in different samples of patients with trauma histories, and specificity of such features compared to other psychiatric samples. Profiles of Axis II features, based on relative frequencies of individual disorder "diagnoses" derived from a common measure (Personality Diagnostic Questionnaire-Revised), were compared in three trauma samples: male Vietnam combat veterans with PTSD, female inpatients with a history of childhood sexual abuse, and female outpatients with a history of childhood sexual abuse. The PDQ-R derived profiles in each of the three trauma samples were then compared with similar PDQ-R derived profiles in published reports of psychiatric samples selected for other diagnoses. Each of the three Spearman rank correlations among the three trauma samples were significant, ranging from .72 to .94. There was a clear pattern of higher correlations within the trauma samples (average correlation of .81) than between the trauma and nontrauma samples (average correlations of .11, .36, and .25 between the nontrauma samples and the combat sample, inpatient sexual abuse sample, and outpatient sexual abuse sample, respectively). The findings suggest that a pattern of personality disorder features may be distinctly associated with individuals with trauma histories, at least of the type examined here. Future studies using more clinically valid measures of personality features and including other types of trauma samples are needed to determine the generalizability of the current findings. Also needed are studies with longitudinal designs to address questions of causal pathways that may underlie such associations.


(1999) **Interdisciplinary clinical assessment of patients with illness attributed to environmental factors.**

Patients with health problems attributed to environmental factors such as chemical pollutants and electromagnetic fields often do not present evidence of an environmental etiology of their symptoms. It has been postulated, that their problems are due to disorders diagnosed by other medical disciplines, especially allergology and psychiatry. Our study was designed to subject these patients to a comprehensive
diagnostic program involving several medical disciplines in order to achieve diagnoses appropriate to explain the patients' symptoms. Fifty patients consecutively referred to the department of environmental medicine in the university hospital of Aachen, Germany, were submitted to the following examinations: (i) environmental medicine (history, clinical examination, biological and/or ambient monitoring for environmental agents); (ii) allergological examination (history, clinical examination, skin tests); (iii) psychiatric examination (psychopathological examination, psychometric and neuropsychological testing). In addition, the patients were examined in other hospital departments according to the symptoms presented. The findings were discussed in case conferences attended by the physicians involved in order to achieve individual diagnoses. The numbers of patients to whom diagnoses were given by different medical disciplines are as follows: psychiatry (32 patients), dermatology (4), allergology (2), neurology (2), rheumatology (2), gynaecology (1), haematology (1). The most frequent mental disorders diagnosed by the psychiatrists were somatoform disorders (19), followed by schizophreniform and delusion disorders (7). In spite of extensive diagnostic efforts, patients with health problems attributed to the environment usually do not present sufficient evidence of an environmental aetiology of their symptoms. On the other hand the symptoms often meet the diagnostic criteria of other diseases, especially of mental disorders.

(1999) Effectiveness of an occupational and environmental medicine curriculum as indicated by evaluation of medical student performance on an objective structured clinical examination.

Medical students must learn to recognize occupational and environmental-related illness. An occupational and environmental medicine curriculum can achieve this goal. The curriculum must be evaluated to ensure that medical students are learning to recognize exposure-related health conditions and to evaluate if this ability correlates with medical interviewing skills. A case, formatted for an Objective Structured Clinical Examination (OSCE), was developed to evaluate student performance on an exposure-related clinical problem. The OSCE results were analyzed to identify the areas that differentiated the students who recognized an exposure-related medical condition from those who did not. We conclude that an OSCE is an effective curriculum evaluation tool to assess whether a core occupational and environmental-related curriculum is contributing to student learning in exposure history-taking and associated clinical reasoning skills.

(1999) Paraoxonase/MCS.
Rotman, G and Shiloh, Y Journal/Oncogene. 18: 6135-44.

The ATM protein kinase is the product of the gene responsible for the pleiotropic recessive disorder ataxia-telangiectasia. ATM-deficient cells show enhanced sensitivity and greatly reduced responses to genotoxic agents that generate DNA double strand breaks (DSBs), such as ionizing radiation and radiomimetic chemicals, but exhibit normal responses to DNA adducts and base modifications induced by other agents. Therefore, DSBs are most likely the predominant signal for the activation of ATM-mediated pathways. Identification of the ATM gene triggered extensive research aimed at elucidating the numerous functions of its large multifaceted protein product. While ATM has both nuclear and cytoplasmic functions, this review will focus on its roles in the nucleus where it plays a central role in the very early stages of damage detection and serves as a master controller of cellular responses to DSBs. By activating key regulators of multiple signal transduction pathways, ATM mediates the efficient induction of a signaling network responsible for repair of the damage, and for cellular recovery and survival.


Whereas most idiosyncratic environmental sensitivity complaints do not fit known diagnoses, the multiple chemical sensitivities syndrome (MCS) is an extreme presentation that has defined diagnostic criteria. MCS symptomatics claim that they acquired a sensitized state as the result of a chemical exposure, usually to a solvent or pesticide, but not to a fragrance. Before this exposure, they did not experience symptoms. Following sensitization, symptoms increasing in number and severity with time are attributed by the MCS symptomatic to various exposures that are innocuous to most individuals. Although phenomenological studies have provided no evidence that particular odors elicit MCS symptoms, low levels of fragrances and perfumes are frequently associated with the reporting of MCS symptoms. This evaluation examines proposed mechanisms by which odorants and fragrances might cause either sensitization or elicitation of MCS symptoms, including altered odor sensitivity, primary irritancy or irritancy-induced upper airway reactivity, neurogenic switching of trigeminal
irritancy signals, time-dependent sensitization and limbic kindling, CNS toxicity, and various psychiatric conditions. In no case was there persuasive evidence that any olfactory mechanism involving fragrance underlies either induction of a sensitized state or the triggering of MCS symptoms. Fragrances and other odorants could, however, be associated with symptoms as claimed by MCS symptomatics, because they are recognizable stimuli, but fragrance has not been demonstrated to be causal in the usual sense.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10329337

---------------------------------------------------------------


The subset of patients reporting chemical sensitivity with neurocognitive complaints usually exhibits specific abnormalities of brain metabolism consistent with neurotoxicity, on imaging with single photon emission computed tomography (SPECT). These recurrent neurotoxic patterns are characterized by a mismatch in tracer uptake between early- and late-phase imaging, multiple hot and cold foci throughout the cortex, temporal asymmetry and increased tracer uptake into the soft tissues and, sometimes, the basal ganglia. Previous studies confirm these neurotoxic findings in patients with neurotoxic chemical exposures and breast implants. Affective processes such as depression do not, alone, show this pattern. These abnormalities in SPECT images correlate with documented neurocognitive impairment. Controlled challenges to ambient chemicals can induce profound neurotoxic changes seen on SPECT imaging in chemically sensitive patients. Detoxification treatment techniques frequently produce significant improvement on brain SPECT brain imaging in these patients. Neurotoxicity appears to be characteristic in many cases of chemical sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416294

---------------------------------------------------------------


In the physician's practice in past decades, an increasing number of patients suffering from polysomatic complaints with a subjective feeling of allergy against environmental noxious agents have been seen. Various names for this condition include "Eco-Syndrome" or "Multiple Chemical Sensitivity" (MCS), "Multiorgan Dysesthesia" or
“Idiopathic Environmental Intolerances”. The uncertainty in the nomenclature reflects the deficiency in the knowledge of the etiopathophysiology and accordingly the diagnostic and therapeutic procedures. Most patients have completed an odyssey of visiting various specialists including psychiatrists and undergone many kinds of so-called alternative or parascientific procedures. We studied such patients since the early 1980s performing intensive interdisciplinary and allergological investigations. In about two third of the patients psychiatric or psychosomatic disturbances were obvious, but in one third of the patients somatic pathophysiological conditions were regarded as predominant cause of the present complaints. Many patients exhibited various pathophysiological patterns including somatic and psychosomatic alterations. Measurements of indoor air pollutants in the dust or in the air showed in some cases increased values of aromatic hydrocarbons, terpenes etc., without, however, explaining the main complaints. We conclude from our experience that patients presenting with hypersensitivity phenomena related to indoor air pollution are a heterogeneous group. There is no evidence, that "MCS" really exists, often it is diagnosed by the patients themselves. The term "eco-syndrome" describes a "working diagnosis" in order to apply careful interdisciplinary investigations for this heterogeneous group of patients. For the practical management of these patients mutual confidence is a prerequisite for success. The role of indoor air pollutants in triggering unspecific complaints beyond the exclusively toxicological field remains to be elucidated by future studies.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10507129

(1999) Multiple chemical sensitivity--is the environment really to blame?

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10692881

Ranheim, P Journal/Am Fam Physician. 60: 392, 402.

(1999) Pioneers in providing a competency inventory.


Primary Sjogren Syndrome is a chronic autoimmune disease characterized by exocrine gland dysfunction. Here we present evidence of the activation of nitric oxide signaling cascade by circulating antibodies of patients with Sjogren Syndrome in rat submandibular glands. Constitutive nitric oxide synthase and cyclic GMP levels are modulated by Sjogren IgGs through the activation of muscarinic acetylcholine receptors on the glands. The effects are similar to those produced by the agonist carbachol and blocked by the antagonist atropine. The involvement of M1 subtype of muscarinic receptors is proposed since both a synthetic peptide homologous to an extracellular domain of M1 receptor and pirenzepine, a selective M1 antagonist, partially blocked the effects. We conclude that Sjogren Syndrome antibodies can activate nitric oxide signaling in submandibular glands by interacting with muscarinic acetylcholine receptors.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10623324

Individuals with multiple chemical sensitivity (MCS) also commonly report symptoms of asthma, but, as far as we have been able to determine, no one has yet suggested that an abnormal cholinergic system may provide the link between asthma and MCS. The present brief review provides evidence for such a link by summarizing recent findings in a genetic animal model of cholinergic hyperresponsiveness. The Flinders Sensitive Line (FSL) rats were developed by selective breeding for increased responses to an anticholinesterase agent similar to commonly used organophosphate pesticides. Relative to their control line, the Flinders Resistant Line (FRL) rats, the FSL rats are more sensitive to drugs that stimulate acetylcholine receptors, alcohol, diazepam, and drugs that have a selective effect on dopamine or serotonin receptors. These findings raise the possibility that the FSL rats may resemble individuals with MCS. Hyperresponsiveness of the airways is a hallmark of asthma. The procedure known as whole-body plethysmography, where breathing can be monitored in freely moving animals, was employed to study the FSL and FRL rats. The FSL rats exhibited a greater index of bronchoconstriction than the FRL rats in response to both a cholinergic agonist and an allergen challenge. Thus, the FSL rats are more sensitive both to a variety of drugs unrelated to the cholinergic system and to cholinergic- and allergen-induced bronchoconstriction. An abnormal cholinergic system may therefore contribute to both MCS and asthma.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10487361

Norback, D, Bjornsson, E, Janson, C, Palmgren, U and Boman, G Journal/Int J Tuberc Lung Dis. 3: 368-76.

SETTING: Study of current asthma in adults in relation to the indoor environment. OBJECTIVES: To assess the effect of building dampness in dwellings on the occurrence of current asthma, and biochemical signs of inflammation. DESIGN: A nested case-control study with 98 prevalent cases of asthma and 357 controls, within a stratified random population sample (20-45 years) from the Uppsala, Sweden, part of the European Community Respiratory Health Survey (ECRHS). Current asthma was defined as a combination of bronchial hyperresponsiveness and at least one asthma symptom (wheeze or attacks of breathlessness). Statistical calculations were made by multiple linear or logistic regression, adjusting for age, sex and smoking. RESULTS: Building dampness was found in 27% of dwellings. Current asthma was more common among subjects living in damp dwellings (odds ratio [OR] 1.8; 95% confidence interval [CI] 1.1-3.0), particularly with dampness in the floor construction (OR = 4.6; 95% CI 2.0-10.5). The average forced expiratory flow in one second (FEV1) was lower and peak expiratory flow (PEF) variability was higher in subjects from dwellings with floor dampness, and blood eosinophil count was increased in damp dwellings. No relation
was found between immediate type allergy to house dust mites and current asthma or building dampness. Immediate type allergy to moulds (Cladosporium or Alternaria) was more prevalent in damp dwellings (9.3% vs 3.9%), and was related to current asthma (OR = 3.4; 95% CI 1.4-8.5). CONCLUSIONS: Building dampness is common in dwellings in Sweden, and seems to be related to an increase in current asthma and biochemical signs of inflammation. Immediate type allergy to house dust mites does not seem to be the explanation, but immediate type allergy to moulds could explain some of the findings.


The objective of this study was to examine the influence of chronic toxic encephalopathy (CTE) on Trail Making Test (TMT) performance, with special focus on the discriminative potential of this test. We assessed TMT performance in patients diagnosed with CTE, patients with similar symptoms but no diagnosis, and healthy participants. Inferior performance was seen in CTE, and increasing age had a negative effect on TMT performance only for the CTE group. This effect was most pronounced in TMT-B. However, the ability of the TMT to identify CTE was low, whereas all healthy participants were identified as healthy. Thus, the sensitivity of TMT alone was low, but it succeeded in correctly classifying normal subjects. The pattern of results indicates that normal TMT performance may be seen in individuals with mild to moderate brain syndromes, such as CTE, whereas poor performance should not be expected in healthy individuals.


Evolutionarily stable strategies for survival and reproduction may lead to addiction. The game theory of multiple chemical sensitivity (MCS) assumes that: (1) the MCS patient responds to low-level toxicants as stressors or as direct threats to their survival and reproductive fitness, (2) this activates the cortico-mesolimbic dopamine system, (3) this system is a survival motivation center—not a 'reward center', (4) the subject emits a counter-response that is in the same direction as the naive response to the chemicals, (5) previously neutral stimuli associated with chemicals also trigger conditioned responses that mimic those to the chemicals, (6) these counter-responses further activate the dopaminergic survival motivation system, and (7) this produces a positive feedback loop that leads to strong neural sensitization in these structures and in behavior controlled by this system, despite a small initial response. Psychologically, the MCS patient with a sensitized cortico-mesolimbic dopamine system is behaving as though his/her survival is directly threatened by these chemicals. Non-MCS subjects have counter-responses opposite in direction to those of the chemicals and show tolerance. An autoshaping/sign-tracking model of this game is discussed. This evolutionary game makes several specific, testable predictions about differences between MCS subjects, non-MCS controls, and substance abusers in laboratory experiments, and between sensitized and nonsensitized animals.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416283


Whereas a variety of neuroreceptors and ion channels have been demonstrated to be affected by ethanol including GABAA receptors, NMDA receptors, non-NMDA glutamate receptors, 5-HT3 receptors and voltage-gated calcium channels, neuronal nicotinic acetylcholine receptors (nnAChRs) have recently emerged as a new target site of ethanol. The nnAChRs are different from the muscle type nicotinic AChRs with respect to their molecular architecture and pharmacology. This article briefly reviews the structure, distribution and function of nnAChRs for which a considerable amount of information has been rapidly accumulated during the past 5-10 years. The potent and unique action of ethanol on nnAChRs has been unveiled only during the past few years. Most recent developments along this line of ethanol action are discussed in this paper.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10405997

(1999) Long-range oxidative damage to DNA: effects of distance and sequence.

INTRODUCTION: Oxidative damage to DNA in vivo can lead to mutations and cancer. DNA damage and repair studies have not yet revealed whether permanent oxidative lesions are generated by charges migrating over long distances. Both photoexcited *Rh(III) and ground-state Ru(III) intercalators were previously shown to oxidize guanine bases from a remote site in oligonucleotide duplexes by DNA-mediated electron transfer. Here we examine much longer charge-transport distances and explore the sensitivity of the reaction to intervening sequences. RESULTS: Oxidative damage was examined in a series of DNA duplexes containing a pendant intercalating photooxidant. These studies revealed a shallow dependence on distance and no dependence on the phasing orientation of the oxidant relative to the site of damage, 5'-GG-3'. The intervening DNA sequence has a significant effect on the yield of guanine oxidation, however. Oxidation through multiple 5'-TA-3' steps is substantially diminished compared to through other base steps. We observed intraduplex guanine oxidation by tethered *Rh(III) and Ru(III) over a distance of 200 A. The distribution of oxidized guanine varied as a function of temperature between 5 and 35 degrees C, with an increase in the proportion of long-range damage ( > 100 A) occurring at higher temperatures. CONCLUSIONS: Guanines are oxidized as a result of DNA-mediated charge transport over significant distances (e.g. 200 A). Although long-range charge transfer is dependent on distance, it appears to be modulated by intervening sequence and sequence-dependent dynamics. These discoveries hold important implications with respect to DNA damage in vivo.


The paper gives a brief review of human molybdenum metabolism and toxicity and presents the first known case of acute clinical poisoning with molybdenum from the dietary molybdenum (Mo) supplement in a male patient in late thirties. In over 18 days, the patient had consumed a cumulative dose of 13.5 mg Mo (300-800 micrograms Mo day). Followed the development of acute psychosis with visual and auditory hallucinations, a series of petit mal seizures, and one life threatening grand mal attack. The symptoms remitted several hours after the start of chelation therapy with calcium ethylene diamine tetraacetic acid (CaEDTA). A battery of neuropsychological tests and Spectral Emission Computer Tomography demonstrated evident frontal cortical damage of the brain. One year after the Mo poisoning, the patient was diagnosed toxic encephalopathy with executive deficiencies, learning disability, major depression, and post-traumatic stress disorder. The paper strongly advocates issuance of and strict adherence to written warnings on the instruction labels not to mix potentially harmful neurotoxic substances, such as molybdenum, with other nutriceuticals and to
instructions stating maximal single and cumulative doses. Molybdenum is a new and unwelcome member of the "metal madness" family.


Milner, IB and Axelrod, BN Journal/Public Health Rev. 27: 263-77.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11081353

Millqvist, E, Bengtsson, U and Lowhagen, O Journal/Allergy. 54: 495-9.

BACKGROUND: In earlier studies, we have shown that patients with a history of sensory hyperreactivity develop asthma-like symptoms when exposed to strong scents, even if they cannot smell any scent. METHODS: For study of possible pathophysiologic mechanisms behind sensory hyperreactivity, the patients' airways and eyes were separately exposed to a common inducing factor, perfume. Eleven patients with a history of hyperreactivity to chemical trigger factors, such as perfume, were provoked single-blindingly in a placebo-controlled, randomized study. During airway exposure, the eyes were covered and, during the eye exposure, the patients inhaled fresh air. A special face mask or a nose clip was used to avoid any smell. RESULTS: During the 30-min exposure to perfume, there was a gradual increase in three main symptoms; i.e., eye irritation, cough, and dyspnea, after both the airway and eye exposures. The increases were significant compared with placebo. CONCLUSIONS: Asthma-like and other symptoms, such as irritation of the eyes, may be induced by exposure of both the airways and the eyes in patients with sensory hyperreactivity. This points to the importance of studying the sensory nervous system, not only in the airways, but also in other organs.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10380782

Using the Environmental Exposure and Sensitivity Inventory (EESI), a standardized instrument for measuring chemical sensitivity, we obtained and compared ratings of symptoms, chemical (inhalant) intolerances, other intolerances (e.g., drugs, caffeine, alcohol, skin contactants), lifeimpact, and masking (ongoing exposures) in five populations: multiple chemical sensitivity (MCS) patients who did (n = 96) or did not (n = 90) attribute onset of their illness to a specific exposure event, patients with implanted devices (n = 87), Gulf War veterans (n = 72), and controls (n = 76). For each patient group, mean scores on the first four scales were significantly greater than for controls. MCS patients reported avoiding more chemical exposures (were less masked) than the other groups. Across groups, for a given level of symptoms, as masking increased, mean scores on the Chemical Intolerance Scale decreased. In contrast, mean scores on the Other Intolerance Scale appeared to be less affected by masking. These findings suggest that some patients with antecedent chemical exposures, whether exogenous (chemical spill, pesticide application, indoor air contaminants) or endogenous (implant), develop new chemical, food, and drug intolerances. Reports of new caffeine, alcohol, medication, food, or other intolerances by patients may signal exposure-related illness. Masking may reduce individuals' awareness of chemical intolerances, and, to a lesser degree, other intolerances.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416290


The lack of a generally accepted case definition for multiple chemical sensitivity (MCS) and the absence of a standardized approach for measuring salient aspects of chemical sensitivity that would permit cross-comparison of findings by different investigators have hindered progress in this area. Based upon findings from an earlier study of 112 persons with self-reported chemical sensitivity who attributed their chemical sensitivity to a well-defined exposure event, we developed an instrument with self-rating scales to assess Symptom Severity, Chemical (Inhalant) Intolerances, Other Intolerances (e.g., foods, medications, alcohol), Life Impact, and Masking (a measure of ongoing chemical exposures). When administered to four patient groups and controls, the scales showed good reliability and validity overall (n = 421) and in each group. Used
together, the scales provided sensitivity of 92% and specificity of 95% in differentiating chemically sensitive persons from controls. Our results support use of these scales individually or collectively for a variety of applications including the selection of chemically sensitive subjects and controls for research, assessment of chemical sensitivity in various study populations, cross-comparison of groups studied by different investigators, pre- and post-assessment of therapeutic interventions, clinical evaluation of complex patients who report intolerances, and teaching medical residents and students how to evaluate patients for chemical sensitivity and MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416289

Miller, CS, Gammage, RB and Jankovic, JT Journal/Toxicol Ind Health. 15: 398-402.

We report exacerbation of symptoms and chemical intolerances in three of four self-described chemically sensitive women following relocation to a newly constructed office building. Levels of total volatile organic compounds (TVOCs) in this building prior to occupancy were approximately 200 micrograms/m3 (toluene equivalent units) with a myriad of individual components present. By day 50 after occupancy, the concentration of TVOCs in the building dropped to approximately 50 micrograms/m3. Nevertheless, three women reported significant worsening of their symptoms with spreading of their sensitivities to previously tolerated chemical exposures. One woman relocated to another building, while the other two managed their symptoms by reducing time spent in the building or by using a room air cleaner. By day 600 following occupancy, although TVOCs had increased significantly (perhaps due to cleaning agents), there were fewer individual VOCs present in the air, and some of the women were able to tolerate the air in the building. We conclude that complex mixtures of VOCs at very low levels tolerated by the majority of building occupants may pose problems for persons who report pre-existing chemical sensitivities. TVOC measurements may not correlate with symptoms in these individuals. Reasonable accommodations by an employer can reduce problem exposures, making it possible for some affected individuals to continue productive employment.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416291


'Toxicant-induced loss of tolerance' (or TILT) describes a two-step disease process in which (1) certain chemical exposures, e.g., indoor air contaminants, chemical spills, or pesticide applications, cause certain susceptible persons to lose their prior natural tolerance for common chemicals, foods, and drugs (initiation); (2) subsequently, previously tolerated exposures trigger symptoms. Responses may manifest as addictive or abdictive (avoidant) behaviors. In some affected individuals, overlapping responses to common chemical, food, and drug exposures, as well as habituation to recurrent exposures, may hide (mask) responses to particular triggers. Accumulating evidence suggests that this disease process might underlie a broad array of medical illnesses including chronic fatigue, fibromyalgia, migraine headaches, depression, asthma, the unexplained illnesses of Gulf War veterans, multiple chemical sensitivity, and attention deficit disorder.


The skin is very often the target organ of allergic reactions. This may be explained by many immunological competent cells in this organ such as the Langerhans cell, mast cells, lymphocytes, neutrophils and eosinophils. This is especially true for the antigen-presenting Langerhans cell. Therefore in many cases, the skin is a signalling organ for allergic reactions. Examples include food allergy which precipitates with signs and symptoms of skin diseases in about 45% and drug allergy to beta-lactam-antibiotics in about 90%. Also the skin serves as a test organ in allergic diseases of other organs such as rhinitis allergica or asthma. Examples include Reibtest, prick-, intracutaneous-, scratch- and patch test. Therefore it is no surprise, that allergic diseases of the skin are the most often diagnosed skin diseases such as urticaria, angioedema, vasculitis, contact dermatitis and atopic dermatitis. At these diseases, their diagnose and therapy and especially the promising progress in research with regard to these diseases which has been obtained during the last years will be focussed in this review.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10501144


Allergy and chemical sensitivity are closely related disorders in which environmental exposures produce inflammatory reactions. For allergy, environmental proteins bind to IgE antibody on mast cells leading to the release of inflammatory mediators. In chemical sensitivity, low molecular weight chemicals bind to chemoreceptors on sensory nerve C-fibers leading to the release of inflammatory mediators. Clinical manifestations are similar in the two conditions. The overlap between the two conditions has a basis in mechanism, so the similarity of clinical manifestations and high percentage of individuals with both conditions may have a biological basis. Chronic exposures can lead to adaptation phenomena. Depression has been associated with both allergy and chemical sensitivity. Both the allergic and chemical irritant responses may be subjected to conditioning so that the response is triggered by other stimuli. Evidence for conditioning is strongest for allergy. Both allergy and chemical sensitivity can be acquired in association with irritant exposures.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416285


Buildings with indoor air quality (IAQ) complaints frequently have high airborne concentrations of Penicillium species, while buildings with few IAQ complaints have an indoor air (IDA) fungal ecology similar to outdoor air (ODA), where Cladosporium species is usually the dominant microorganism. These studies compared fungal air profiles, measured continually over 6 h in a documented sick building, in IDA in a room experiencing IAQ problems with fungal profiles measured concurrently in ODA. The dominant species collected at both sites were Penicillium species, Cladosporium species, and Alternaria species. In the IDA, Penicillium species were always the dominant organisms, ranging from 150 to 567 cfu/m3 (89.8-100% of the total fungi). In
the ODA, Cladosporium species were dominant in four samples (40.0-70.6%), while Penicillium species were dominant (52.7-79.6%) in two. These data demonstrate that, even though ODA fungal profiles are changing continuously, IDA fungal profiles in "sick" buildings tend to remain unchanged.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9841779

McCampbell, A Journal/Am Fam Physician. 59: 2111-2; author reply 2115-6.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10221300


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10433191

(1999) [An extreme case of environmental neurosis].
Laumann, S, Bacharach-Buhles, M, Pohlau, D and Altmeyer, P Journal/Hautarzt. 50: 659-64.

A 64 year old female patient was diagnosed with scleroderma and has been bed-ridden for 25 years. She wears no clothing whatsoever on the grounds of an intolerance to textiles, and has spent the last eight years uninterruptedly in bed in a construction of kitchen paper towels and rubber bed sheets. A somatic disease has been be ruled out and cenesthesic schizophrenia diagnosed. As differential diagnoses, somatization, somatiform disorders and hypochondria were considered. The patient refused any psychiatric treatment.


The purpose of this study was to determine whether Gulf War Illness (GWI) can be explained by the presence of psychiatric disorders as assessed by DSM-III-R. To reduce the heterogeneity amongst Persian Gulf War veterans with GWI (PGV-F), only those were studied who presented with severe fatigue as a major complaint and also fulfilled clinical case definitions for Chronic Fatigue Syndrome, Idiopathic Chronic Fatigue, and/or Multiple Chemical Sensitivity. A total of 95 Registry PGVs were examined; 53 presented with GWI and 42 did not report any post-war health problems (PGV-H). All subjects were assessed for the presence of DSM-III-R Axis I psychiatric disorders. Compared to PGV-Hs, 49% of PGV-Fs had similar post-war psychiatric profiles: either no, or only one, psychiatric disorder was diagnosed. Psychiatric profiles of the remaining 51% of PGV-Fs were significantly different from PGV-Hs in that most of these veterans suffered from multiple post-war psychiatric diagnoses. The presence of psychiatric disorders as assessed by DSM-III-R criteria cannot explain symptoms of Gulf War Illness among all Persian Gulf veterans with severe fatiguing illness.


Six million children live in poverty in America's inner cities. These children are at high risk of exposure to pesticides that are used extensively in urban schools, homes, and day-care centers for control of roaches, rats, and other vermin. The organophosphate insecticide chlorpyrifos and certain pyrethroids are the registered pesticides most heavily applied in cities. Illegal street pesticides are also in use, including tres pasitos
(a carbamate), tiza china, and methyl parathion. In New York State in 1997, the heaviest use of pesticides in all counties statewide was in the urban boroughs of Manhattan and Brooklyn. Children are highly vulnerable to pesticides. Because of their play close to the ground, their hand-to-mouth behavior, and their unique dietary patterns, children absorb more pesticides from their environment than adults. The long persistence of semivolatile pesticides such as chlorpyrifos on rugs, furniture, stuffed toys, and other absorbent surfaces within closed apartments further enhances urban children's exposures. Compounding these risks of heavy exposures are children's decreased ability to detoxify and excrete pesticides and the rapid growth, development, and differentiation of their vital organ systems. These developmental immaturities create early windows of great vulnerability. Recent experimental data suggest, for example, that chlorpyrifos may be a developmental neurotoxicant and that exposure in utero may cause biochemical and functional aberrations in fetal neurons as well as deficits in the number of neurons. Certain pyrethroids exert hormonal activity that may alter early neurologic and reproductive development. Assays currently used for assessment of the toxicity of pesticides are insensitive and cannot accurately predict effects to children exposed in utero or in early postnatal life. Protection of American children, and particularly of inner-city children, against the developmental hazards of pesticides requires a comprehensive strategy that monitors patterns of pesticide use on a continuing basis, assesses children's actual exposures to pesticides, uses state-of-the-art developmental toxicity testing, and establishes societal targets for reduction of pesticide use.


Children form a unique subgroup within the population who require special consideration in risk assessment. Children are not little adults. Their tissues and organs grow rapidly, developing and differentiating. These development processes create windows of great vulnerability to environmental toxicants. Furthermore, the exposure patterns of children to environmental chemicals are very different from those of adults. Traditional risk assessment has generally failed to consider the special exposures and the unique susceptibilities of infants and children. Adoption of a new child-centered agenda for research and risk assessment is necessary if disease in children of toxic environmental origin is to be identified, understood, controlled, and prevented. This agenda needs to be multidisciplinary. Specific requirements within the agenda include: (1) exploration and quantification of unique patterns of exposure for children; (2) adoption of new, more sensitive approaches to testing chemicals that can recognize the consequences of exposure during early development; (3) identification, through clinical and epidemiologic studies, of etiologic associations between environmental exposures and pediatric diseases; and (4) elucidation, at the cellular and molecular levels, of the pathogenetic mechanisms of pediatric environmental illness. In the United States, an important start toward adoption of this new agenda has
occurred since passage of the Food Quality Protection Act in 1996. A Presidential Executive Order on Children's Health and the Environment has been promulgated. This Order requires all federal agencies to make protecting the health of children against environmental hazards a high priority. A new Office of Children's Health Protection has been established at the U.S. Environmental Protection Agency. Programs in children's environmental health have been created at the Centers for Disease Control and Prevention, the Agency for Toxic Substances and Disease Registry, and the National Institute of Environmental Health Sciences. A national network of eight new Children's Environmental Health Research and Disease Prevention Centers has been formed. These developments will enhance research on previously understudied issues in the environmental health of children and will provide a scientific basis for child-centered risk assessment.

(1999) Comments on "PM2.5 and mortality in long-term prospective cohort studies: cause-effect or statistical associations?"


Patients presenting with new clinical syndromes such as multiple chemical sensitivities (MCS) or other environmental illnesses confront us with the necessity to have valid models of how psychological, environmental, social and biological factors interact with each other. Whilst MCS is influenced by psychiatric and psychological factors, the scientific evidence does not allow to regard MCS as a psychiatric disorder only. Objective environmental factors have to be taken into account as well. As causation of MCS seems to be very complex, a complex model is needed to integrate the various pathogenetical factors. After reviewing the psychiatric research findings on MCS, such a model is introduced in the paper; it is called the dialectical model of environmental psychosomastics. This model has implications for further research and clinical practice; it advocates a process of simultaneous diagnostic processes covering biological environmental analysis as well as psychiatric diagnostics.


To describe the prevalence and correlates of reports about sensitivities to chemicals, questions about chemical sensitivities were added to the 1995 California Behavior Risk Factor Survey (BRFS). The survey was administered by telephone to 4,046 subjects. Of all respondents, 253 (6.3%) reported doctor-diagnosed "environmental illness" or "multiple chemical sensitivity" (MCS) and 643 (15.9%) reported being "allergic or unusually sensitive to everyday chemicals." Sensitivity to more than one type of chemical was described by 11.9% of the total sample population. Logistic regression models were constructed. Hispanic ethnicity was associated with physician-diagnosed MCS (adjusted odds ratio (OR) = 1.82, 95% confidence interval (CI) 1.21-2.73). Female gender was associated with individual self-reports of sensitivity (adjusted OR = 1.63, 95% CI 1.23-2.17). Marital status, employment, education, geographic location, and income were not predictive of reported chemical sensitivities or reported doctor diagnosis. Surprising numbers of people believed they were sensitive to chemicals and made sick by common chemical exposures. The homogeneity of responses across race-ethnicity, geography, education, and marital status is compatible with a physiologic response or with widespread societal apprehensions in regard to chemical exposure.


Toxicopy can be understood as an analogon to placebo but within any setting. Placebo is state-of-the-art since decades with relevant consequences: Only those effects may be considered as being pharmacon-specific, that go beyond non-pharmacological ("Placebo") effects. Placebo--theory is a limitation for the applicability of Morgans Canon (4), which is/was accepted within medicine like an axiom: When searching for the causes of disease physiological causes need to be ruled out, before other especially psychological etiologies can be taken into consideration. Toxicopy principle could be confirmed in different settings all over the world, in old and young, male and female, rich and poor and in different cultures. Therefore Morgans Cannon is falsified. Toxicopy principle is accepted as state-of-the-art and part of stand court rulings of the Austrian administrative tribunal. The plant law in Austria--and in Germany--provides for the protection of citizens against health hazards caused by plants, regardless of their etiologies. Therefore, non-toxicological threats must also be considered in plant approval proceedings in future.
(1999) **Prevalence of chronic fatigue and chemical sensitivities in Gulf Registry Veterans.**

More than 68000 of the 700000 veterans of the Gulf War have become members of the Veteran Affairs' Gulf War Registry. In 1995, we undertook a questionnaire study of the symptoms and medical histories reported by a randomly selected subsample of 1935 of these veterans to characterize their complaints. All results reported were based on questionnaire responses without face-to-face evaluation or physical examinations. Inasmuch as initial registry symptoms overlapped those of Chronic Fatigue Syndrome and Multiple Chemical Sensitivities, we also included standard questions for these syndromes in the questionnaire. A total of 1161 (60%) individuals responded, and there were no major demographic biases; therefore, 15.7% of registry veterans qualified for Chronic Fatigue Syndrome in accordance with the 1994 Centers for Disease Control definition. In addition, 13.1% qualified for multiple chemical sensitivities in accordance with a widely used definition, and 3.3% of the respondents had both conditions. There were no effects of gender, race, branch, duty status (active or reserve), or rank, although Multiple Chemical Sensitivities was somewhat more prevalent in women and African Americans. The data gleaned in this study suggested that the unexplained symptom syndromes of Chronic Fatigue and Multiple Chemical Sensitivities may characterize an appreciable portion of the complaints of those who volunteered for the Veteran Affairs' Gulf War Registry, and further investigation is warranted.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10501146

(1999) **Invited commentary: sensitivities to chemicals--context and implications.**

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10400548

(1999) **Neurotoxicity from airborne chemicals around a superfund site.**
A pilot investigation had shown that 88 people living within 2.4 km of a waste chemical disposal and oil-reprocessing facility which operated from 1966 to 1983 had reduced neurobehavioral performance compared to 66 regional referents. A geographic model of dispersal predicted less effect with greater distance from the distilling. To explore this gradient and the boundaries of the adverse effects, we tested 408 residents in random proportional samples of concentric zones from the center out to 4.8 km that were divided by compass octants. Reaction times, balance, blink reflex latency, color discrimination, Culture Fair, pegboard, and Trail Making A and B were measured. Exposed subjects' had diminished reaction time, balance, color score, and scores for Culture Fair, pegboard, and Trail Making A and B compared to referents. Functional impairment was not correlated with distance or direction from the site but subjects with short durations of residence had better function on one test. Combinations of these factors were not predictive.

Kilburn, KH Journal/Arch Environ Health. 54: 150.

Kilburn, KH Journal/Environ Res. 80: 244-52.

Workers repairing jet engines had respiratory, rheumatic, and neurobehavioral symptoms. They had welded and ground stainless steel parts using hard metal tools and cleaned metal with chlorinated and fluorinated organic solvents. We compared 154 workers and 112 unexposed subjects, all volunteers of similar ages and with similar educational levels, for abnormalities on chest radiographs, spirometric measurements, and questionnaires. Also appraised were performance of reaction time, balance, blink reflex latency, color discrimination, Culture Fair, vocabulary, slotted pegboard, trail making A and B, profile of mood states (POMS), and frequencies of 35 symptoms. Compared to unexposed subjects, workers had significantly more respiratory symptoms but no differences in pulmonary function. They had significantly prolonged simple and choice reaction time (P<0.0001), and abnormal balance with eyes open and eyes closed (P<0.0001), and abnormal color discrimination. Blink reflex latency was abnormal in both exposed workers and in local unexposed compared to other reference groups. Focus of the inquiry on lung disease helped ensure that for neurobehavioral tests confounding factors were minimal and known
biases were small. We tentatively attribute the neurobehavioral impairments and increased symptom frequencies to chlorinated solvent exposure. Excessive respiratory symptoms are attributed to welding stainless steel combined with cigarette smoking. Specifically, manganese exposure may have affected the respiratory and the central nervous systems.

-------------------------------------------------------------------------------------------------------------------------------

(1999) 'Multiple chemical sensitivity', the relevance of toxic, neurobiological and psychic effect mechanisms.

The review deals mainly with the key question of chemical causation of multiple chemical sensitivity (MCS). There are only few human studies with valid information on chemical exposure and in no study the chemical toxic causation hypothesis is supported. The animal model of olfactory-limbic/neural sensitization is of heuristic value to explain MCS phenomena and includes both chemical and non-chemical stressors. However, in animal studies seldom chemical substances and exposure levels were used which might be of relevance in the formation of MCS. The problem is demonstrated for toluene exposures in human and animal sensitization studies. In accordance with the sensitization hypotheses, human studies prove a generalized vulnerability to environmental stimuli in subjects with self-reported MCS. However, study designs do not allow to deduce whether the strong responsivity is a premorbid or comorbid phenomenon or is related to exposure. Alternative study approaches to evaluate dose-response relationships are proposed.


-------------------------------------------------------------------------------------------------------------------------------


BIOSIS COPYRIGHT: BIOL ABS. Allergy to natural rubber latex (NRL) is one of the major health concerns of the century. Type I anaphylactic reactions are caused by sensitivity to natural latex sap proteins remaining in latex products. Type IV contact dermatitis reactions are caused by chemical additives used to manufacture rubber products. Populations at high risk to develop latex allergy include latex industry workers, health care workers, adults and children undergoing multiple surgeries for conditions such as spina bifida dants. The mainstay of management of latex allergy is avoidance of exposure to latex. The Food and Drug Administration and The American Academy and American College of Allergy, Asthma and Immunology have made recommendations to reduce the risk of allergic reactions and occupational asthma.
caused by latex. This paper reviews the salient features of allergy to natural rubber latex.


Magnetic resonance spectroscopy allows neurochemistry to be probed noninvasively in vivo. Recent advances in our understanding of the biochemical significance of the various neurochemicals that are observable allow a variety of pathologic states of relevance to encephalopathies and neurodegenerative disorders to be observed. Measurements of brain glutamate and glutamine allow observation of neuronal/glial substrate cycling and ammonia detoxification. Myo-inositol allows changes in cerebral osmolarity and gliosis to be observed. N-acetylaspartate is a marker of neuronal health and number. Lactate allows nonoxidative glycolysis to be observed. These molecules are now being used to ask etiologic questions that are of relevance to encephalopathies and neurodegeneration, as well to probe longitudinally both natural history and therapeutic interventions in these conditions. Combined with recent advances in anatomic magnetic resonance imaging as well as perfusion magnetic resonance imaging, magnetic resonance spectroscopy has the potential to aid greatly in our understanding of neuronal dysfunction in a wide variety of neurologic pathologies, even in single patients.

(1999) [Changed working conditions result in new tasks for specialists in occupational and environmental medicine].
Jarvholm, B Journal/Lakartidningen. 96: 5079-84.


OBJECTIVE: To investigate the generation of reactive oxygen species (ROS) in serum and venous blood as well as the serum antioxidative activity (AOA) in patients and healthy controls by means of a simplified chemiluminescence (CL) methodology.
STUDY PARTICIPANTS: 48 Atopic eczema, 23 psoriasis, 15 multiple chemical sensitivity (MCS) and 35 cancer patients together with 22 healthy volunteers.
METHODS: ROS generation/photon emission in blood and serum samples under basal conditions and after light exposure as well as the AOA of the serum samples was investigated at room temperature (22 degrees C) in all 143 fasted subjects. The 3-step methodology resumes in adding a constant amount of blood or serum to a constant amount of CL substrate (or to an ROS-generating mixture for the AOA test), followed by a short preincubation and registration of the photon counts over a 600-second time interval. RESULTS: In the basal and light exposure tests significantly higher photon counts (> 14,000 counts/600 s) were registered in venous blood in all patient groups when compared to healthy controls (p < 0.001), suggesting increased amounts of activated leukocytes and light-sensitizing compounds, respectively. By contrast, most patient sera showed in all three CL tests a strongly inhibited light emission (p < 0.005), suggesting an adaptive antioxidative response to oxidant stress factors. CONCLUSIONS: Atopic, psoriasis, MCS and cancer patients are exhibiting significantly changed blood and serum CL patterns when compared to healthy controls. The described assays are simple, well reproducible and enable a fast assessment of ROS generation and AOA in biological samples at low operational costs.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10649000

(1999) [Dangerous drug intolerance].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10577007


A symposium of this title was presented at the 37th Annual Meeting of the Society of Toxicology held in Seattle, Washington during March of 1998. The symposium focused on heritable variations in metabolism, DNA replication, and DNA repair that may predispose humans to environmental diseases. Human metabolic, replication, and repair enzymes function in protective roles. Metabolic enzymes are protective because they detoxify a stream of chemicals to which the body is exposed. Replication and repair enzymes are also protective; they function to maintain the integrity of the human genome. Polymorphisms in the genes that code for some of these enzymes are known to give rise to variations in their protective functions. For example, functional polymorphisms of the N-acetyltransferases, paraoxonases, and microsomal epoxide
hydrolases vary in their capacity to metabolize environmental chemicals. Specific isoforms of the N-acetyltransferases and microsomal epoxide hydrolases are increasingly associated with incidences of cancer attributable to exposure to these chemicals. Thus, maintenance of cellular-growth homeostasis, normally and in the face of environmental challenge, is dependent on an inherited assortment of metabolic isoforms. Since replication and repair are also protective cellular functions, and since mutations in genes that code for these functions are associated with tumorigenesis, one can reasonably speculate that common functional polymorphisms of replication and repair enzymes may also impart susceptibility to environmental disease.


The objective of this study was to identify a parsimonious set of questions that has high sensitivity and specificity for screening for individuals with multiple chemical sensitivity (MCS) syndrome. We performed a cross-sectional survey using a case-control design. Subjects were derived from patients seen at an academically based Occupational and Environmental Medicine Clinic. Cases consisted of patients who fulfilled the Cullen definition for MCS. Controls were patients who had diagnoses excluding MCS and asthma and who were matched to cases by age and sex. Cases and controls filled out a screening questionnaire that, among things, elicited responses as to whether and how subjects reacted to 122 different types of environmental exposures. Data from 44 pairs of cases and controls were available for analysis. The average age of cases was 50.2 years, and 91% was female. Among cases, the most common exposure that was purported to incite MCS was 'indoor air quality contaminants (unspecified)' (59%), followed by solvents (27.3%). After randomly excluding five cases and controls, a stepwise selection procedure for two-group discriminant analysis revealed that the main contributors to the discrimination of the remaining cases and controls were self-reported reactions to copy machine emissions, marking pens, aftershave, window cleaner, nylon fabric, pine-scented products, and rayon material. When a positive response to these factors was used as the sole method for discriminating cases from controls, only one of 41 cases was misclassified as a control while none of the controls was misclassified as a case. When the same method was applied to the five excluded cases and five excluded controls, only one of the five cases was misclassified while none of the five controls was misclassified as a case. Among patients with MCS defined by the Cullen criteria in this clinical setting, having a reaction to these seven common potential exposures comprised a parsimonious set of factors that discriminated between MCS patients and age- and sex-matched normal controls. These questions may have utility in screening for individuals with MCS in general population survey studies.
Soldiers returning from the Gulf War in 1991 described a range of symptoms, including some consistent with the chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. Well-defined adverse health events attributable to service in the Gulf occurred. However, controlled epidemiological studies in Gulf War veterans and controls describe significant excesses of symptoms that were not clearly associated with pathologic disease. At least 12% of veterans currently receive some form of disability from the Department of Veterans Affairs. A number of reports outline theories proposed to explain the excess, but few are scientifically supported. Management guidelines for this spectrum of disorders resemble that of many of "emerging overlap syndromes," including multiple chemical sensitivity, chronic fatigue syndrome, and fibromyalgia. They include the establishment of a trusting doctor-patient relationship, negotiations around a common ground of scientific and etiologic beliefs, non-labeling of the disorder, and work toward recovery in the absence of clear etiologic answers.

Those who believe that electric appliances trigger adverse symptoms have coined the label hypersensitivity to electricity. Scientific research has not been able to identify a direct link between electromagnetic fields and symptoms, and no diagnostic criteria exist. Groups with reported hypersensitivity are very heterogeneous. A need exists for an operational working definition and improved characterization of groups. We report an investigation of symptoms and risk indicators associated with reported hypersensitivity to electricity-based on a survey at a high-technology, multinational telecommunications corporation. Comparisons are also made with patients referred to a university department of occupational and environmental health. No association was found between specific psychosocial work characteristics nor personal traits and hypersensitivity to electricity. We present skin and neurovegetative symptom indices. Results indicate that skin, and not neurovegetative symptoms, characterize the syndrome, at least during the first years of illness. For characterization, we proposes a set of dimensions, including triggering factors, behavior, and duration of symptoms.

OBJECTIVE: To evaluate the natural history of chronic fatigue syndrome (CFS) in a severely ill group of patients at three points in time. DESIGN: Patients were enrolled from April 1992 to February 1994 and were evaluated three times. Time 1 (at enrollment): history, physical evaluation, and psychiatric evaluation; Time 2 (median = 1.6yrs after initial evaluation): postal questionnaire to assess current condition; Time 3 (median = 1.8 yrs after Time 2): medical and psychiatric evaluations. SETTING: The New Jersey CFS Cooperative Research Center, an ambulatory setting. PATIENTS: Twenty-three patients fulfilled the 1988 case definition for CFS and had symptom complaints that were substantial or worse in severity. All patients were ill less than 4.5 years; and none had a DSM-III-R psychiatric disorder in the 5 years before illness onset; none had substance abuse in the 10 years before enrollment. MAIN OUTCOME MEASURES: Severity of CFS symptoms was assessed by self-report questionnaires, laboratory tests, and medical examination. Psychological status was assessed using the Q-D15 and the Centers for Epidemiological Study-Depression Scale. At each time of evaluation, patients were categorized as severe, slightly improved, improved, and recovered. RESULTS: Over the 4 years of the study, 13 patients remained severely ill, 9 improved but still fulfilled the 1994 case definition for CFS, and 1 recovered. Illness duration, mode of onset, psychiatric status or depressed mood at intake, or chemical sensitivity did not predict illness outcome. One patient was diagnosed with an alternate illness, but it probably did not explain her CFS symptoms. Mood improved for those patients whose illness lessened. CONCLUSIONS: The prognosis for recovery was extremely poor for the severely ill subset of CFS patients. The majority showed no symptom improvement and only 4% of the patients recovered. Illness severity between Times 2 and 3 remained stable.

Multiple chemical sensitivities (MCSs) consists of a pattern of unexplained symptoms (headache, respiratory problems, exhaustion, muscular aches and cognitive disorders) attributed to very low levels of exposure to a variety of unrelated chemicals. Current research on MCS in the United States and in Germany is presented. Controversial issues on mechanisms, open questions and needs for research on causes and aetiophysiology of these diseases are highlighted.

The phenomenon referred to as environmental illness, especially multiple chemical sensitivity, is an extremely controversial and puzzling issue. Despite the seeming gestalt of the disease there is no objective measure for diagnosis and pathophysiology. Psychological and psychosocial factors have a significant role in the presentation and prospects of the disease. Medical neglect of the suffering of the patients as well as iatrogenic attribution towards a chemical intoxication might both increase the risk of chronification and social isolation of patients up to a point of no return. Several observations and results from studies with environmental patients and in related fields are presented and discussed with the aim to encourage continuous research and a critical approach towards a phenomenon where the political necessity to decide is more advanced than the ability to understand.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10507125

(1999) Association of low PON1 type Q (type A) arylesterase activity with neurologic symptom complexes in Gulf War veterans.

Previously Haley et al. described six possible syndromes identified by factor analysis of symptoms in Gulf War veterans and demonstrated that veterans with these symptom complexes were more neurologically impaired than age-sex-education-matched well controls. They also uncovered strong associations (relative risks 4-8) suggesting that these symptom complexes were related to wartime exposure to combinations of organophosphate pesticides, chemical nerve agents, high concentration DEET insect repellant, and symptoms of advanced acute toxicity after taking pyridostigmine. Here we have shown that compared to controls, ill veterans with the neurologic symptom complexes were more likely to have the R allele (heterozygous QR or homozygous R) than to be homozygous Q for the paraoxonase/arylesterase 1 (PON1) gene. Moreover, low activity of the PON1 type Q (Gln192, formerly designated type A) arylesterase allozyme distinguished ill veterans from controls better than just the PON1 genotype or the activity levels of the type R (Arg192, formerly designated type B) arylesterase allozyme, total arylesterase, total paraoxonase, or butyrylcholinesterase. A history of advanced acute toxicity after taking pyridostigmine was also correlated with low PON1 type Q arylesterase activity. Type Q is the allozyme of paraoxonase/arylesterase that most efficiently hydrolyzes several organophosphates including sarin, soman, and diazinon. These findings further support the proposal that neurologic symptoms in some Gulf War veterans were caused by environmental chemical exposures.


Biological hazard index (BHI) is defined as biological level tolerable for exposure to mixture, and is calculated by an equation similar to the conventional hazard index. The BHI calculation, at the present time, is advocated for use in situations where toxicokinetic interactions do not occur among mixture constituents. The objective of this study was to develop an approach for calculating interactions-based BHI for chemical mixtures. The approach consisted of simulating the concentration of exposure indicator in the biological matrix of choice (e.g. venous blood) for each component of the mixture to which workers are exposed and then comparing these to the established BEI values, for calculating the BHI. The simulation of biomarker concentrations was performed using a physiologically-based toxicokinetic (PBTK) model which accounted for the mechanism of interactions among all mixture components (e.g. competitive inhibition). The usefulness of the present approach is illustrated by calculating BHI for varying ambient concentrations of a mixture of three chemicals (toluene (5-40 ppm), m-xylene (10-50 ppm), and ethylbenzene (10-50 ppm)). The results show that the interactions-based BHI can be greater or smaller than that calculated on the basis of additivity principle, particularly at high exposure concentrations. At lower exposure concentrations (e.g. 20 ppm each of toluene, m-xylene and ethylbenzene), the BHI values obtained using the conventional methodology are similar to the interactions-based methodology, confirming that the consequences of competitive inhibition are negligible at lower concentrations. The advantage of the PBTK model-based methodology developed in this study relates to the fact that, the concentrations of individual chemicals in mixtures that will not result in a significant increase in the BHI (i.e. > 1) can be determined by iterative simulation.
Enhanced mRNA expression of neurofilament subunits in the brain and spinal cord of diisopropyl phosphorofluoridate-treated hens.


Diisopropyl phosphorofluoridate (DFP) is an organophosphorus ester, and a single injection of this compound (1.7 mg/kg, s.c.) produces delayed neurotoxicity (OPIDN) in hens in 7-14 days. Clinically, the disease is marked by hindlimb ataxia followed by paralysis after some time. A characteristic feature of this neuropathy is axonal swelling in the initial stages and comparative dissolution of the accumulated material and degeneration of distal axons with disease progression. Axonal swelling consists of aggregated neurofilaments, microtubules, and proliferated smooth endoplasmic reticulum. We studied expression of neurofilament (NF) mRNAs in brain regions and spinal cord to elucidate their role in OPIDN. There was a 50-200% increase in NF transcripts in 24 hr after DFP administration. The NF-L mRNA level started falling after 1-5 days and came down to control level in susceptible brain regions (i.e. cerebellum and brainstem) and spinal cord, but not in cerebral cortex, which does not show degeneration of axons in OPIDN. Cerebral cortex exhibited elevated levels of both NF-L and NF-M transcripts in DFP-treated hens throughout the period of observation. The induction of NF messages is consistent with the previously reported effect on extension of neurites of human neuroblastoma cells in culture. The transient increase in NF messages in susceptible tissues either may be responsible for the delayed degeneration of axons in OPIDN or is the result of interruption of regulatory signal due to progressive degeneration of axons.

---------------------------------------------------------------

Tau phosphorylation by diisopropyl phosphorofluoridate (DFP)-treated hen brain supernatant inhibits its binding with microtubules: role of Ca2+/Calmodulin-dependent protein kinase II in tau phosphorylation.

Gupta, RP and Abou-Donia, MB Journal/Arch Biochem Biophys. 365: 268-78.

Diisopropyl phosphorofluoridate (DFP) produces organophosphorus ester-induced delayed neurotoxicity (OPIDN) in hen, human, and other sensitive species. This is characterized by mild ataxia, which progresses to severe ataxia or paralysis in a few days. Ultrastructurally, OPIDN is associated with the degeneration of axons in central and peripheral nervous systems. Bacterially expressed longest human tau protein (htau40) phosphorylated by DFP-treated hen brain supernatant showed a decrease in microtubule binding in a shorter time than that phosphorylated by control hen brain supernatant. The decrease in htau40-microtubule binding observed on htau40 phosphorylation by the recombinant Ca2+/calmodulin (CaM)-dependent protein kinase II (CaM kinase II) alpha-subunit showed that CaM kinase II present in brain supernatant could participate in tau phosphorylation even in the absence of Ca2+/CaM and decrease tau-microtubule binding. In addition, use of htau40 mutants, htau40m1 (Ala416) and htau40m6 (Asp416), suggested that replacement of Ser416 by neutral or acidic amino acid produced some change in htau40 conformation that caused
diminished binding with microtubules phosphorylated by brain supernatant in the presence of ethylene glycol bis(beta-aminoethyl ether) N, N'tetraacetic acid (EGTA). The change in conformation produced by Ser416 phosphorylation, however, was different from that produced by mutants since only nonmutated htau40 showed a significant decrease in binding with microtubules on phosphorylation by recombinant CaM kinase II in the presence of Ca2+/CaM compared to that obtained by phosphorylation in the presence of EGTA. This study showed that enhanced Ca2+ CaM-dependent protein kinase activity in DFP-treated hen brain supernatant may cause decreased tau-microtubule binding and destabilization of microtubules and may be involved in axonal degeneration in OPIDN.


Serious waterborne and wilderness infections are common and usually treatable if diagnosed early. The differential diagnosis for these infections requires a careful and thorough history and physical examination. Common clinical presentations include acute febrile illnesses, altered mental status, diarrhea, or pneumonia. Pathogens causing serious infections include bacteria, fungi, viruses, and protozoa. Epidemiologic help can be obtained from local or state health departments as well as the Centers for Disease Control.


OBJECTIVE: To review critically the scientific literature on multiple chemical sensitivity (MCS). Definitions of MCS vary but, for this review, a broad definition of MCS was adopted as symptoms in more than one organ system elicited by various unrelated chemicals at very low levels of exposure. METHODS: A systematic literature search identified several hundred references from which key papers were selected. Two questions are considered, does MCS exist and what causes MCS. RESULTS AND CONCLUSIONS: Despite extensive literature on the existence of MCS, there is no unequivocal epidemiological evidence; quantitative exposure data are singularly lacking; and qualitative exposure data are, at best, patchy. There is also some evidence to suggest that MCS is sometimes used as an indiscriminate diagnosis for undiagnosed disorders. Despite this, the collated evidence suggests that MCS does exist although its prevalence generally seems to be exaggerated. Many causal mechanisms have been proposed, some suggesting a physical origin--such as MCS reflecting an immunological overload (total body load)--others favouring a psychological
basis—such as MCS symptoms being evoked as part of a conditioned response to previous trauma. The available evidence seems most strongly to support a physical mechanism involving sensitisation of part of the midbrain known as the limbic system. However, it is increasingly being recognised that the psychological milieu of a person can considerably influence physical illness, either through generating a predisposition to disease or in the subsequent prognosis. Work is needed to establish the prevalence of MCS and to confirm or refute selected causal mechanisms.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10448311

(1999) Simple tandem repeat polymorphisms in the neuronal nitric oxide synthase gene in different ethnic populations.

Allelic frequencies of a CA dinucleotide repeat in exon 29 and an intronic AAT trinucleotide repeat in the neuronal nitric oxide synthase (NOS1) gene were determined by simple sequence length polymorphism (SSLP) in 305 American-Caucasian and 105 African-American healthy subjects. There were highly significant differences in allele frequencies between the two ethnically diverse study populations.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10364677

(1999) [Mutual features of chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivity].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10572528


The nervous system is main target of the toxic action of most of organic solvents. There is little doubt that occupational solvent exposure may result in persisting neurobehavioural disturbances—the organic solvent syndrome. Recently, the solvents
are quoted among possible causes of the abnormal condition referred to as multiple chemical sensitivity (MCS), and which is characterized by a psychosomatic over-reactivity to a variety of chemicals present in food or ambient air. According to some authors, MCS is a manifestation of the time-dependent sensitization (TDS), a phenomenon of progressive increase in responsiveness to chemical agents following acute or intermittent exposure, and related to some functional aberrations within limbic structures. TDS is commonly induced by psychostimulant drugs. The purpose of the present paper was to show, based on the literature data, that under circumstances of acute and repeated exposure, some solvents (mainly toluene) exert effect on behaviour and on the functional state of some neurotransmitter systems similar to that exerted by drugs known to induce TDS. Of special importance is the fact that in case of solvents the behavioural and biochemical changes suggestive of sensitization appear after exposure at levels close to those admissible in the occupational exposure, and that the concentration-effect relationship is nonlinear (an inverted U curve). To date, however, only a few of the existing data may be regarded as a direct evidence of the solvent-induced TDS. It is mainly due to the fact that the experimental protocol of a TDS study does not match the experimental routine of neurotoxicity assessment. Some data suggest that some solvents are possibly unable to induce TDS. The necessity to assess the commonly used solvents for their ability to induce TDS has been emphasized.


To determine whether nitric oxide (NO) acts as a modulator of muscarinic acetylcholine receptor (mACh-R) function, we performed a radioligand receptor assay using [3H]quinuclidinyl benzylate ([3H]QNB), the NO radical (NO\(^*\)) donor 3-(2-Hydroxy-1-methyl-2-nitrosohydrazino)-N-methyl-1-propanamin e (NOC7) and a gerbil brain cortical membrane preparation. NOC7 (at 10 microM, 100 microM or 1 mM concentrations) significantly reduced the [3H]QNB binding Kd values (from 0.196 +/- 0.009 nM in the control, to 0.151 +/- 0.013, 0.144 +/- 0.012 and 0.153 +/- 0.007 nM respectively). NOC7 did not alter the displacement curves of atropine or carbachol. Reduction of SH groups with dithiothreitol, in the presence of the NO donor, significantly increased [3H]QNB binding affinity whereas alkylation by N-ethylmaleimide
markedly decreased it. The observed enhancing effect on mACh-R binding affinity for [3H]QNB, may reflect conformational changes in the receptors mediated by the NO generated, and these changes might be explained by NO reactions with such groups through conditions supporting redox reactions intrinsic to the NO molecule, similar to those occurring in redox regulatory sites reported for other neurotransmitter pathways in the CNS.

Gollub, B and Morton, L Journal/Am Fam Physician. 59: 2110-1; author reply 2112, 2115.


This paper examines hope, as measured by the Herth Hope Scale, and its predictors in a sample of 305 people self-identified with multiple chemical sensitivity. The sample had relatively low levels of hope with scores unrelated to gender, severity or length of illness, income loss as a result of illness, or reported iatrogenic harm. Hope scores were positively correlated with perceived social support, having found personal growth through illness, age, reported level of supportiveness from a partner, an improved course of illness and level of reported safety of the home environment in regard to chemical exposures. Negative correlations were found with attitude toward healthcare delivery, fatigue and reported abuse/ostracism from family members other than partner. Social support, Healthcare Orientation, growth through illness, fatigue and age predicted hope scores accounted for 55% of the variance. Implications and suggestions for future research are discussed.


(1999) Can traditional epidemiology detect cancer risks caused by occupational exposure to pesticides? 
In order to investigate the possible relationship between cancer and occupational exposure to pesticides, we reviewed the latest literature of the epidemiological studies in this area coming to the conclusion that, while several studies indicate a link between certain pesticides and certain tumors, this information is still insufficient, and further research on the health consequences of exposure to pesticides is needed. Moreover, provided there is a risk, it is often too limited to be detected by available epidemiological techniques. Therefore, in addition to the epidemiological studies, the development of new biology, gene technology and medical biotechnology methods may significantly enhance the specificity of the epidemiological studies. Thus, the fusion of molecular biology and epidemiology into molecular epidemiology may provide more specific methods for monitoring the occupational dependent carcinogenic risk of individuals and groups.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10221297

Freeman, R, Landsberg, L and Young, J Journal/Neurology. 53: 2151-7.

OBJECTIVE: To study the therapeutic effect and mechanism of action of 3,4-DL-threodihydroxyphenylserine (DL-DOPS) in neurogenic orthostatic hypotension.
METHODS: The blood pressure (BP) response to an orthostatic challenge on DL-DOPS was compared with that of placebo in a randomized, double-blind, placebo-controlled, crossover trial in 10 patients. The mechanism of action of DOPS was studied by measuring forearm vascular resistance and changes in supine and upright plasma DL-DOPS and norepinephrine levels. The effect of DL-DOPS on the quality of life was determined by questionnaire. RESULTS: DL-DOPS increased the supine (p<0.001) and upright (p<0.05) systolic blood pressure (SBP) and diastolic blood pressure (DBP) (both p<0.01). The peak SBP on DL-DOPS in the supine position occurred 300 minutes after ingestion of the medication. The increase in BP was accompanied by an increase in plasma levels of norepinephrine and DL-DOPS in both the supine and upright positions after DL-DOPS ingestion (p<0.0001). There was a trend toward improvement in symptoms of orthostatic intolerance. CONCLUSION:
DL-DOPS improved features of neurogenic orthostatic hypotension in patients with central and peripheral autonomic nervous system disease. There was an increase in plasma norepinephrine. No major side effects occurred.


(1999) Intradermal testing for food and chemical sensitivities: a double-blind controlled study.

BACKGROUND: Confirming adverse reactions to foods and chemicals is fundamental in providing a basis for diagnosis and treatment of patients with reported environmental sensitivities. Provocation-neutralization testing is widely used in this respect but has not been thoroughly evaluated, therefore remaining a controversial and unproven technique. OBJECTIVE: This study investigated the validity of intradermal testing for evaluation of reported adverse reactions to a variety of incidents within the patient population at the Nova Scotia Environmental Health Centre. METHODS: A total of 132 people who were referred to the Nova Scotia Environmental Health Centre, a dedicated government-funded research and treatment facility for suspected environmental sensitivities, were tested by the technique of provocation-neutralization by the guidelines set out by the American Academy of Environmental Medicine. A panel of 13 foods, 9 chemicals, and 4 placebos (normal saline solution) was evaluated in a double-blind, randomized study. Symptoms and skin reactions were recorded, and response rates were determined for all substances, including saline solution injections. RESULTS: Seventy percent of the patients reported symptoms to 1 or more of the 4 saline solution injections. In comparison, 15% of patients experienced a skin reaction (wheal) to 1 or more injections of saline solution. Only 5% of individuals experienced a wheal to more than 1 saline solution injection, although 40% of the patients reported symptoms to more than 1 saline injection. Patients who experienced 1 or more reactions (wheal or symptoms) to saline solution were more reactive to injected allergens, on average reacting to 67% of active substances. Patients who experienced no reaction to the saline solution did experience a reaction to 48% of injected substances on average. Reaction by symptoms to foods, chemicals, and normal saline solution showed a random pattern, although wheal reactions showed a distinct pattern. Subsequent observations have indicated that experiencing no reaction to previous saline solution injections does not accurately predict response to saline solution in later testing. Some individuals who did not experience a reaction to saline solution in an
initial screening later experienced a reaction to saline solution during further testing. CONCLUSIONS: Provocation of symptoms in usual testing conditions is not a useful tool for discriminating between reactions to saline solution and reactions to specific chemicals or foods. Skin response alone may be a more reliable indicator and will require cross-validation with other tests, such as oral and inhalation challenges and comparison with a control population. Heightened sensitivity and chaotic responses may be a feature of chemical sensitivity. Meanwhile, the results of provocation-neutralization testing, using symptoms alone as an indicator of neutralization, should not be used as a basis for clinical intervention.


After the spraying of insecticides against cockroaches in a kindergarten insecticide residues were detected over several months in spite of extensive decontamination. This prompted measurements in a home for asylum seekers, where insect pests had been controlled regularly by a commercial firm; here the presence of various biocides was demonstrated. As the insecticides could not be sufficiently decontaminated, the further administration was discontinued and instead cockroach traps and baits were set up. This alternative method which was well accepted by the inhabitants of the home as well as the administrative staff was subsequently successfully employed in other public institutions, e.g. a school and another kindergarten.


The purpose of the present study was to investigate whether women with chemical sensitivity rated the intensity and pleasantness of three odorants [peppermint, vanilla, and propylene glycol (PG)] and odorless room air differently than women without chemical sensitivity. The ratings of the experimental group (women with self-reported chemical sensitivity and no history of sexual abuse) were compared to those of two control groups who did not report chemical sensitivity [sexually abused (SA) women and healthy women without sexual abuse history]. All subjects were exposed to odorants and odorless control stimuli once a week for 3 consecutive weeks. Our findings indicate that women with chemical sensitivity perceive odorants as neither more or less intense nor more or less pleasant than women without chemical sensitivity. Moreover, the control women without sexual abuse outperformed the women in the other two groups by correctly identifying the target bottle containing the odorant. These findings suggest that perception of odorants alone is unlikely to account for the symptoms associated with chemical sensitivity. These findings, along
with those of Doty et al. (1988), support the notion that olfactory-sensory function does not differ between individuals with and without chemical sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10560135

---------------------------------------------------------------


This study tested the sensitization model proposed by Bell et al. [Bell I.R., Miller C.S. and Schwartz G.E. An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationship to kindling and affective spectrum disorders. Biol. Psychiatry 1992: 32: 218-242] to study chemical sensitivity. The sensitization model indicates that a pharmacological stimulus or a traumatic event which elicits a strong response can sensitize limbic and/or mesolimbic pathways; and subsequent less intense trauma or stimuli, in the same or different modality, can elicit an amplified response. Three groups of subjects were tested: (1) women who reported chemical sensitivity and no sexual abuse (chemically sensitive, CS); (2) sexually abused (SA) women without chemical sensitivity; and (3) healthy women without chemical sensitivity or sexual abuse history (normal, N). All subjects were exposed to odorant and nonodorous control stimuli once a week for 3 weeks. Electroencephalographic activity was recorded while subjects sniffed the odorant and control stimuli. Results of the study revealed that both the CS and the SA group showed electroencephalogram (EEG) alpha sensitization across experimental sessions, while the N group showed little change over time. Additionally, EEG findings revealed that the CS group generated significantly greater alpha activity than the other two groups. Finally, while the groups were different on measures of psychological distress, these differences did not diminish the EEG findings. In summary, these findings suggest that intermittent exposure to chemicals elicits sensitization in CS and SA women without chemical sensitivity, supporting our expectations that chemical sensitivity is, in part, a manifestation of time-dependent sensitization (TDS). Additionally, these EEG findings indicate that CS women are unlike SA and healthy women in the amount of EEG alpha activity they generate. Finally, these findings indicate that psychological factors as assessed in this study do not explain electrophysiological differences between chemically and non-chemically-sensitive women.

---------------------------------------------------------------

This paper describes symptoms and findings in a 57-year-old painter who had been exposed to various organic solvents for over 30 years. He began to work as a painter at 16 years of age, frequently working in poorly ventilated areas; he used solvents to remove paint from the skin of his arms and hands at the end of each work shift. The patient and his family noticed impaired short-term memory function and changes in affect in his early forties, which progressed until after he stopped working and was thus no longer exposed to paints and solvents. After the patient's exposures had ended, serial neuropsychological testing revealed persistent cognitive deficits without evidence of further progression, and improvement in some domains. Magnetic resonance imaging revealed global and symmetrical volume loss, involving more white than gray matter. The findings in this patient are consistent with chronic toxic encephalopathy and are differentiated from other dementing processes such as Alzheimer's disease, multi-infarct (vascular) dementia, and alcoholic dementia. Previous descriptions in the literature of persistent neurobehavioral effects associated with chronic exposure to organic solvents corroborate the findings in this case.

-----------------------------------------------

(1999) [The hypothesis of environmental causes of damage to the endocrine system: science of sensationalism?].

AN EMERGING TOPIC: It has been hypothesized that exposure to certain chemical compounds in the environment could lead to reproduction and development anomalies. VARIABLE MECHANISMS OF ACTION, SUSCEPTIBILITIES AND EFFECTS: The incriminated environmental agents could have several targets in the endocrine system. As hormones play a cardinal role in regulating differentiation during early stages of life, developing organisms would be particularly vulnerable. AN EVALUATION METHODOLOGY: Although the hypothesis of endocrine perturbation is theoretically plausible, solid scientific data is still lacking to conclude that environmental compounds have a deleterious effect in humans after low-dose exposure. The ubiquitous nature of the intermediary metabolism of these compounds, the existence of critical periods of life, the complexity of the cell processes involved, and the differed timing of the effects make it difficult to assess risk. Current research is being conducted to develop specific methodologies to better understand this risk. AN INTERNATIONAL EFFORT: Different international and national entities have organized scientific committees with the task of identifying chemical compounds susceptible of perturbing endocrine function. In 1998, an international convention set up regulatory control of sales of certain chemical compounds.

-----------------------------------------------

Elliott, EM Journal/Am Fam Physician. 59: 2109-10; author reply 2112, 2115.
(1999) **Deltamethrin-induced testicular apoptosis in rats: the protective effect of nitric oxide synthase inhibitor.**

This study is the first to examine and characterize the testicular apoptosis which might be induced due to exposure of male rats to deltamethrin. Furthermore, the role which might be played by nitric oxide (NO), as well as the other reactive oxygen species (ROS) in controlling this testicular apoptosis was assessed. Apoptosis was evaluated by DNA fragmentation detected by agarose gel electrophoresis and cellular morphology on testicular tissue sections. It was found that administration of deltamethrin (1 mg/kg daily for 21 days) to animals resulted in characteristic DNA migration patterns (laddering), thereby providing evidence that apoptosis is the major mechanism of cell death in the testicular tissues. In addition, histopathological examination of testicular tissue sections showed that apoptosis was confined to the basal germ cells, primary and secondary spermatocytes. These changes, in addition to the appearance of Sertoli cell vacuoles in deltamethrin-intoxicated animals, indicates the suppression of spermatogenesis. At the same time, the plasma levels of both NO and lipid peroxides measured as malondialdehyde (MDA) were found to be significantly increased in deltamethrin-treated animals. Administration of NO synthase (NOS) inhibitors such as N(G)-nitro monomethyl L-arginine hydrochloride (L-NMMA, 1 mg/kg) to rats 2 h before exposure to deltamethrin was effective in the reduction of the typically testicular apoptotic DNA fragmentation pattern and the associated histopathological changes. These findings may suggest that deltamethrin-induced testicular apoptosis is mediated by NO. Therefore, the pharmacological manipulation of apoptosis by selective NOS inhibitors such as L-NMMA may offer new possibilities for the control of deltamethrin-induced testicular dysfunction and infertility in the future.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10199576

(1999) **[Chronically ill due to the environment. Does study involvement help?].**
Eis, D Journal/MMW Fortschr Med. 141: 16.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10897991
This contribution outlines the historic development of Clinical Ecology (CE) and the differences it poses to scientific environmental medicine. The pathogenic, diagnostic and therapeutic concepts of clinical ecology are presented and critically acknowledged. Particular attention is given to behavioral and mental illnesses which, according to the beliefs of clinical ecologists, are related to food and chemicals, whereby this occurrence is considered a "cerebral allergy". The term "allergy" is, however, understood in the broader sense, as opposed to the usual medical term, to include non-immunological, pseudo-allergic and other intolerance reactions. Below are details of the validity and effectiveness of clinical ecology methods. Clinical ecology is concerned, not least, with unspecified, little understood health disorders and chronically fluctuating illnesses which are mainly attributed by clinical medicine to psychosomatic complaints. Many patients are critical of the lack of an adequate, literally "integral" treatment, i.e. one which also includes psychosocial aspects. They tend to search for simple answers and "alternative" treatment possibilities associated with it. Clinical ecologists and other "alternative practitioners" respond to this demand. They initially confirm or suggest to the patient the possibility of poisoning and offer a therapy that is allegedly causal and effective. The iatrogene fixation of patients with environment related illnesses has become a problem for the person in question, clinical medicine and the insured. Of course, those affected interpret their situation in another way. They consider themselves to be the victims of medical ignorance. The challenge posed by unconventional schools of medical thought should be met by increased efforts to create "sound medical practice" and by the attempt to achieve generally binding criteria for quality in the sense of effective "consumer protection".

Recognizing toxicokinetic and toxicodynamic variability is important in risk assessment of chemicals and may help to explain interindividual differences in susceptibility in exposed populations. Both toxicokinetic and toxicodynamic factors may be influenced by age and disease processes and show genetic polymorphic variation. Decreased metabolic activity in the very young or very old may enhance chemical toxicity caused by the parent chemical. Similarly, disease processes affecting hepatic metabolism and renal excretion may delay inactivation of many xenobiotics. Genetic polymorphisms may enhance toxicity in rapid metabolizers when the toxicity is caused by a reactive
intermediate and increase toxicity in slow metabolizers when the toxicity is caused by a parent chemical. Some cells of the developing conceptus are exquisitely sensitive to chemical exposure. Also, organs and tissues of newborns and elderly individuals may show increased responses toward xenobiotics. In addition, disease-induced altered receptor sensitivity and tissue repair may result in enhanced chemical toxicity. Further, tissue antioxidant defense against radical damage may be compromised under nutritional deficiencies and starvation. Hereditary peculiarities in individual responses to environmental chemicals may be due to polymorphic variation of receptor proteins and tissue repair enzymes, although the database for such variation is quite limited.


Under the Federal Insecticide, Fungicide and Rodenticide Act, the Toxic Substances Control Act and the Clean Water Act, the U.S. Environmental Protection Agency (EPA) is charged with determining if the manufacture, use, or disposal of a chemical will present an unreasonable risk of harm to the environment. Typically, management decisions are based on protecting populations of organisms. However, the Endangered Species Act requires that, in some cases, managers must estimate the take of individuals to determine if the loss of individuals might adversely affect a population of an endangered or threatened (listed) species. The most direct assessment would be to determine the sensitivity of a listed species to a particular contaminant or perturbation. However, this direct approach would be time consuming and expensive because it might require development of organism culturing and handling procedures, some species may not be amenable to culture, there might be multiple species to be considered, and would be contaminant specific. This research project had two objectives: (1) determine the relative sensitivity to contaminants of listed species using standard acute toxicity tests; and (2) determine the degree of protection afforded listed fish species through the use of standard species used in whole effluent toxicity tests.

(1999) **Prevalence and overlap of chronic fatigue syndrome and fibromyalgia syndrome among 100 new patients.**

(1999) **On the recognition of multiple chemical sensitivity in medical literature and government policy.**

(1999) **Dysphonia and delayed food allergy: a provocation/neutralization study with strobovideolaryngoscopy.**

In most cases the cause of intermittent dysphonia remains undiagnosed. This descriptive study explores the relationship between this problem and delayed food allergy. Double-blind intradermal provocation/neutralization skin tests to food antigens were used to do 12 tests in 10 subjects with food allergies. Strobovideolaryngoscopy was used to document changes in the vocal folds and in the quality of the voice. Double-blind measurements of signs and symptoms, digital audio recordings of the voice for perceptual and acoustic analysis, and aerodynamic laryngeal airflow and resistance measurements were done. The cause of dysphonia appeared to be associated with an increase in thick mucus production and irregular and asymmetric glottic edge edema of the vocal folds. Elimination of the positive specific foods resulted in cessation of dysphonia in all the test subjects. Statistical analysis was not done because of the lack of parametric data for paired analysis, lack of sufficient data points for resampling statistics, and the small sample size.

(1999) **On "Scents and Sensitivity".**

Previous in vitro and in vivo studies have determined that the d isomer of methadone has N-methyl-D-aspartate (NMDA) receptor antagonist activity. The present studies examined the ability of d-methadone to attenuate the development of morphine tolerance in mice and rats and to modify NMDA-induced hyperalgesia in rats. A decrease in the percentage of mice analgesic (tail-flick response) after 5 days of once-daily morphine (7 mg/kg s.c.) was completely blocked by coadministration of d-methadone given s.c. at 10 mg/kg. Morphine given s.c. to mice on an escalating three times per day dosing schedule resulted in a nearly 3-fold increase in the tail-flick ED50 dose of morphine which was prevented by s.c. coadministered d-methadone at 15 mg/kg. In rats, intrathecal (i.t.) morphine produced a 38-fold increase in the ED50, which was completely prevented by the coadministration of i.t. d-methadone at 160 micrograms/rat. A decrease in thermal paw withdrawal latency induced by the i.t. administration of 1.64 micrograms/rat NMDA was completely blocked by pretreatment with 160 micrograms/rat d-methadone. Thus, systemically coadministered d-methadone prevents systemically induced morphine tolerance in mice, i.t. d-methadone attenuates tolerance produced by i.t. morphine in rats, and i.t. d-methadone, at the same dose which modulates morphine tolerance, blocks NMDA-induced hyperalgesia. These results support the conclusion that d-methadone affects the development of morphine tolerance and NMDA-induced hyperalgesia by virtue of its NMDA receptor antagonist activity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10215686


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416296

(1999) [Similarities of chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivity].
Social phobia was initially classified with phobic anxiety states and was believed to be quite rare, but it is now gaining due recognition as a widespread and often crippling disorder. The boundaries of social phobia merge into traits of shyness and universal performance anxiety, with symptoms commonly appearing in the teenage years. If left untreated, social phobia is a remarkably persistent condition, leading to potentially lifelong impairment in social development and occupational functioning. It may also give rise to other co-morbid disorders, particularly dysthymia, depression, obsessive-compulsive disorder, other phobic disorders, and substance abuse. Over the years, social phobia has been all too frequently viewed as a somewhat trivial, minor form of psychiatric illness and has received little clinical attention. This erroneous perception is now giving way under the mounting evidence in support of the extensive morbidity and disability associated with social phobia and the probable role of genetic and environmental influences. Furthermore, data from multiple controlled clinical trials reveal that this is a treatable condition, responding to both psychosocial and pharmacologic interventions. Here we examine issues to consider in the differential diagnosis of social phobia, review the goals of treatment, and summarize evidence in support of the effectiveness of individual pharmacologic treatments.

---

37th Annual Meeting of the Society of Toxicology symposium on alterations in cytokine receptors by xenobiotics (Seattle, Washington, USA).

BIOSIS COPYRIGHT: BIOL ABS. A symposium entitled Alterations in Cytokine Receptors by Xenobiotics was held at the 37th Annual Meeting of the Society of Toxicology (SOT) in Seattle, Washington. The symposium was sponsored by the Immunotoxicology Specialty Section of SOT and was designed to present information on the effect of several difference classes of xenobiotics on various aspects of receptor function (i.e., post-receptor signal transduction of receptor expression), or the involvement of cytokine receptors in the actio

The highly reactive free radical gas, nitric oxide, serves a variety of biomodulatory functions and has been implicated in a growing array of physiological and pathophysiological states. The striking differences between this labile substance and other, more conventional, signaling molecules highlight the tight degree of nitric oxide regulation that is required in order to maintain appropriate cellular homeostasis. The generation of nitric oxide represents a common component of the signal transduction pathways of a number of chemical signaling molecules that act via binding to G protein-coupled receptors. This review focuses on the relationship between this receptor superfamily, the generation of nitric oxide via the actions of the nitric oxide synthases and some of the inter- and intracellular roles of nitric oxide.


OBJECTIVE: To report a case of angioedema associated with the angiotensin II receptor antagonist losartan. CASE SUMMARY: A 62-year-old African-American woman was admitted to the hospital for acute renal failure and uncontrolled hypertension. After attempting blood pressure control with three different agents, captopril was combined with metoprolol. The patient noted swelling of the lips combined with shortness of breath after four days of captopril. Losartan was substituted for captopril, which then produced similar swelling of the lips (without shortness of breath) after only one dose. These symptoms resolved after discontinuation of losartan and administration of antihistamines. DISCUSSION: Losartan, like other angiotensin II receptor antagonists, blocks the action of angiotensin II at the receptor level. Five published case reports involved patients with a prior history of intolerance to the angiotensin-converting enzyme inhibitors. Two published case reports of similar reactions also occurred in patients with renal compromise. The mechanism for this reaction from losartan is not known, but may not be due to bradykinin excess. CONCLUSIONS: Clinicians should be aware that angiotensin receptor antagonists may not be safe alternatives in patients who have a history of angioedema secondary to the angiotensin-converting enzyme inhibitors.

Thus far, no neuropsychological study has examined the cognitive profile of multiple chemical sensitivity (MCS) within the framework of Bell's Olfactory-Limbic Model. It predicts that cognitive weaknesses will be associated more with limbic (i.e., frontal and or temporal lobe) than with non-limbic (i.e., posterior cortex) brain regions. Matched MCS, asthma, and healthy control groups (n = 63) were tested on cognitive measures with localizing value. Between-group comparisons found that the MCS group performed as well as controls on all cognitive tasks. Within-group comparisons found that both the MCS and asthma groups performed significantly more poorly on tasks that were sensitive to frontal and temporal regions than to posterior regions. Additional research is needed before concluding that the Olfactory-Limbic Model adequately describes the cognitive strengths and weaknesses of MCS. Confounding factors such as medication use and chronic illness need to be considered.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10337606


Institutions are increasingly being asked to accommodate individuals with multiple chemical sensitivity (MCS). Most establishments have chosen to provide such accommodations on a case-by-case basis only. This paper investigates feasible actions that may be taken by institutions to reduce exposure of MCS individuals as well as the general institutional population to pesticides and other substances. Emphasis is placed on procedures that can be instituted on a regular basis and may be combined with case-by-case management for better resolution of problems.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416297

(1999) Children's asthma can be deadly, even when it's 'mild'.

(1999) Sociosomatics and illness in CFS.
Bohr, T Journal/Psychosom Med. 61: 256.


The term "idiopathic environmental intolerances" (IEI)"multiple chemical sensitivities" (MCS) is used to describe a complex of heterogeneous somatic symptoms without a diagnoseable organic disease. Symptoms are believed to be triggered by exposure to low levels of environmental chemicals that are usually well tolerated by the general population. There is no widely accepted definition for the phenomenon. A number of contradictory etiologic hypotheses and therapeutic concepts are discussed. One of the different case definitions, etiologic and therapeutic concepts and of studies examining the frequency of psychiatric morbidity in patients with IEI. Additionally, a diagnostic algorithm and a concept of behavioral therapy for IEI/MCS patients with somatoform disorders are described.

(1999) [Idiopathic environmental intolerance (IPI)--formerly multiple chemical sensitivity (MCS)--from the psychiatric perspective].

The term "idiopathic environmental intolerances" (IEI)"multiple chemical sensitivities" (MCS) is used to describe a complex of heterogeneous somatic symptoms without a diagnosable organic disease. Symptoms are believed to be triggered by exposure to low levels of environmental chemicals that are usually well tolerated by the general population. There is no widely accepted definition for the phenomenon. A number of contradictory etiologic hypotheses and therapeutic concepts are discussed. One of the crucial questions is whether IEI/MCS should be understood as an own entity of disease. It has been demonstrated that a majority of patients with IEI/MCS meet diagnostic criteria for psychiatric diseases. Most frequently, somatoform, affective and anxiety disorders can be diagnosed. Therefore, psychiatric and psychotherapeutic therapy seems appropriate. The present paper provides a review of the different case definitions, etiologic and therapeutic concepts and of studies examining the frequency
of psychiatric morbidity in patients with IEI/MCS. Additionally, a diagnostic algorithm and a concept of behavioral therapy for IEI/MCS patients with somatoform disorders are described.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10327313


The multiple chemical sensitivities (MCS) syndrome is characterized by unexplained physical and psychiatric complaints attributed by patients and some of their physicians to low-level chemical exposures. In this study, we interviewed 15 subjects with MCS and 21 controls about their first-degree relatives using the Family History-Research Diagnostic Criteria (FH-RDC). Subjects with MCS were more likely than controls to report their relatives to have major depression, alcoholism, panic disorder, obsessive-compulsive disorder, and antisocial personality disorder. They were also likely to have past suicide attempts, and to have received some form of psychiatric treatment (hospitalization, medication or electroconvulsive therapy, or counseling). Nearly 30% of the relatives of subjects with MCS were reported to have MCS themselves. Possible reasons for the findings are discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416293


We sought to assess quality of life and health-services utilization variables in persons with symptoms suggestive of multiple chemical sensitivity/idiopathic environmental intolerance (MCS/IEI) among military personnel. We conducted a cross-sectional telephone survey of a population-based sample of Persian Gulf War (PGW) veterans from Iowa and a comparison group of PGW-era military personnel. A complex sample survey design was used, selecting subjects from four domains: PGW active duty, PGW National Guard/Reserve, non-PGW active duty, and non-PGW National Guard Reserve. Each domain was substratified by age, gender, race, rank, and military branch. The criteria for MCS/IEI were developed by expert consensus and from the medical literature. In the total sample, 169 subjects (4.6%) of the 3695 who
participated (76% of those eligible) met our criteria for MCS/IEI. Persons who met the criteria for MCS/IEI more often reported the following than did other subjects: more than 12 days in bed due to disability, Veteran's Affairs disability status, Veteran's Affairs disability compensation, medical disability, and unemployment. MCS/IEI cases also had higher outpatient rates of physician visits, emergency department visits, and inpatient hospital stays. Subjects who met the criteria for MCS/IEI more often reported impaired functioning on each Medical Outcomes Study 36-Item Short Form subscale, compared with those who did not meet the criteria. We concluded that although the diagnosis of MCS/IEI remains controversial, the persons who met our criteria for the disorder are functionally impaired.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10529949

(1999) [Neuroendocrine disorders cause stress-related disease. "Civilization syndrome" is a growing health problem].

Although the relationship between stress and serious diseases, such as ischaemic heart disease, is well known, the underlying mechanisms have proved difficult to identify. With a new technique available today, the hypothalamic-pituitary-adrenocortical axis can be shown to constitute a central physiological factor in the interplay between stress and disease. This technique opens up new diagnostic possibilities, and thus therapeutic and preventive options, in stress-related diseases which represent a growing health problem in modern society.


(1999) Patterns of waking EEG spectral power in chemically intolerant individuals during repeated chemical exposures.
Previous studies indicate that low level chemical intolerance (CI) is a symptom of several different controversial conditions with neuropsychiatric features, e.g., chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity, and "Persian Gulf Syndrome". Prior studies suggest that limbic and/or mesolimbic sensitization may contribute to development of CI. The purpose of this report was to document the waking electroencephalographic (EEG) patterns of individuals with CI during chemical exposures presented over repeated sessions. Three groups of adult subjects who were recruited from the community participated in the study: self-reported CI who had made associated lifestyle changes due to their intolerance (CI/ LSC), self-reported CI who had not made such changes (CI), and normal controls without self-reported CI.

Subjects underwent two sessions involving one-minute EEG recordings during exposures to low level chemical odors (a probe for limbic activation). The CI, but not the CI/ LSC, subjects had increased absolute delta power after the chemical exposures during the second, but not the first, session. The findings support the neural sensitization hypothesis for intolerance to low levels of environmental chemicals in vulnerable individuals. As in human studies of stimulant drug sensitization, those with the strongest past history with sensitizing agents may not show-term sensitization to low level exposures in the laboratory.


This paper summarizes theory and evidence for a neural sensitization model of hyperresponsivity to low-level chemical exposures in multiple chemical sensitivity (MCS). MCS is a chronic polysymptomatic condition in which patients report illness from low levels of many different, structurally unrelated environmental chemicals (chemical intolerance, CI). Neural sensitization is the progressive host amplification of a response over time from repeated, intermittent exposures to a stimulus. Drugs, chemicals, endogenous mediators, and exogenous stressors can all initiate sensitization and can exhibit cross-sensitization between different classes of stimuli. The properties of sensitization overlap much of the clinical phenomenology of MCS. Animal studies have demonstrated sensitization to toluene, formaldehyde, and certain pesticides, as well as cross-sensitization, e.g., formaldehyde and cocaine. Controlled human studies in persons with self-reported CI have shown heightened sensitizability in the laboratory to nonspecific experimental factors and to specific chemical exposures. Useful outcome measures include spectral electroencephalography, blood pressure, heart rate, and plasma beta-endorphin. Findings implicate, in part, dopaminergic mesolimbic pathways and limbic structures. A convergence of evidence suggests that persons with MCS or with low-level CI may share some characteristics.
with individuals genetically vulnerable to substance abuse: (a) elevated family histories of alcohol or drug problems; (b) heightened capacity for sensitization of autonomic variables in the laboratory; (c) increased amounts of electroencephalographic alpha activity at rest and under challenge conditions over time. Sensitization is compatible with other models for MCS as well. The neural sensitization model provides a direction for further systematic human and animal research on the physiological bases of MCS and CI.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416281

Bartha, L and al., e Journal/Arch Environ Health. 54: 147-9.

Consensus criteria for the definition of multiple chemical sensitivity (MCS) were first identified in a 1989 multidisciplinary survey of 89 clinicians and researchers with extensive experience in, but widely differing views of, MCS. A decade later, their top 5 consensus criteria (i.e., defining MCS as [1] a chronic condition [2] with symptoms that recur reproducibly [3] in response to low levels of exposure [4] to multiple unrelated chemicals and [5] improve or resolve when incitants are removed) are still unrefuted in published literature. Along with a 6th criterion that we now propose adding (i.e., requiring that symptoms occur in multiple organ systems), these criteria are all commonly encompassed by research definitions of MCS. Nonetheless, their standardized use in clinical settings is still lacking, long overdue, and greatly needed--especially in light of government studies in the United States, United Kingdom, and Canada that revealed 2-4 times as many cases of chemical sensitivity among Gulf War veterans than undeployed controls. In addition, state health department surveys of civilians in New Mexico and California showed that 2-6%, respectively, already had been diagnosed with MCS and that 16% of the civilians reported an "unusual sensitivity" to common everyday chemicals. Given this high prevalence, as well as the 1994 consensus of the American Lung Association, American Medical Association, U.S. Environmental Protection Agency, and the U.S. Consumer Product Safety Commission that "complaints [of MCS] should not be dismissed as psychogenic, and a thorough workup is essential," we recommend that MCS be formally diagnosed--in addition to any other disorders that may be present--in all cases in which the 6 aforementioned consensus criteria are met and no single other organic disorder (e.g., mastocytosis) can account for all the signs and symptoms associated with chemical exposure. The millions of civilians and tens of thousands of Gulf War veterans who suffer from chemical sensitivity should not be kept waiting any longer for a standardized diagnosis while medical research continues to investigate the etiology of their signs and symptoms.
(1999) [Role of positron emission tomography (PET) and single photon emission tomography (SPECT) in so-called "multiple chemical sensitivity"].
Bartenstein, P, Grunwald, F, Herholz, K, Kuwert, T, Tatsch, K, Sabri, O and Weiller, C
Journal/Nuklearmedizin. 38: 297-301.

Functional imaging with SPECT and PET is increasingly used to prove evidence for the existence of a syndrome "Multiple Chemical Sensitivity" (MCS) and plays a major role in legal trials to justify compensation for the exposure to solvents. This paper critically reviews the literature on the use of SPECT and PET for the determination of MCS. The authors come to the conclusion that the current data are not sufficient to justify the claim of the existence of such a syndrome. The low specificity of the observed PET and especially SPECT-findings makes it very difficult to establish a cause-result relationship and therefore makes the use of these methods in legal trials on this issue doubtful.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10599070

Bartell, SM, Lefebvre, G, Kaminski, G, Carreau, M and Campbell, K

BIOSIS COPYRIGHT: BIOL ABS. The comprehensive aquatic systems model (CASM) was adapted for estimating ecological risks posed by toxic chemicals in rivers, lakes, and reservoirs in Quebec, Canada. Populations of aquatic plants, invertebrates, and fish characteristic of these aquatic ecosystems were identified and generic food webs were constructed. Bioenergetics parameters that determine the growth dynamics of these populations were derived from published values for these same or similar species. Input values of light, water temperature, concentrations of dissolved nitrogen (N), phosphorus (P), and silica (Si) were constructed from available regional data or data from similar Canadian systems at similar latitudes. The model provides the capability to estimate the probability of changes in the biomass of multiple populations of primary producers and consumers as a function of the concentration of dissolved chemical contaminant. The CASM permits the evaluation of direct toxic effects, as well as indirect toxic effects that result from changes in competitive or predator-prey relations in complex aquatic food webs. Hypothetical risk assessments were constructed for pentachlorophenol, copper, mercury, and diquat dibromide in generalized rivers, lakes, and reservoirs in Quebec. Numerical sensitivity and uncertainty analyses were used to describe the relative contributions of direct and indirect toxic effects on overall ecological risks estimated for functional guilds of producers and consumers in these ecosystems. This aquatic ecosystem model may become one component in a decision support system for assessing ecological risks.

The term functional somatic syndrome has been applied to several related syndromes characterized more by symptoms, suffering, and disability than by consistently demonstrable tissue abnormality. These syndromes include multiple chemical sensitivity, the sick building syndrome, repetition stress injury, the side effects of silicone breast implants, the Gulf War syndrome, chronic whiplash, the chronic fatigue syndrome, the irritable bowel syndrome, and fibromyalgia. Patients with functional somatic syndromes have explicit and highly elaborated self-diagnoses, and their symptoms are often refractory to reassurance, explanation, and standard treatment of symptoms. They share similar phenomenologies, high rates of co-occurrence, similar epidemiologic characteristics, and higher-than-expected prevalences of psychiatric comorbidity. Although discrete pathophysiologic causes may ultimately be found in some patients with functional somatic syndromes, the suffering of these patients is exacerbated by a self-perpetuating, self-validating cycle in which common, endemic, somatic symptoms are incorrectly attributed to serious abnormality, reinforcing the patient's belief that he or she has a serious disease. Four psychosocial factors propel this cycle of symptom amplification: the belief that one has a serious disease; the expectation that one's condition is likely to worsen; the "sick role," including the effects of litigation and compensation; and the alarming portrayal of the condition as catastrophic and disabling. The climate surrounding functional somatic syndromes includes sensationalized media coverage, profound suspicion of medical expertise and physicians, the mobilization of parties with a vested self-interest in the status of functional somatic syndromes, litigation, and a clinical approach that overemphasizes the biomedical and ignores psychosocial factors. All of these influences exacerbate and perpetuate the somatic distress of patients with functional somatic syndromes, heighten their fears and pessimistic expectations, prolong their disability, and reinforce their sick role. A six-step strategy for helping patients with functional somatic syndromes is presented here.

Baldwin, CM, Bell, IR and O'Rourke, MK Journal/Toxicol Ind Health. 15: 403-9.

This is a community-based study of odor sensitivity and respiratory complaints for persons reporting asthma (n = 14/141), hay fever (n = 72/140), and chemical odor intolerance (CI) (n = 41/181). CI, a symptom of multiple chemical sensitivity (MCS), was determined from self-ratings of feeling 'moderately' to 'severely' ill using the
Chemical Odor Intolerance Index (CII). Index odors included perfume, pesticide, drying paint, new carpet odor, and car exhaust. Six additional odors [natural gas, disinfectants, chlorinated water, room deodorizers, and environmental tobacco smoke (ETS)] were also assessed in the health and environment survey. Asthmatics reported feeling 'frequently' to 'almost always' ill from the CII index odors of drying paint, new carpet odor, perfume, and cleaning agents compared to nonasthmatics. People with hay fever documented feeling 'frequently' to 'almost always' ill from pesticides, drying paint, and car exhaust compared to individuals without hay fever. The CI cited illness from air freshener, natural gas and chlorinated water, in addition to the index odors of perfume, paint, pesticides, new carpeting and auto exhaust. All three groups were significantly more likely to report feeling ill from ETS. People with asthma were significantly more likely to report lower lung complaints, such as wheeze and dyspnea. People with hay fever cited more chest tightness. The CI were significantly more likely to report upper and lower respiratory symptoms. Given this overlap in respiratory complaints, it could be that CI may serve to amplify these traditional immune-related disorders and/or suggest that having asthma or hay fever could make one more vulnerable to CI.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416292


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10221292


There is increasing evidence that human exposure to levels of chemicals once thought to be safe--or presenting insignificant risk--are, in fact, harmful. So-called low-level exposures are now known to be associated with adverse biological effects including cancer, endocrine disruption, and chemical sensitivity. This requires that we change both (1) the way we design research linking chemicals and health, and (2) the solutions we devise to address chemically caused injury. The new and emerging science of low-level exposure to chemicals requires appropriate social policy responses which include regulation of toxic substances, notification of those exposed, and compensation and reasonable accommodation to those affected. Research and social policy need to be focused towards two distinct groups: (1) those individuals who could become chemically intolerant as a result of an initiating exposure, and (2) those
individuals who have already become chemically intolerant and are now sensitive to chemicals at low levels.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10416295

-------------------------------------------------------------------------------------------------------------------------------------


Changes in both technology and international trade are altering the world economy and hence are affecting the demand and supply of labor and the nature of work and working conditions. New materials, faster and more powerful computers, electronic and mobile communications, alternative energy systems, miniaturization, robotics, and biotechnology pose new opportunities, problems, and challenges. The tremendous expansion in information-based technologies in both manufacturing and services has resulted in impressive increases in productivity and demand for new skills, but they also have brought about the displacement and de-skilling of some labor by capital, the lowering of wages, and the increase of contingent, part-time, and temporary work. Special populations, in particular, may be differentially impacted.

-------------------------------------------------------------------------------------------------------------------------------------


Multiple chemical sensitivity (MCS) is characterized by heightened self-reported sensitivity to extremely low concentrations of chemicals. It has numerous symptoms in common with the sick building syndrome, the Gulf War syndrome, and chronic fatigue. Despite much research, reproducible objective findings are lacking for MCS, as is a sound model to explain it. This paper proposes a 2-step model combining the needed epidemiologic terminology with that of psychophysiological activation and sensitization. It is suggested that different environmental stressors act as initiators. After initiation, the limbic system and other parts of the brain become sensitized and hyperreactive to environmental triggers. Odor acts as one important trigger. Future research should use more biological assessments in combination with environmental and psychosocial data and involve patient groups with similar symptoms, although diagnosed as suffering from different entities. The similarities and differences of patients with such entities need to be understood before the entities themselves can be understood, diagnosed, treated, and prevented.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10884155
(1999) [Multiple chemical sensitivities: case definition, etiology and relations to allergy, poisoning, psychogenic illness etc].

Multiple Chemical Sensitivities (MCS) have been defined as an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects; no single widely accepted test of physiologic function can be shown to correlate with symptoms (Cullen MR, 1987). The etiology of MCS is hypothesized as a toxicant-induced loss of tolerance to multiple chemicals with subsequent manifestation of multiple-organ symptoms triggered by low-level exposure to such chemicals. The involvement of multiple organs might be attributed to a neurogenic switching mechanism. The final diagnosis of MCS is to rely on provocation of symptoms in an exposure chamber by a double-blind method. Relations of MCS to allergy, poisoning, psychogenic illness, chemical sensitivity, idiopathic environmental intolerances etc. are discussed in terms of case definition and etiology of these disorders.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10540848


Acrylamide (35 mg kg(-1) body wt, i.p.) and mercuric chloride (1 mg kg(-1)body wt, i.m.) were administered as specific and non-specific toxins, respectively, to induce neurotoxicity in rats for a period of 10 days. Two different concentrations (35 and 70 mg kg(-1) body wt, i.p.) of lipoic acid were given as prophylactic therapy to mitigate the toxic neuropathies. Homogenates of cerebrum, cerebellum and sciatic nerves were used for the determination of the activities of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), neuron-specific enolase (NSE), hexokinase, phosphoglucoisomerase, aldolase and glucose-6-phosphatase. Inhibition of the activities of these glucose-metabolizing enzymes by the neurotoxins emphasizes the reduction in glucose utilization by the neural tissues to impart its normal function. The degree of inhibition of the enzymes varies with both of the toxins. Acrylamide seems to be a specific inhibitor of GAPDH and NSE, whereas the inhibition caused by HgCl(2) on the enzymes was more general. Enhanced activities of the enzymes indicate increased glucose utility on lipoate administration. This result may be due to the detoxifying potency and possibly due to the cofactor vitality of lipoate.

Many of the symptoms described in Sick Building Syndrome (SBS) and multiple chemical sensitivity (MCS) resemble the symptoms known to be elicited by airborne irritant chemicals. Irritation of the eye, nose, and throat is common to SBS, MCS, and sensory irritation (SI). Difficulty of breathing is often seen with SBS, MCS, and pulmonary irritation (PI). We therefore asked the question: can indoor air pollutants cause SI and/or PI? In laboratory testing in which mice breathed the dilute volatile emissions of air fresheners, fabric softeners, colognes, and mattresses for 1 h, we measured various combinations of SI and PI as well as airflow decreases (analogous to asthma attacks). Air samples taken from sites associated with repeated human complaints of poor air quality also caused SI, PI, and airflow limitation (AFL) in the mice. In previous publications, we have documented numerous behavior changes in mice (which we formally studied with a functional observational battery) after exposure to product emissions or complaint site air; neurological complaints are a prominent part of SBS and MCS. All together, these data suggest that many symptoms of SBS and MCS can be described as SI, PI, AFL, and neurotoxicity. All these problems can be caused by airborne irritant chemicals such as those emitted by common commercial products and found in polluted indoor air. With some chemical mixtures (e.g., emissions of some fabric softeners, disposable diapers, and vinyl mattress covers) but not others (e.g., emissions of a solid air freshener), the SI response became larger (2- to 4-fold) when we administered a series of two or three 1-h exposures over a 24-h period. Since with each exposure the intensity of the stimulus was constant yet the magnitude of the response increased, we concluded that there was a change in the sensitivity of the mice to these chemicals. The response was not a generalized stress response because it occurred with only some mixtures of irritants and not others; it is a specific response to certain mixtures of airborne chemicals. This is one of the few times in MCS research that one can actually measure both the intensity of the stimulus and the magnitude of the response and thus be allowed to discuss sensitivity changes. The changing SI response of the mice might serve as a model of how people develop increasing sensitivity to environmental pollutants. Intensive study of this system should teach us much about how people respond to and change sensitivity to airborne irritant chemicals.

This study included consecutive case histories and audiometry of 100 patients with hypersensitivity to sounds. There are several different conditions with the symptom of hypersensitivity to sounds. Hyperacusis is one of those and is seldom described in the literature. The term hyperacusis is often used synonymously with hypersensitivity to sound. We propose that there is a specific condition that could be termed hyperacusis. Hyperacusis is often elicited by loud sounds or by a number of other traumata or diseases. It is not typical of occupational noise exposure (with the exception of exposure to music). The typical patient is relatively young, the mean age being approximately 10 years less than for a population of patients with tinnitus or noise-induced hearing loss. In addition to hypersensitivity to sound, the patients often suffer from tinnitus (86%). Sounds are frequently painful and exposure to loud sounds worsens the condition for some time. The patients often have headaches. Pure tone audiograms show normal hearing or a slight high tone loss. The uncomfortable loudness level is markedly decreased, mostly less than 90 dB HL. Patients with hyperacusis may also be divided into those hypersensitive to the loudness of sounds with a decreased pure tone uncomfortable loudness level and those hypersensitive to certain specific sounds irrespective of loudness showing relatively high pure tone uncomfortable loudness levels and decreased uncomfortable loudness levels to specific sounds. With a careful history other conditions with the symptom of hypersensitivity to sound can be excluded.


An association between polyneuropathy and occupational exposure to trichloroethylene, trichloroethane, perchloroethylene, or similar solvents alone or in combination is controversial. We sought to determine whether workers previously diagnosed with solvent-induced toxic encephalopathy had objective evidence of polyneuropathy. Thirty railroad workers previously diagnosed with toxic encephalopathy were examined in the context of litigation against their employers. All described long-term occupational solvent exposure averaging 20 years in duration (range, 10 to 29 years) and producing acute intoxication on a regular basis. The diagnosis of subclinical or clinical polyneuropathy was established using a combination of symptoms, signs, and nerve conduction study (NCS) measures, consistent with standard clinical practice. Potential confounders were identified. NCS results were compared with historical controls, including unexposed workers matched by gender, age, and body mass index. Dose-response relationships were evaluated using simple linear and stepwise regression models. Three workers fulfilled clinical polyneuropathy criteria. The only worker fulfilling NCS criteria for confirmed clinical polyneuropathy had diabetes mellitus. Mean NCS values for most measures were similar to control values,
and existing differences in sensory amplitudes disappeared when compared with the matched control group. NCS measures were not significantly influenced by exposure duration or job title. Separation into groups on the basis of the presence or absence of polyneuropathy symptoms, previous diagnosis of polyneuropathy, disability status, and severity or type of encephalopathy did not demonstrate significant NCS differences. The complaints of these workers claiming neurotoxic injury from occupational solvent exposure are not explained by peripheral nervous system dysfunction.

(1999) **Gln --> Arg 191 polymorphism of paraoxonase and Parkinson's disease.**

We investigated the Gln --> Arg 191 polymorphism in paraoxonase (PON1) in St. Petersburg population, in three clinically differentiated groups of patients with Parkinson's disease (PD) and in the symptomatic tremor group. A new approach for Gln --> Arg 191 PON1 polymorphism genotyping is suggested. No significant differences in the groups studies as compared to the controls was observed.

(1999) **Idiopathic environmental intolerances.**
AAAAI Board Of, D Journal/Journal of Allergy and Clinical Immunology. 103: 36-40.

BIOSIS COPYRIGHT: BIOL ABS. IEI - also called environmental illness and multiple chemical sensitivities has been postulated to be a disease unique to modern industrial society in which certain persons are said to acquire exquisite sensitivity to numerous chemically unrelated environmental substances. The patient experiences wide-ranging symptoms, but evidence of pathology or physiologic dysfunction in such patients has been lacking in studies to date. Because of the subjective nature of the illness, an objective case definition is not possible. Allergic, immunotoxic, neurotoxic, cytotoxic, psychologic, sociologic, and iatrogenic theories have been postulated for both etiology and production of symptoms, but there is an absence of scientific evidence to establish any of these mechanisms as definitive. Most studies to date, however, have found an excess of current and past psychopathology in patients with this diagnosis. The relationship of these findings to the patient's symptoms is also not apparent.


Consensus criteria for the definition of multiple chemical sensitivity (MCS) were first identified in a 1989 multidisciplinary survey of 89 clinicians and researchers with extensive experience in, but widely differing views of, MCS. A decade later, their top 5 consensus criteria (i.e., defining MCS as [1] a chronic condition [2] with symptoms that recur reproducibly [3] in response to low levels of exposure [4] to multiple unrelated chemicals and [5] improve or resolve when incitants are removed) are still unrefuted in published literature. Along with a 6th criterion that we now propose adding (i.e., requiring that symptoms occur in multiple organ systems), these criteria are all commonly encompassed by research definitions of MCS. Nonetheless, their standardized use in clinical settings is still lacking, long overdue, and greatly needed--especially in light of government studies in the United States, United Kingdom, and Canada that revealed 2-4 times as many cases of chemical sensitivity among Gulf War veterans than undeployed controls. In addition, state health department surveys of civilians in New Mexico and California showed that 2-6%, respectively, already had been diagnosed with MCS and that 16% of the civilians reported an "unusual sensitivity" to common everyday chemicals. Given this high prevalence, as well as the 1994 consensus of the American Lung Association, American Medical Association, U.S. Environmental Protection Agency, and the U.S. Consumer Product Safety Commission that "complaints [of MCS] should not be dismissed as psychogenic, and a thorough workup is essential," we recommend that MCS be formally diagnosed--in addition to any other disorders that may be present--in all cases in which the 6 aforementioned consensus criteria are met and no single other organic disorder (e.g., mastocytosis) can account for all the signs and symptoms associated with chemical exposure. The millions of civilians and tens of thousands of Gulf War veterans who suffer from chemical sensitivity should not be kept waiting any longer for a standardized diagnosis while medical research continues to investigate the etiology of their signs and symptoms.


In a bid to provide better protection for children's health, U.S. Senators Barbara Boxer (D-California) and Frank Lautenberg (D-New Jersey) introduced the Children's Environmental Protection Act (CEPA), on 24 May 1999. CEPA is an amendment to the Toxic Substances Control Act of 1976 and seeks to protect children from exposures to hazardous substances such as toxic air pollutants and pesticides sprayed in schools. The act would also provide parents with the information necessary to make decisions about how to protect their children against such health threats.


(1999) Climate-controlled disease?

Children are exposed to potentially carcinogenic pesticides from use in homes, schools, other buildings, lawns and gardens, through food and contaminated drinking water, from agricultural application drift, overspray, or off-gassing, and from carry-home exposure of parents occupationally exposed to pesticides. Parental exposure during the child's gestation or even preconception may also be important. Malignancies linked to pesticides in case reports or case-control studies include leukemia, neuroblastoma, Wilms' tumor, soft-tissue sarcoma, Ewing's sarcoma, non-Hodgkin's lymphoma, and cancers of the brain, colorectum, and testes. Although these studies have been limited by nonspecific pesticide exposure information, small numbers of exposed subjects, and the potential for case-response bias, it is noteworthy that many of the reported increased risks are of greater magnitude than those observed in studies of pesticide-exposed adults, suggesting that children may be particularly sensitive to the carcinogenic effects of pesticides. Future research should include improved exposure assessment, evaluation of risk by age at exposure, and investigation of possible genetic-environment interactions. There is potential to prevent at least some childhood cancer by reducing or eliminating pesticide exposure.

Young, RS, Jones, AM and Nicholls, PJ Journal/J Pharm Pharmacol.  50: 11-7.  

This review provides a clear explanation of the current status of two common airborne contaminants, lipopolysaccharide and (1-->3)-beta-D-glucan, in the induction of indoor air-related disease. A full description of the origin of these two products is given together with information of their structure and function. Details of the biochemical mechanisms by which they interact with human cells and the physiological consequences of these interactions are outlined. Both compounds play a key role in the induction of airway inflammation and this paper highlights the environmental importance in the work place and home of these inhaled agents in terms of respiratory disease.


A group of operating room personnel at a medical center in Connecticut reported severe respiratory irritation manifested by either proxysmal cough or throat irritation suggestive of a noxious fume exposure, 13 April 1994. However, persistent complaints on 14 April 1994 were significantly different and more suggestive of a psychological reaction. By careful interviewing, physical examination, toxicological assays, and epidemiological investigation, the true nature of a mixed physiological and
psychological episode was delineated. Enlightened management policy enabled rapid restoration of return to work with minimal economic loss.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9542287


This study shows that activation of M1 muscarinic receptors, when coexpressed in Chinese hamster ovary (CHO)-K1 cells with neuronal nitric oxide (NO) synthase (nNOS), produces early and late phases of elevation of both intracellular Ca2+ concentration and nNOS activity. We examined the relationship between receptor-mediated increases in intracellular Ca2+ concentration and activation of nNOS over both short and long intervals using guanosine 3',5'-cyclic monophosphate (cGMP) formation as a measure of nNOS activity. The rapid phase of nNOS activation was dependent on release of Ca2+ from intracellular stores in both the CHO M1/nNOS transfected cells and in neuroblastoma (N1E-115) cells, in which muscarinic receptors and nNOS are endogenously expressed. Two single point mutations in the M1 muscarinic receptor that have previously been shown to uncouple differentially the receptor from phosphoinositide hydrolysis produced parallel attenuation of the rapid phase of nNOS activation. Characterization of the prolonged phase of nNOS activation was done using the conversion of L-[3H]arginine to L-[3H]citrulline as well as cGMP formation following stimulation of M1 muscarinic receptors for 60 min. Both responses were dependent on influx of extracellular Ca2+ and were accompanied by prolonged formation of NO at functionally effective levels as late as 60 min following receptor activation. Therefore, this study demonstrates for the first time the existence of two mechanistically distinct phases of nNOS activation that are dependent on different sources of Ca2+.


Multiple chemical sensitivity (MCS) has been described as an acquired multiple organ disease typically characterized by central nervous irritative and/or gastrointestinal symptoms. Advocates of this suspected syndrome attribute these disorders to overstressing of the organism caused by exposure to external noxae. Opponents of the theory of MCS attribute all the symptoms to classical conditioning or other psychopathological processes. In so far as controlled data exist, there is no indication of a toxic or immunological cause for this syndrome.

Whiteside, TL and Friberg, D Journal/The American Journal of Medicine. 105: 27S-34S.

Chronic fatigue syndrome (CFS) is associated with insidious and persistent immunologic abnormalities that have proved difficult to reproduce. The heterogeneity of CFS, the variable quality of immunologic assays and their performance, along with an almost complete absence of longitudinal studies of cellular immune abnormalities in CFS may explain this difficulty. However, in a significant proportion of cases, low levels of natural killer (NK) cell activity have been reported. This article will explore the mechanisms responsible for low NK cell activity, discuss the relation between levels of NK cell activity and health/disease, describe new findings on NK cell-brain interactions, and put forth a specific hypothesis for the role of NK cells in the pathogenesis of CFS.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-7/242ab3dab1f0f72fe8ee87eb7bf4a05b9

White, RF Journal/Govt Reports Announcements & Index. NTIS ADA347712, Product re.

TD3: Persian Gulf War (PGW) veterans have reported a constellation of health symptoms referred to as Gulf War Syndrome. Suggested causes of these symptoms include exposure to environmental hazards and biological or chemical warfare agents. Some of the symptoms reported overlap with those of post-traumatic stress disorder (PTSD), multiple chemical sensitivity (MCS) or chronic fatigue syndrome (CFS). Both exposure to neurotoxicants and the disorders noted above are known to produce cognitive impairments. This study evaluates the neuropsychological functioning of PGW era veterans who are seeking treatment or evaluation for any type of health or adjustment complaint. PGW deployed patients will be compared with non-deployed patients. These subjects will also be compared with subjects from a (non-treatment
seeking) research sample of PGW veterans. All patients and research subjects will additionally be administered a standardized set of questionnaires and interviews to identify their health symptoms inclu

------------------------------------------------------------------------------------------------------------------


Chemical sensitivity Syndromes refers to aggregations of symptoms marked by largely subjective neurobehavioral complaints and hypothesized links to immune system dysfunction. The entities reviewed here consist of the Multiple Chemical Sensitivity Syndrome, the Sick Building Syndrome, the Chronic Fatigue Syndrome, and the Gulf War Syndrome. Except for the Chronic Fatigue Syndrome, toxic chemical exposures are accorded a significant role in their etiology. The connections are ambiguous because of the variety of chemical agents cited and, for the most part, the relatively low levels at which exposures occur. Conventional clinical signs are also typically lacking. Explanatory mechanisms include psychiatric diagnoses such as somatization, behavioral mechanisms such as conditioning and generalization, neuropharmacological mechanisms such as sensitization, and psychoneuroimmunological mechanisms such as those involving the hypothalamic-pituitary-adrenal axis. Laboratory animal experimentation and controlled clinical trials, especially with inhaled material, provide the means for exploring the proffered explanations.


----------------------------------------------------------------------


OBJECTIVE: To determine whether physiological severity of asthma is associated with increased psychological symptoms in children. METHOD: Participants were 337 children, aged 7 to 19 years (mean 11.9, SE 0.13), and a parent of each child. Children's asthma severity was rated by experienced pediatric asthma specialists using current guidelines from the National Heart, Lung, and Blood Institute. Children filled out the Children's Manifest Anxiety Scale and the Weinberger Adjustment Inventory. Parents reported on their child's medical history, completed the Child Behavior Checklist (CBCL) about their child, and completed the Pennebaker Inventory of Linguid Languidness as a measure of their own physical symptoms. RESULTS: Child-rated anxiety symptoms were unrelated to asthma severity or to markers of asthma functional morbidity. Parental ratings of internalizing symptoms in their children were
related to severity. Parent physical symptoms explained 10.2% of the variance in CBCL Internalizing symptoms, and asthma severity added an additional 6.7% to the variance. CONCLUSIONS: Asthma severity may be a more salient stressor to parents, who in turn report higher levels of child internalizing symptoms for children with severe asthma, than to children themselves. Contrary to prior hypotheses, children with severe asthma did not rate themselves as having higher levels of anxiety than those with mild or moderate asthma or than standardized norms.


(1998) **Putting chemical and environmental sensitivities in perspective.**

Chemical sensitivity has been recognized for an extended period. Over the last 30 years or more, there has been a growing number of chemicals to which humans are being exposed. Some people have become sensitive to one or more of these chemicals and present this sensitivity in a wide variety of signs or symptoms. Single or multiple organ systems may become involved. This article is intended to give an overview on the existence and recognition of chemical sensitivities and how they may be diagnosed and treated. The important item is to educate physicians to the existence of chemical sensitivity and to consider this in their differential diagnosis when the patient presents with the signs, symptoms, or clinical pattern that is explained.


(1998) **Environmental control to maintain stabled COPD horses in clinical remission: effects on pulmonary function.**

The objective of this study was to test the hypothesis that stabled COPD horses can be maintained in clinical remission by replacing hay by grass silage and bedding made of wood shavings (Period B) and of wheat straw (Period C) during 6 weeks, respectively. At the end of these different periods, the pulmonary function of the horses was assessed by mechanics of breathing and arterial blood analyses. These results were compared to those measured in clinical remission obtained after 2 months in pasture (Period A). No significant difference was observed between these 3 periods neither to values obtained for healthy horses placed during 6 weeks in a hay environment. For all that, COPD horses placed in contact with hay in the same barn developed within mean
+/- s.d. 8+/−3 days clinical signs of heaves and significant alterations of pulmonary function parameters.


Multiple chemical sensitivity (MCS) is a controversial disorder of uncertain etiology, characterized by recurrent symptoms referable to multiple organ systems, occurring as a response to chemically unrelated compounds at doses far below those established to cause harmful effects in the general population. The fundamental question is whether the MCS is primarily a toxicodynamic phenomenon (a pathological interaction between a chemical agent and organ systems, possibly acting through a mechanism different from those known in toxicology) or a psychogenic disorder (an emotional reaction to perceived toxic agents). This paper presents some recent theories of etiopathogenesis of the MCS discussing the role of immunological, inflammatory, metabolic, psychophysiological, and neurochemical mechanisms, as well as the role of neural sensitization in the etiology of the disorder. The paper foregrounds the complex relation between psychiatric disorders and social factors, on one hand, and the MCS on the other. A particular emphasis is put on the relevance of the MCS research for clinical practice, public health, and regulatory decisions.


Nitric oxide (NO) production in macrophages by inducible nitric oxide synthase (NOS2) has multiple tissue damaging effects and is involved in the pathogenesis of inflammation and graft rejection. Haem oxygenase (HmOx) is the enzyme which degrades haem. Its inducible isoform, HmOx1, was recently shown to increase cellular resistance against oxidative stress and to decrease inflammation and graft rejection. Since haem is an essential cofactor for NOS2 activity, we investigated the effects of HmOx1-induction upon NO secretion in macrophages. We induced HmOx1 in BALB/c bone-marrow-derived macrophages by short-term exposure to haem (20 micromol/l, 30 min); then we incubated them for 24 h to allow maximal expression of HmOx1 activity. Next, we activated the macrophages with lipopolysaccharide (LPS) and measured their NO production and their NO-dependent cytotoxicity against P815 cells. We found that HmOx induction 24 h before LPS activation in mouse macrophages
suppresses their production of NO, while HmOx inhibition (with zinc protoporphyrin) increases NO secretion. NOS2 inhibition is reflected by the decrease of macrophage NO-dependent cytotoxicity against the P815 targets. We therefore propose that HmOx1 is a physiological inhibitor of NOS2 in activated macrophages because it decreases haem availability for NOS2 synthesis. NOS2 inhibition may explain the antinflammatory effects of HmOx induction which could also be used therapeutically in situations when NO hyperproduction leads to cytotoxic effects such as inflammation or transplant rejection.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9851535
---------------------------------------------------------------

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9865340
---------------------------------------------------------------
(1998) Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data.

Chronic fatigue syndrome (CFS) has been widely studied by neuroimaging techniques in recent years with conflicting results. In particular, using single-photon emission computed tomography (SPECT) and perfusion tracers, hypoperfusion has been found in several brain regions, although the findings vary across research centers. The objective of this study was to investigate brain metabolism of patients affected by CFS, using [18F]fluorine-deoxyglucose (18FDG) positron emission tomography (PET). We performed 18FDG PET in 18 patients who fulfilled the criteria of the working case definition of CFS. Twelve of the 18 patients were females; the mean age was 34 +/- 15 years (range, 15-68) and the median time from CFS diagnosis was 16 months (range, 9-138). Psychiatric diseases and anxiety/neurosis were excluded in all CFS patients. CFS patients were compared with a group of 6 patients affected by depression (according to DSM IV-R) and 6 age-matched healthy controls. The CFS patients were not taking any medication at the time of PET, and depressed patients were drug-free for at least 1 week before the PET examination. The PET images examined 22 cortical and subcortical areas. CFS patients showed a significant hypometabolism in right midofrontal cortex (P = 0.010) and brainstem (P = 0.013) in comparison with the healthy controls. Moreover, comparing patients affected by CFS and depression, the
latter group showed a significant and severe hypometabolism of the medial and upper frontal regions bilaterally (P = 0.037-0.001), whereas the metabolism of brain stem was normal. Brain 18FDG PET showed specific metabolism abnormalities in patients with CFS in comparison with both healthy controls and depressed patients. The most relevant result of our study is the brain stem hypometabolism which, as reported in a perfusion SPECT study, seems to be a marker for the in vivo diagnosis of CFS.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-C/286f1957d62c4b0d8585c2cc716164b15


Multiple chemical sensitivities (MCS) is a chronic condition of irritation and inflammation of sensory organs, gastrointestinal distress, fatigue, and compromised neurological function, including learning and memory deficits, unpleasant smells, tingling of nerves, and sensory discomfort. Victims report these symptoms after exposure to unfamiliar chemicals. Some studies have linked MCS to immune system dysregulation. MCS is believed to be a disease that spreads between various target organs, and is caused by sensitization to chemicals with very different structures. MCS is often attributed to free radical production and stress, which indirectly cause spreading because of damage to the immune system.


Asthma is a common disease affecting approximately 5 percent of the population and is a major cause of disability. Research interest in the condition is high because of frequent reports that the incidence, prevalence, severity, and mortality rates have been rising in recent years. Although the etiology remains elusive, knowledge about its pathophysiology is extensive and detailed, which in turn has spawned an impressive array of effective and safe drugs to prevent and treat acute exacerbations. Pharmacotherapy is enhanced by appropriate environmental control measures and immunotherapy for the significant number of asthmatics with an allergic component to their disease. The pregnant asthmatic may pose special requirements for the small minority with severe corticosteroid-dependent disease or those subject to frequent attacks. However, the great majority of asthmatic women need not face much risk of adverse effects on the course of the pregnancy or significant fetal or perinatal abnormalities, as long as appropriate preventive measures and monitoring are taken.

This study aimed to determine symptom patterns in patients with chronic fatigue syndrome (CFS), in summer and winter. Comparison data for patients with seasonal affective disorder (SAD) were used to evaluate seasonal variation in mood and behavior, atypical neurovegetative symptoms characteristic of SAD, and somatic symptoms characteristic of CFS. Rating scale questionnaires were mailed to patients previously diagnosed with CFS. Instruments included the Personal Inventory for Depression and SAD (PIDS) and the Systematic Assessment for Treatment Emergent Effects (SAFTEE), which catalogs the current severity of a wide range of somatic, behavioral, and affective symptoms. Data sets from 110 CFS patients matched across seasons were entered into the analysis. Symptoms that conform with the Centers for Disease Control and Prevention (CDC) case definition of CFS were rated as moderate to very severe during the winter months by varying proportions of patients (from 43% for lymph node pain or enlargement, to 79% for muscle, joint, or bone pain). Fatigue was reported by 92%. Prominent affective symptoms included irritability (55%), depressed mood (52%), and anxiety (51%). Retrospective monthly ratings of mood, social activity, energy, sleep duration, amount eaten, and weight change showed a coherent pattern of winter worsening. Of patients with consistent summer and winter ratings (n = 73), 37% showed high global seasonality scores (GSS) >=10. About half this group reported symptoms indicative of major depressive disorder, which was strongly associated with high seasonality. Hierarchical cluster analysis of wintertime symptoms revealed 2 distinct clinical profiles among CFS patients: (a) those with high seasonality, for whom depressed mood clustered with atypical neurovegetative symptoms of hypersomnia and hyperphagia, as is seen in SAD; and (b) those with low seasonality, who showed a primary clustering of classic CFS symptoms (fatigue, aches, cognitive disturbance), with depressed mood most closely associated with irritability, insomnia, and anxiety. It appears that a subgroup of patients with CFS shows seasonal variation in symptoms resembling those of SAD, with winter exacerbation. Light therapy may provide patients with CFS an effective treatment alternative or adjunct to antidepressant drugs.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-R/2
bca0f329a08c1876baaa5dbd5cc9f51f

(1998) Assessing adherence to a rotary diversified diet, a treatment for 'environmental illness'.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-R/2
bca0f329a08c1876baaa5dbd5cc9f51f
OBJECTIVES: To develop and test a method to assess adherence to a rotary diversified diet (RDD), a treatment for environmental illness, which is a putative disorder characterized by multiple sensitivities to foods, chemicals, or inhalants. The RDD requires the elimination of prohibited foods and rotation of remaining nonprohibited foods and their "food families" within a 4- to 7-day cycle. The regimen has yet to be validated to the satisfaction of the scientific community. DESIGN: Details of the 2 components of the RDD prescription, elimination and rotation, were documented, and a food record method of assessing adherence was developed. Adherence to the RDD was then assessed in a cohort of women who were enrolled in a larger prospective study. Test-retest reliability of the adherence assessment method was determined by calculating ratings twice on the same set of patient food records, with 1 week between trials. SUBJECTS/SETTING: All patients were contacted through a private environmental medicine clinic in Toronto, Canada. Eight patients provided the food records needed for development of the method; adherence was then assessed in 22 women aged 25 to 67 years. STATISTICAL ANALYSES: Means, standard deviations, and 95% confidence intervals for adherence ratings were calculated. The reliability of the adherence assessment method was determined by calculating Pearson correlation coefficients for adherence ratings from each trial. A paired t test was also used to determine if the mean differences in ratings between trials were significant. RESULTS: Patients experienced difficulties following both components of the RDD: 37% to 44% of foods consumed were either prohibited or allowed, but were consumed on the incorrect day. The adherence assessment method was found to have high levels of reliability. APPLICATIONS: The adherence assessment method can be used in future evaluations of the RDD, although further testing of the method is recommended. Increased involvement of dietitians with patients diagnosed with environmental illness is recommended.


The inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine directly cause an increase in conductance to Cl- by binding to ligand-operated ion channel receptors at the postsynaptic membranes, so that opening of Cl- channels usually leads to a net hyperpolarization. The GABA(A) receptor has separate but allosterically interacting binding sites for GABA, benzodiazepines, barbiturates, anesthetic steroids and the convulsant picrotoxinin. The GABA(C) receptor also forms a Cl- channel, however its pharmacology differs from that of the GABA(A) receptor. Neurotoxic organochlorine pesticides belonging to the group of polychlorocycloalkanes (cyclodienes and gamma-hexachlorocyclohexane or lindane) induce in mammals an hyperexcitability syndrome that can progress until the production of tonic-clonic
convulsions. They act as non-competitive GABA antagonists interacting with the picrotoxinin site both in membranes and in intact cultured neurons, thereby inhibiting the GABA-induced Cl- flux following activation of either GABA(A) or GABA(C) receptors. We also report the effects of polychlorocycloalkanes on glycine-induced 36Cl- flux in primary neuronal cultures. The delta isomer of hexachlorocyclohexane is a depressant compound, that increases the GABA-induced Cl- flux and allosterically increases benzodiazepine binding at the GABA(A) receptor. We discuss the mechanism of action of these compounds in relation to the disruption of ligand-operated Cl- channel receptors and the relevance of their convulsant/depressant actions.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9745914

Stenn, PG and Binkley, K Journal/Psychosomatics. 39: 393-4.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9691712

Stenn, P and Binkley, K Journal/Psychosomatics. 39: 547-50.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9819957


Despite considerable research on chronic fatigue syndrome (CFS) and conditions associated with unexplained chronic fatigue (CF), little is known about their prevalence and demographic distribution in the population. The present study describes the epidemiology and characteristics of self-reported CF and related conditions in a diverse urban community. The study used a cross-sectional telephone screening survey of households in San Francisco, followed by interviews with fatigued and nonfatigued residents. Respondents who appeared to meet case definition criteria for CFS, based
on self-reported fatigue characteristics, symptoms, and medical history, were classified as CFS-like cases. Subjects who reported idiopathic chronic fatigue (ICF) that did not meet CFS criteria were classified as ICF-like cases. Screening interviews were completed for 8,004 households, providing fatigue and demographic information for 16,970 residents. Unexplained CF was extremely rare among household residents <18 years of age, but was reported by 2% of adult respondents. A total of 33 adults (0.2% of the study population) were classified as CFS-like cases and 259 (1.8%) as ICF-like cases. Neither condition clustered within households. CFS- and ICF-like illnesses were most prevalent among women and persons with annual household incomes below $40,000, and least prevalent among Asians. The prevalence of CFS-like illness was elevated among African Americans, Native Americans, and persons engaged in clerical occupations. Although CFS-like cases were more severely ill than those with ICF-like illness, a similar symptom pattern was observed in both groups. In conclusion, conditions associated with unexplained CF occur in all sociodemographic groups but appear to be most prevalent among women, persons with lower income, and some racial minorities.

e9faeb06d49cc77c94e9d3c991a1a507

(1998) Repeated low-level formaldehyde exposure produces cross-sensitization to cocaine: possible relevance to chemical sensitivity in humans.

Sensitivity to chemicals in humans has been proposed to be an acquired disorder in which individuals become increasingly sensitive to chemicals in the environment. A possible link between the manifestation of psychiatric symptoms in individuals claiming sensitivity to chemicals was investigated based on a leading hypothesis put forth by Bell and co-workers (1992) to explain the amplification of symptoms after chemical exposure. The hypothesis is that chemical sensitivities may be akin to sensitization observed in rodents after repeated psychostimulants. Repeated exposure to psychostimulants enhances behavioral activity and the underlying neurochemical responses in specific limbic pathways; a similar sensitization of limbic pathways has been proposed to occur in individuals who become sensitive to chemicals. To test this hypothesis, female Sprague-Dawley rats were exposed to either air or formaldehyde (Form) for 1 h/day for 7 days or 20 days (5 days/week x 4 weeks). Two to 4 days after the last exposure, rats were given a cocaine challenge (= early withdrawal) followed by an additional cocaine challenge 4-6 weeks later (= late withdrawal). No differences in cocaine-induced locomotor activity were noted between groups after 7 days of exposure. However, after 20 days of exposure to Form, vertical activity was significantly elevated at both early and late withdrawal times. These studies demonstrate that behavioral sensitization occurs after long-term, but not short-term,
low-level exposure to Form, and lends support to the limbic system sensitization hypothesis of sensitivity to chemicals in humans.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9536452


The forensic psychiatrist must be able to perform a credible psychiatric evaluation and render a competent psychiatric opinion in hotly contested multiple chemical sensitivity (MCS) litigation. Forensic psychiatrists are often requested to evaluate MCS claimants by third party payers, employers, lawyers, and government agencies regarding health care costs and disability payments, workers’ compensation claims, unemployment benefits, workplace accommodation reimbursements for special housing and environmental needs, civil litigation, and other claims. The credible forensic psychiatric evaluation of MCS litigants is described using the multiaxial diagnostic system of DSM-IV. Forensic psychiatrists must avoid becoming polarized by the current MCS controversy. The ethical requirements of honesty and striving for objectivity can be met by keeping separate the roles of therapist and expert, staying abreast of the scientific literature regarding MCS, and understanding the role of the psychiatric expert in MCS litigation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9785280

(1998) [Topical problems in the study of the influence of environmental factors on the health of the population].
Sidorenko, GI, Rumiantsev, GI and Novikov, SM Journal/Gig Sanit. 3-8.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9721494

Cognitive behavior therapy (CBT) is a form of nonpharmacologic treatment. It is based on a model of chronic fatigue syndrome (CFS) that hypothesizes that certain cognitions and behavior may perpetuate symptoms and disability—that is, act as obstacles to recovery. Treatment emphasizes self-help and aims to help the patient to recover by changing these unhelpful cognitions and behavior. There is now good evidence from 2 independent randomized clinical trials to support the efficacy of CBT in patients with CFS. The treatment effect is substantial, although few patients are cured. The urgent clinical need is to make this form of treatment available to patients with CFS. One approach is to incorporate the principles of CBT into routine clinical practice. The preliminary evaluation of these simpler forms of CBT are promising, although the results of controlled trials are awaited. At present, intensive individual CBT administered by a skilled therapist remains the treatment of choice for patients with CFS.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-N/2
c76422004af076a8b58b322634fabb6

(1998) Another vicious cycle?
Serb, C Journal/Hosp Health Netw. 72: 24-8, 30, 3.

Just when HMOs seemed to break the old indemnity underwriting cycle, along came last year's landslide losses. Now analysts see a more deliberate pattern shaping up: When profits soar, marketers win rate cuts. When the bottom line finally bottoms out, underwriters prevail--and rate hikes follow.

(1998) Capsaicin receptors mediate free radical-induced activation of cardiac afferent endings.

OBJECTIVE: The effects of capsaicin on sensory neurons are mediated by its interaction with a specific membrane receptor and opening of a non-selective cation channel. In the rat heart, capsaicin-sensitive nerve endings are known to be activated by oxygen radicals. We investigated the possibility that free oxygen radicals stimulate sensory nerve endings by acting upon the capsaicin receptor. METHODS: We studied the effects of capsaicin (0.16-16.0 nmol), bradykinin (0.1-10 nmol), H2O2 (1.5-30 mumol), and xanthine + xanthine oxidase (X + XO, 1 mumol + 0.03 mU) applied to the surface of the rat heart for 30 s on the activity of cardiac, capsaicin-sensitive, vagal and sympathetic afferent fibers before and after blockade of capsaicin receptors with capsazepine (200 micrograms/kg, i.v.), a specific antagonist for the capsaicin receptor. RESULTS: Application of capsaicin (0.32-16.0 nmol), H2O2 (9-30 mumol), bradykinin (1-10 nmol), and X + XO increased cardiac vagal and sympathetic afferent activity.
Administration of capsazepine had no effect on the baseline activity of either vagal or sympathetic cardiac afferents, but it abolished the response of the afferent fibers to all doses of capsaicin, H2O2, and X + XO tested. Capsazepine had no effect on afferent activation by bradykinin. Administration of another capsaicin receptor blocker, ruthenium red (780 micrograms/kg, i.v.), had similar effects. CONCLUSIONS: The results of these experiments indicate that blockade of capsaicin receptors inhibits activation of vagal and sympathetic cardiac afferent fibers by free oxygen radicals. The fact that capsazepine and ruthenium red did not affect the afferent response to bradykinin suggests that this effect of the blockers was specific for capsaicin receptors. The possible functional implications of this interaction are discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9709395


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9832475


In the International Drinking Water Supply and Sanitation Decade (1981-90), the development of a consensus on the concept of sanitation and the planning and implementation of effective and efficient sanitation programmes was not emphasized. Yet lack of good sanitation is a growing burden and environmental threat. Significant improvement of human health cannot be achieved without good environmental sanitation conditions and practices. A consensus on what makes a sanitation programme successful can help to conserve limited funds and spend those available more wisely. It will also help to reduce the increasing flows of waste poisoning precious sources of drinking water. This article was written to stimulate discussion on what attributes can be taken as characteristic of good environmental sanitation programmes, and on which indicators can be used to assess those attributes in actual sanitation programmes.

(1998) Positive perceptions of parental caring are associated with reduced psychiatric and somatic symptoms.

OBJECTIVE: In a previous 35-year follow-up investigation to the Harvard Mastery of Stress Study, positive ratings of parental caring obtained in healthy male college students were found to be predictive of substantially reduced disease incidence (including cardiovascular disease, ulcers, and alcoholism) in mid-life. The present cross-sectional study examined the relationship between perceptions of parental caring, current psychiatric and somatic symptoms, and defensiveness, in a University of Arizona sample of females and males. METHOD: The Harvard Parental Caring Scale (HPCS), the SCL90R, and the Marlowe-Crowne (MC) scale (a measure of defensiveness) were administered to 398 students at the University of Arizona. RESULTS: Cronbach alphas were .83 for HPCS ratings of mothers and .88 for fathers. High HPCS ratings were associated with reduced symptoms reports in both females and males (p < .00002). Ratings of HPCS showed a small correlation with defensiveness (r = .141). The relationship between HPCS and symptoms was strongest in the least defensive subjects. CONCLUSIONS: Positive perceptions of love and caring from parents, typically the most important source of social support for children, are associated with reduced psychiatric and somatic symptoms. Defensiveness may play a protective role psychologically (but not necessarily physiologically) in reducing the conscious awareness of symptoms accompanying low perceptions of parental love and caring.

Rowe, PC and Calkins, H Journal/The American Journal of Medicine.  105: 15S-21S.

A substantial body of clinical evidence now supports an association between various forms of hypotension and both idiopathic chronic fatigue and the chronic fatigue syndrome (CFS). Patients with CFS have a high prevalence of neurally mediated hypotension, and open treatment of this autonomic dysfunction has been associated with improvements in CFS symptoms. Randomized trials are now in progress to evaluate the efficacy of treatments directed at neurally mediated hypotension in those with CFS patients, and the results of these trials should help guide more basic inquiries into the mechanisms of orthostatic intolerance in affected individuals.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-5/2dbfb338c4c26e656b2f096df4239a1

The central nervous, immune, and endocrine systems communicate through multiple common messengers. Over evolutionary time, what may be termed integrated defense system(s) (IDS) have developed to coordinate these communications for specific contexts; these include the stress response, acute-phase response, nonspecific immune response, immune response to antigen, kindling, tolerance, time-dependent sensitization, neurogenic switching, and traumatic dissociation (TD). These IDSs are described and their overlap is examined. Three models of disease production are generated: damage, in which IDSs function incorrectly; inadequate/inappropriate, in which IDS response is outstripped by a changing context; and evolving/learning, in which the IDS learned response to a context is deemed pathologic. Mechanisms of multiple chemical sensitivity (MCS) are developed from several IDS disease models. Model 1A is pesticide damage to the central nervous system, overlapping with body chemical burdens, TD, and chronic zinc deficiency; model 1B is benzene disruption of interleukin-1, overlapping with childhood developmental windows and hapten-antigenic spreading; and model 1C is autoimmunity to immunoglobulin-G (IgG), overlapping with spreading to other IgG-inducers, sudden spreading of inciters, and food-contaminating chemicals. Model 2A is chemical and stress overload, including comparison with the susceptibility/sensitization/triggering/spreading model; model 2B is genetic mercury allergy, overlapping with: heavy metals/zinc displacement and childhood/gestational mercury exposures; and model 3 is MCS as evolution and learning. Remarks are offered on current MCS research. Problems with clinical measurement are suggested on the basis of IDS models. Large-sample patient self-report epidemiology is described as an alternative or addition to clinical biomarker and animal testing.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9539008


This review is intended to provide the reader with an overview of the all-purpose topical insect repellent N,N-diethyl-3-methylbenzamide (deet), with emphasis on its pharmacokinetics, formulation, and safety aspects. N,N-diethyl-3-methylbenzamide is effective against a variety of mosquitoes, flies, fleas, and ticks, and its protection efficacy depends on factors such as type of formulation, application pattern, physical activity of the user, environment, and species and feeding behavior of the insects. It offers an inexpensive and practical means of preventing the attack of biting insects and, more importantly, the transmission of vector-borne diseases. In both humans and animals, deet skin penetration and biodistribution are rapid and extensive, and metabolism and elimination appear to be complete. As evidenced by over 4 decades of human experience and rigorous animal testing, deet is generally safe for topical use if applied as recommended, although it has occasionally been related to side effects.
such as toxic encephalopathy, seizure, acute manic psychosis, cardiovascular toxicity, and dermatitis, along with a few cases of death due to extensive skin absorption. N,N-diethyl-3-methylbenzamide may compete in metabolism with and alter the biodistribution properties of other compounds to which a subject is simultaneously exposed, resulting in an added risk of side effects. The appropriate use of formulation techniques and new formulation excipients not only offers a way to extend the duration of protection, but also reduces deet skin penetration. In addition to extended repellency, minimal skin penetration of deet should be an important consideration in the evaluation of a deet formulation during new product development.


The purpose of this study was to determine if Gulf War veterans with complaints of severe fatigue and/or chemical sensitivity (n = 72) fulfill case definitions for chronic fatigue syndrome (CFS) and/or multiple chemical sensitivity (MCS) and to compare the characteristics of those veterans who received a diagnosis of CFS (n = 24) to a group of non-veterans diagnosed with CFS (n = 95). Thirty-three veterans received a diagnosis of CFS with 14 having MCS concurrently; an additional six had MCS but did not fulfill a case definition for CFS. The group of fatigued veterans receiving a diagnosis of CFS was comprised of significantly fewer women and fewer Caucasians than the civilian group, and significantly fewer veterans reported a sudden onset to their illness. Veterans with CFS had a milder form of the illness than their civilian counterparts based on medical examiner assessment of the severity of the symptoms, reported days of reduced activity, and ability to work. Since CFS in veterans seems less severe than that seen in civilians, the prognosis for recovery of veterans with this disorder may be better.


The use of calculating and gravimetric methods for examining the grain dust pollution of the ambient air at the site of an elevator determined the maximum single, mean daily, and mean annual concentrations at different distances from the source of dust
emission. The mean ratio of these concentrations was 12.1:4.3:1, respectively. The calculated concentration-effect and concentration-time relationships provided evidence for the maximum single, mean daily, and mean annual allowable concentrations for grain dust in the ambient air.


BACKGROUND: One possibility, among others, for explaining the persistence of asthma symptoms in occupational asthma (OA) after the cessation of exposure to the causal agents may be that subjects become sensitized to ubiquitous inhalants. OBJECTIVE: The aim of this study was to evaluate the development or increase of IgE-mediated sensitization to ubiquitous allergens, both to high- and low-molecular-weight agents, in 100 subjects with OA after cessation of exposure. METHODS: Subjects were evaluated on a first visit, at the time of diagnosis of OA, coinciding with the cessation or diminution of exposure to the causal agent, and on a second visit, 5.8+/-3.3 years afterwards. At each visit, a history of ocular, nasal and asthmatic symptoms related to exposure to common allergens was obtained together with spirometry and assessment of bronchial responsiveness to methacholine. We analysed total IgE and specific IgE to Dermatophagoides farinae, D. pteronyssinus, birch, ragweed and timothy grass pollens, cat and dog danders, and Alternaria, using enzyme allergosorbent test (EAST) from blood samples taken on each visit. RESULTS: Total IgE levels showed a tendency to diminish. No changes were found in the number of positive EAST (presence of detectable levels of specific IgE) or in the levels of specific IgE. Although significantly more symptoms of rhinoconjunctivitis and asthma in contact with house dust (P < 0.05) and pets (P < 0.01) were reported on the second visit than on the first, no significant changes in the frequency of symptomatic sensitized subjects were found. CONCLUSION: Subjects with OA are unlikely to develop IgE-dependent sensitization to common inhalants after removal from exposure to occupational agents.

The benzo(a)pyrene (BaP) metabolite benzo(a)pyrenediolepoxide (BPDE) is strongly implicated as a causative agent of lung cancer. To assess the risk of exposure to BaP, we made a combined analysis of levels of BPDE adducts to hemoglobin (Hb), serum albumin (SA), and lymphocyte DNA in 44 patients with incident lung cancer, as a prototype of a population mainly exposed to tobacco-derived BaP. We also investigated whether genetic polymorphisms of cytochrome P450IA1 (CYPIA1), microsomal epoxide hydrolase (mEH), and glutathione S-transferase M1 (GSTM1), which are involved in BaP metabolism, can be determinants of adduct formation. BPDE-Hb, BPDE-SA, and BPDE-DNA adducts were quantified as BaP tetrols released from hydrolysis of macromolecules and measured by high-resolution gas chromatography-negative ion chemical ionization-mass spectrometry to achieve high specificity and sensitivity. Individuals with detectable Hb adducts were positive for SA adducts but not vice versa, suggesting that BPDE-Hb adducts are less informative indicators of BaP exposure. Using PCR methods on DNA, we characterized GSTM1 deletion, CYPIA1 MspI and exon 7 valine variants, and mEH polymorphisms at amino acid positions 113 (EH3) and 139 (EH4). Levels of BPDE adducts were no different among CYPIA1, mEH, and GSTM1 genotypes. However, individuals with measurable BPDE-SA adducts were CYPIA1 variant carriers more frequently (P = 0.03). There was a slightly higher percentage of DNA detectable adducts in subjects with CYPIA1 exon 7 valine polymorphism. When subjects were classified by both polymorphisms on the mEH gene, those with two slow alleles (EH3 homozygous mutated) and no fast alleles (EH4 homozygous wild type) had a lower frequency of BPDE-SA adducts and no DNA adducts (P = 0.06). These results are based on a small number of observations thus far, but this exploratory study suggests that CYPIA1 and mEH variants might have an impact on BPDE exposure markers such as BPDE-SA adducts. Chemical specificity in adduct measurements is important to identify the biomarkers that reflect BaP exposure more accurately.


OBJECTIVES: This study explores reactions to low-level chemical challenge, aiming at the development of test procedures for assessing individual sensitivity to smells and chemicals. METHODS: Subjects with symptoms and neuropsychological test results compatible with toxic encephalopathy type 2A (TE-2A) and 2B (TE-2B) and unexposed referents (N=12 in each group) were challenged in an exposure chamber. Toluene exposure was started at 11 mg/m³, and it followed a geometric progression scale with a ratio of 2, until reaching 180 mg/m³. In a counterbalanced design, the subjects were similarly exposed to n-butyl acetate starting at a concentration of 14 mg/m³ and increasing to 228 mg/m³. At each exposure level, smell intensity was measured on a 7-step category scale. Mucous membrane irritation and annoyance reactions were rated on visual analogue scales. RESULTS: Both TE groups showed high sensitivity to the low-level solvent challenge, which provoked immediate annoyance and fatigue reactions. In particular the TE-2B group related smell intensity to various annoyance dimensions during exposure to n-butyl acetate, a pattern not observed during toluene exposure. The reference group clearly separated smell intensity and annoyance reactions in both exposure conditions. CONCLUSIONS: The reaction of the TE cases suggests that chemical sensitivity can be distinguished from normal annoyance reactions by the inability to differentiate between smell intensity and an experience of irritation from mucous membranes in air concentrations well below the trigeminal irritation threshold level. Fatigue coreactivity in challenges to single substances below the neurotoxic level may also be important.


Increasingly recognized as a potential public health problem since the outbreak of Legionnaire’s disease in Philadelphia in 1976, polluted indoor air has been associated with health problems that include asthma, sick building syndrome, multiple chemical sensitivity, and hypersensitivity pneumonitis. Symptoms are often nonspecific and include headache, eye and throat irritation, chest tightness and shortness of breath, and fatigue. Air-borne contaminants include commonly used chemicals, vehicular exhaust, microbial organisms, fibrous glass particles, and dust. Identified causes include defective building design and construction, aging of buildings and their ventilation systems, poor climate control, inattention to building maintenance. A major contributory factor is the explosion in the use of chemicals in building construction and furnishing materials over the past four decades. Organizational issues and psychological variables often contribute to the problem and hinder its resolution. This article describes the health problems related to poor indoor air quality and offers solutions.
Niklasson, M, Arlinger, S, Ledin, T, Moller, C, Odkvist, L, Flodin, U and Tham, R

Sixty workers, consecutively admitted due to suspicion of solvent-induced chronic toxic encephalopathy (CTE), were investigated with pure-tone audiometry, determination of speech recognition of monosyllabic words and distorted speech and cortical response audiometry (CRA). Eighteen workers not exposed to occupational solvents and noise were also investigated. The scores in the distorted speech test were significantly lower and the CRA latencies were significantly longer in the solvent group than in the control group. There was no difference between the groups in the pure-tone and monosyllabic speech recognition tests. In the solvent group, 19 subjects had one or several pathological audiological test results (values exceeding the mean result of the control group by 2 SD). Independently of the audiological examination all the workers in the solvent group underwent the traditional clinical assessment of CTE, which is based on symptoms, history of exposure, clinical neurological examination and a neuropsychological investigation. They were classified in three groups--CTE, incipient CTE and non-CTE. There was no correlation between these groups and the audiological test results. A previous report on vestibular pathology in the same group of subjects and the present investigation on hearing deficits suggest that long-term exposure to solvents causes disturbances of the central pathways in the otovestibular system. Hitherto, no attention has been paid to these disturbances in the definition of the CTE syndrome.

Natelson, BH, LaManca, JJ, Denny, TN, Vladutiu, A, Oleske, J, Hill, N, Bergen, MT, Korn, L and Hay, J

The purpose of this study was to evaluate the immune dysfunction hypothesis of chronic fatigue syndrome (CFS) by comparing immunologic data from patients with CFS with data from patients with other fatiguing illnesses--major depression and multiple sclerosis (MS)--and with data from healthy sedentary controls. The subjects were 65 healthy sedentary controls, 71 CFS patients (41 with no axis-I diagnosis), 23 patients with mild MS, and 21 patients with major depression. Blood was sampled and assayed for the following: (1) immunologic serologic variables--circulating immune complexes (i.e., Raji cell and C1q binding), immunoglobulins A, E, G, and M, and IgG subclasses; (2) cell surface activation markers--the proportion of CD4+ cells expressing CD45RA+ and CD45RO+ and the proportion of CD8+ cells expressing CD38+, CD11b-, HLA-DR+ and CD28+; and (3) natural killer (NK) total cell count as well as the proportion of lymphocytes expressing NK cell surface markers (i.e., CD3-CD16+ and CD56+). Of the 18 variables studied, differences between CFS patients and
controls were found only for IgG1 and IgG3. When CFS patients were stratified by the presence or absence of concurrent axis-I disease, it was the group with axis-I disorder that had the lowest IgG1 values—contrary to expectation. When data from patients with MS and major depression were also evaluated, the subclass deficiency was no longer significant. The one group to show evidence for immune activation (i.e., an elevated proportion of CD4+ cells expressing the CD45RA+ activation marker) was the group with mild MS. These data support neither immune dysfunction nor immune activation in CFS or in major depression, for the variables studied. The reductions in IgG subclasses may be an epiphenomenon of patient or control subject composition. In contrast, MS, even in the mild and early stages, as in the patients studied here, is associated with immune activation.

1f603355d81e81fe7d799f132ee5962b

(1998) [MCS, CFS, FMS, SBS and other "modern" illnesses].

Common "environmental illnesses" are outlined with respect to their history and case definition. As no objective diagnostic criteria are available, these diagnoses may only be applied after sufficient exclusion of other known diseases. Profound knowledge regarding the etiology of these conditions is still lacking, and scientifically based somatic concepts for their therapy do not exist. Thus there is room for a multitude of unvalidated methods for diagnosis and therapy, and alleged causes are readily offered. The psychologic and economic consequences for the affected individuals are sometimes deleterious, the costs are a growing public concern. Proposals are made for the management of cases of suspected environmental illness.


(1998) Biological homing: hypothesis for a quantum effect that leads to the existence of life.
biological molecules with an enhanced attraction due to quantum mechanics. I postulate that a biological homing effect arises from the quantum mechanical probability that complementary pairs of molecules will join, and that this phenomenon is the force that drives biology and gives rise to the existence of life. To illustrate the approach, a simplified calculation is given for the interaction cross-section between two molecules, each with N surface charges that have an identical spatial distribution but with paired charges having opposite signs. The resulting cross-section is enhanced by a factor of N^2 over the coulomb-scattering cross-section for a single pair of charges. We hypothesize that the existence of life is a direct and inevitable consequence of the principles presented here.

(1998) Porphyria and porphyrinology--the past fifteen years.
McDonagh, AF and Bissell, DM Journal/Semin Liver Dis. 18: 3-15.

The porphyrias are diseases caused by defective biosynthesis of heme. Leavened by digressions on porphryia trivia, this article presents selected highlights from the last 15 years of research on the chemistry, diagnosis, and treatment of the porphyrias. Thanks largely to genetic analysis and new light shed on the magical chemistry of heme biosynthesis, this period has seen great advances in the understanding of porphyria. Sequence analyses of the genes for all of the enzymes required for heme biosynthesis have revealed the porphyrias as highly heterogeneous, with multiple mutations underlying each type. As a result of technical advances, clinical porphyrin analyses are easier and more detailed, but their misapplication to "multiple chemical sensitivity syndrome" or "intoxication porphyria" is unfortunate. The prospect of gene therapy shines ever brighter but is neither safe nor effective enough to be considered for porphyria. As practical spin-offs, porphyrins are in use increasingly for diagnosis and treatment of cancer and as herbicides and pesticides. Accounts of alleged porphyria in "Prominent People" in the popular press continue to appear, generating fanciful misconceptions, often at the expense of patients with these fascinating diseases.

(1998) [Prevention of chemical risk in pathologic anatomy and cytology].

Individuals meeting the Fukuda et al definition for chronic fatigue syndrome completed a multidisciplinary assessment that included medical, psychiatric, behavioral, and psychological evaluations. Patients were then offered a comprehensive multidisciplinary intervention that included (1) bringing the patient under optimal medical management; (2) treating any ongoing affective or anxiety disorder pharmacologically; and (3) implementing a comprehensive cognitive-behavioral treatment program. Fifty-one patients proceeded to treatment. The cognitive-behavioral component was carried out through the use of a therapist working with the patients in their own environments. The program was individually tailored to patients, but included (1) structured physical exercise and activation; (2) sleep management strategies; (3) careful activity management; (4) regulation of stimulant intake and reductions in use of symptomatic medications; (5) cognitive intervention designed to deal with patients' beliefs concerning the nature of their disorder; (6) participation of patients' family; and (7) efforts to establish specific vocational and avocational goals. Third parties were encouraged to collaborate cooperatively. Employers were urged to provide employment opportunities and facilitate a graduated but time-targeted return to work. Disability carriers were encouraged to provide interim financial support in the form of disability benefits, support therapeutic intervention, but also to establish a clear time-frame to access to benefits. Of 51 treated patients, 31 returned to gainful employment, 14 were functioning at a level equivalent to employment, and 6 remained significantly disabled. Twenty of the original 71 patients were contacted an average of 33 months later. Patients who had been treated showed good maintenance of gains. Untreated patients showed improvement in only a minority of cases.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-P/2
df952023ea53b75fa6988e90e3628ae8


Skin diseases, the psyche and psychological changes are often intertwined, especially in patients presenting for expert dermatologic opinion. In many cases an additional evaluation provided by psychotherapeutic medicine may be necessary. This resource may help with the diagnosis, explanation of the problem and estimation of the degree of disability. The different legal guidelines of the various evaluation boards must be considered. The role of psychotherapeutic evaluation is demonstrated through case examples. The evaluation of new possibly occupationally-related disorders such as multiple chemical sensitivity and mobbing is considered.
Multiple chemical sensitivity (MCS) is a syndrome in which multiple symptoms reportedly occur with low-level chemical exposure. Several theories have been advanced to explain the cause of MCS, including allergy, toxic effects and neurobiologic sensitization. There is insufficient scientific evidence to confirm a relationship between any of these possible causes and symptoms. Patients with MCS have high rates of depression, anxiety and somatoform disorders, but it is unclear if a causal relationship or merely an association exists between MCS and psychiatric problems. Physicians should compassionately evaluate and care for patients who have this distressing condition, while avoiding the use of unproven, expensive or potentially harmful tests and treatments. The first goal of management is to establish an effective physician-patient relationship. The patient's efforts to return to work and to a normal social life should be encouraged and supported.

Toxicokinetics of organic solvents: a review of modifying factors.

This article reviews, with an emphasis on human experimental data, factors known or suspected to cause changes in the toxicokinetics of organic solvents. Such changes in the toxicokinetic pattern alters the relation between external exposure and target dose and thus may explain some of the observed individual variability in susceptibility to toxic effects. Factors shown to modify the uptake, distribution, biotransformation, or excretion of solvent include physical activity (work load), body composition, age, sex, genetic polymorphism of the biotransformation, ethnicity, diet, smoking, drug treatment, and coexposure to ethanol and other solvents. A better understanding of modifying factors is needed for several reasons. First, it may help in identifying important potential confounders and eliminating negligible ones. Second, the risk assessment process may be improved if different sources of variability between external exposures and target doses can be quantitatively assessed. Third, biological exposure monitoring may be also improved for the same reason.
Lloyd, AR Journal/The American Journal of Medicine. 105: 7S-10S.

The subjective symptom of "fatigue" is one of the most widespread in the general population and is a major source of healthcare utilization. Prolonged fatigue is often associated with neuropsychological and musculoskeletal symptoms that form the basis of several syndromal diagnoses including chronic fatigue syndrome, fibromyalgia, and neurasthenia, and is clearly not simply the result of a lack of force generation from the muscle. Current epidemiologic research in this area relies predominantly on self-report data to document the prevalence and associations of chronic fatigue. Of necessity, this subjective data source gives rise to uncertain diagnostic boundaries and consequent divergent epidemiologic, clinical, and pathophysiologic research findings. This review will highlight the impact of the case definition and ascertainment methods on the varying prevalence estimates of chronic fatigue syndrome and patterns of reported psychological comorbidty. It will also evaluate the evidence for a true postinfective fatigue syndrome.

99475f35aa4c03ede085983ac44b99f3

---------------------------------------------------------------


In this study, the authors describe a new "reactive syndrome," Reactive Intestinal Dysfunction Syndrome (RIDS), which has similarities to the previously described clinical syndromes Reactive Airway Dysfunction Syndrome (RADS) and Reactive Upper Airway Dysfunction Syndrome (RUDS). Given that at least 5 neuropeptides are common to both the respiratory tract and digestive tract, the authors propose that the abnormal secretion of these neuropeptides or the abnormal numbers of their receptors play a role in what is perceived clinically as RADS, RUDS, and RIDS. The relatively large surface areas of both the lungs and gut render them especially vulnerable to the environment to which they are exposed constantly.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9766481

---------------------------------------------------------------

RPROJ DESCRIPTION: The objective of the proposed study is to determine how the N-acetyltransferase (NAT) polymorphism, a genetic metabolic trait involved in the metabolism of arylamines, influences individual susceptibility to arylamine-induced DNA damage and carcinogenesis. The finding that there are two polymorphic NATs in humans, each with multiple alleles, adds a new dimension to the investigation of the role of acetylator status in human sensitivity to exogenous chemicals. In this proposal, molecular biological and cell culture techniques will be used to transfect specific alleles of human NATs into mammalian cells (COS cells) and then to determine the susceptibility of the resulting genotype to arylamine-induced DNA damage. Current studies using acetylator congenic and acetylator, Ah-responder double congenic mouse lines will be extended to additional carcinogens and tissues. Further studies will focus on the interaction of the NAT polymorphism with two alternative oxidation pathways for arylamine carcinogens: cytochrome P450 1A subfamily monooxygenases and prostaglandin synthase (PHS) co-oxidation. Inbred and congenic mouse lines that are being developing in this laboratory will be used to model the interaction of NAT with cytochrome P450 1A and NAT with PHS as determinants of human susceptibility to colon and other extra-hepatic cancers. The technique of 32P-postlabeling (and the HPLC method previously developed in this laboratory) will be used to determine genotype-specific and tissue-specific patterns of DNA damage resulting from carbocyclic aromatic amines (e.g. 2-aminofluorene) and heterocyclic aromatic amines (e.g. IQ) produced in cooked foods. An inbred mouse model will also be constructed to determine the contribution of PHS and combinations of PHS and NAT to extra-hepatic DNA damage induced by these aryl- and heterocyclic amines. This model will also be used as a tool to study pharmacological interventions in PHS activity and their effects on prevention or reduction of DNA damage and carcinogenesis.

Levine, PH Journal/The American Journal of Medicine. 105: 100S-103S.

A number of recent reports have emphasized laboratory abnormalities, clinical tests, and therapeutic approaches that appear to have great promise in the evaluation and management of chronic fatigue syndrome (CFS). Because of the heterogeneity of CFS, the cost of many of these assays and procedures, and the frequent lack of skilled consultants able to apply relevant sophisticated procedures, the solo healthcare provider is often left with uncertain options in patient management. This article summarizes current approaches to patient management, utilizing available information relevant to CFS.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-M/22e47acb2663f03042fa02804b51c9d11
Levine, PH Journal/The American Journal of Medicine. 105: 2S-6S.

c1b07109593c52f8c3f76187d35785f6

Lee, P Journal/The American Journal of Medicine. 105: 1S.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-1/2
602db7ec911fe27188bc674529a3987

Lax, MB Journal/Int J Health Serv. 28: 725-45.

Multiple chemical sensitivities (MCS) has emerged as an important and highly controversial issue in occupational health. Debate centers on whether the illness is "physical" or "psychological." A strong corporate-backed campaign has framed the debate and has pushed MCS advocates into a strategy of "proving the physical" nature of MCS. Proponents of both positions, however, share key assumptions that impede long-term efforts to benefit MCS sufferers, including acceptance of the physical psychological dichotomy as a paradigm for the illness, a desire to rid the debate of "politics" to allow "objective scientific" data to be amassed, and a view of MCS as unique without links to other occupational illnesses. While a grassroots movement has benefited MCS sufferers in a number of important ways, the shared assumptions have impeded development of a more complex model for the illness that is reflective of a complex reality, reproduced mainstream expert/non-expert relationships, and failed to connect with the broader occupational health and safety movement. The author outlines an alternative theory and practice to begin addressing these issues, beginning with a recognition of MCS as a problem of developing knowledge within a context of class power.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9842496

The diagnosis of chronic fatigue syndrome (CFS) is made difficult by the absence of specific biomedical markers, and depends primarily on determining whether subjective information provided by the patient meets the clinical case definition of this syndrome. Reported cognitive difficulties and/or complaints of headache may instigate referral for brain imaging. This article will discuss the value of neuroimaging in evaluating CFS, specifically reviewing studies that (1) used static magnetic resonance imaging (MRI) to assess structural abnormalities; and (2) assessed regional cerebral blood flow (rCBF) via detection of Tc-99m hexamethylpropyl-eneamine oxime distribution by single-photon emission computed tomography (SPECT). Future research design considerations are explored including (1) the utilization of positron emission tomography (PET) and other emerging neuroimaging technologies; and (2) methodological concerns, i.e., the influence of psychopathology (such as depression) and neurologic disease (such as multiple sclerosis) as possible confounding factors.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-B/2
30413d1108c16af618af61c6cfd69fe4

--------------------------------------------------------------------------------------------------


The purpose of this study was to determine the effect of exhaustive exercise on cognitive performance of patients with chronic fatigue syndrome (CFS) and sedentary healthy controls (CON). Subjects were 19 women with CFS and 20 CON. A test battery consisting of 4 cognitive tests (CTB) was given pre-, immediately post-, and 24 hours post-treadmill exercise to exhaustion. No differences were seen on the CTB pre-exercise. CFS patients improved at a slower rate than CON on the Symbol Digit Modalities Test (SDMT), Stroop Word Test (SWT), and Stroop Color Test (SCT). When compared with CON, a lower number of correct responses was seen for the CFS immediately postexercise on the SDMT (61 +/- 3 vs 66 +/- 2), SWT (137 +/- 6 vs 146 +/- 6), and SCT (99 +/- 4 vs 107 +/- 3), and 24 hours postexercise on the SDMT (64 +/- 3 vs 69 +/- 2), SWT (134 +/- 7 vs 148 +/- 5), and SCT (101 +/- 4 vs 106 +/- 3). We conclude that after physically demanding exercise, CFS subjects demonstrated impaired cognitive processing compared with healthy individuals.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-D/2
5ec09710d5accfe21283bc6df48ddd7a

--------------------------------------------------------------------------------------------------
Krop, J Journal/J Altern Complement Med. 4: 77-86.

OBJECTIVES: The purpose of this case study is twofold. One, to illustrate a simple method of detoxification using heat chamber depuration (sauna). Second, to raise awareness in the practice of medicine of the importance of taking an environmentally oriented history. SUBJECT: A patient with a chronic, debilitating multisystem disorder of 20-years' duration related to a chemical sensitivity resulting from low-level exposure to toxic chemicals (solvents) at work. INTERVENTIONS: Detoxification treatment consisted of heat chamber depuration (sauna) together with a specific protocol of oral and intravenous therapy. Appropriate advice was offered related to choosing a safe and suitable workplace. OUTCOME MEASURES: Observation of the dynamic interaction and elimination of chlorinated and aromatic hydrocarbons (solvents) from the patient's bloodstream and related clinical improvement during the course of treatment. RESULTS: The patient was able to discontinue, without ill effect, all medications previously prescribed to treat her symptoms. Heat chamber depuration (sauna) detoxification treatment brought substantial release of symptoms and returned the individual to gainful employment. CONCLUSION: The connection between symptoms of chronic degenerative diseases and environmental and/or nutritional factors is missed in many cases due to lack of obtaining an environmentally oriented medical history. Taking such a history and dealing with the cause of illness using avoidance and/or appropriate therapy is preventive and cost-effective for both the patient and society.

(1998) Genetic polymorphism of paraoxonase 1 (PON1) and susceptibility to Parkinson's disease.

Toxicologists have thought that the paraoxonase (PON) enzyme polymorphism might contribute to effects of pollutants and other environmental chemicals on susceptibility to cancer, birth defects and Parkinson's disease (PD). We studied a biallelic PON1 polymorphism at codon 192 (A and B alleles) in 166 patients with sporadic idiopathic PD. The frequency of the B (Arg) allele of PON1 was significantly increased in patients with PD than in healthy controls (chi2=8.75, df=1, P<0.005). The relative risk of PD in homozygotes for the B allele was 1.60 fold higher than individuals with the A (Gln) allele (chi2=7.38, df=1, P<0.01). Our data suggest that environmental neurotoxins metabolized by PON1 might be responsible for neurodegeneration with aging and that the B (Arg) allele form might have genetic susceptibility to PD.
**(1998) Perioperative care of environmentally sensitive patients.**

In today's complex environment, with an increasing number of chemicals and environmental contamination, some individuals have developed sensitivities to their surroundings. Surgical intervention for environmentally sensitive patients provides an opportunity to reach beyond the boundaries of the OR. These patients require highly individualized perioperative nursing assessments and care planning on a multidisciplinary level. Presbyterian Hospital of Dallas has developed a protocol to initiate collaborative planning for these patients and has had the opportunity to successfully care for these patients.


-------------------------------------------------------------------------------------------------------------------------------

**(1998) Diet and Environmental Illness: Barriers Encountered by Women Sufferers.**

Environmental illness is characterized by an ill-defined constellation of signs and symptoms of unknown etiology. It is assumed that exposure to low dose irritants in the environment initiates a chronic and relapsing disorder in susceptible individuals. Although diet is central in the treatment of environmental illness, there is little research to describe how those living with environmental illness view diet and the barriers they encounter. The objective of this work was to look at the perceptions of food and nutrition in a small group of women with a confirmed diagnosis of environmental illness so as to identify common barriers to meeting food needs and to suggest roles for dietitians/nutritionists in assisting those with environmental illness. Eight subjects recruited from a government sponsored Environmental Illness Clinic participated in focus group discussions. Following each session, transcripts were coded and used to generate categories and crosslinks. The most significant barrier encountered by all subjects was the financial cost, be it for treatment, purchasing special foods and nutrient supplements, or misdiagnosis. The next most important variable was time required to complete activities of daily living. Although all participants followed a special diet, this alone was not perceived to be an intrusion. All subjects commented on the social isolation and the way the diagnosis of environmental illness had altered all aspects of their life. Participants identified education and advocacy as the most important areas where dietitians/nutritionists could make a contribution to the health and well-being of this nutritionally vulnerable group.

-------------------------------------------------------------------------------------------------------------------------------

**(1998) Simultaneous active sensitization to multiple chemicals.**

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9536418

-------------------------------------------------------------------------------------------------------------------------------


Sensitization to cocaine refers to the behavioral model of cocaine addiction where the motor stimulant effect of cocaine is augmented for months after discontinuing a regimen of repeated cocaine injections. There has been speculation that the neuroadaptations mediating this sensitization phenomenon may, in part, underlie the behavioral changes produced by chronic cocaine abuse, including paranoia, craving and relapse. Criteria are proposed that may assist in determining which neuroadaptations are most relevant in this regard. Using these criteria, a model is presented that endeavors to incorporate neuroadaptations issuing directly from the pharmacological effects of cocaine and those arising from learned associations the organism makes with the cocaine injection procedure and pharmacological actions. It is proposed that the pharmacological neuroadaptations predominate in the manifestation of cocaine-induced paranoia, while the changes derived from learning may provide more critical underpinnings for cocaine craving and relapse.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9584968

-------------------------------------------------------------------------------------------------------------------------------


-------------------------------------------------------------------------------------------------------------------------------

(1998) Bringing epidemiology manuals and books onto the Internet through the Epilink.

The objective of this study was to determine from the published epidemiological literature whether there is evidence for a causal association between service in the Gulf War and illness in U.S. veterans. Eleven published studies were analyzed using standardized epidemiologic criteria for assessing causality. A consistent association was found between deployment to the Gulf and self-reports of symptoms. No consistency was seen in physical findings or laboratory results. Strength of association varied with different study designs. Dose-response information is limited, because of lack of quantitative data on exposures. Biological plausibility varies for different risk factors. Specificity of association is not seen. Frequency of self-reported symptoms is increased in U.S. Gulf War veterans compared to other veterans of the same era, but specific causes of illnesses cannot be ascertained. Major gaps in data that impeded this analysis include (1) lack of objective data on specific environmental exposures (2) lack of baseline health assessments, and (3) lack of objective measures of post-deployment health status. In future deployment of U.S. troops, accurate exposure and health data will be needed if the causes of subsequent illnesses are to be accurately assessed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9841805

---------------------------------------------------------------------


The selectivity of the muscarinic toxin MT3 from green mamba snake venom was corroborated by inhibition of the binding of [3H]NMS, a classical muscarinic radioligand, to native and cloned muscarinic receptors, showing 214-fold higher affinity for m4 than for m1 subtype, without significant binding to the others. The highest concentrations of MT3 sites (putative m4 receptors) in the rat brain were found in striatum and olfactory tubercle, intermediate concentration in dentate gyrus and CA1, and lower but still conspicuous levels in CA3 and frontal cortex. MT3 caused retrograde amnesia of an inhibitory avoidance task, when injected into the dorsal hippocampus of rats after training, suggesting a positive role of these MT3 sensitive sites, which are probably m4 muscarinic receptors, in memory consolidation of this task.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9631438

---------------------------------------------------------------------

The present study assessed the prevalence of chronic fatigue syndrome (CFS) in a sample of nurses. There is a paucity of studies on the prevalence of CFS in healthcare professionals. Two samples of nurses were recruited through mailed questionnaires. Data were collected on demographic characteristics and symptoms. In addition from the sample, those nurses with CFS-like symptoms were more comprehensively evaluated using a structured clinical interview and reviewing their medical records. A physician review team estimated the prevalence of CFS to be 1,088 per 100,000. These findings suggest that nurses might represent a high-risk group for this illness, possibly due to occupational stressors such as exposure to viruses in the work setting, stressful shift work that is disruptive to biologic rhythms, or to other possible stressors in the work settings (e.g., accidents).

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-J/2 0d116ea094e1cfb60b111832859a2b56

---------------------------------------------------------------

Jahn, O Journal/Atemwegs- Und Lungenkrankheiten. 24: S81-S83.

BIOSIS COPYRIGHT: BIOL ABS. Electrosmog, a new word for troubles with electromagnetic fields, adds the spectrum of environmental syndromes, like sick building syndrome, multiple chemical sensitivity syndrome. The real background of the complaints is very difficult to explore, but an exact medical investigation with implementing social and work environment has to be done. In spite of missing physical facts, the real success of treatment is very rare.

---------------------------------------------------------------


---------------------------------------------------------------
(1998) **Building-associated pulmonary disease from exposure to Stachybotrys chartarum and Aspergillus versicolor.**

The authors present an outbreak of disease associated with exposure to Stachybotrys chartarum and Aspergillus species. A courthouse and two associated office buildings had generated discomfort among employees for two years since initial occupancy. Multiple interventions had been unsuccessful. An initial evaluation of 14 individuals identified three with potential asthma and three with symptoms consistent with interstitial lung disease. A clinical screening protocol to identify individuals who should be removed from work identified three likely and seven possible cases of building-related asthma. Detailed environmental and engineering assessments of the building identified major problems in mechanical system design, building construction, and operational strategies leading to excess moisture and elevated relative humidities. Moisture-damaged interior surfaces in both buildings were contaminated with S. chartarum, A. versicolor, and Penicillium species. Aspergillus species, especially A. versicolor, at concentrations of 10\(^{-1}\) to 10\(^{-4}\)/m\(^3\) dominated the indoor air under normal operating conditions. Bulk samples also revealed large quantities of Stachybotrys. A questionnaire survey of the three case and two control buildings documented between three- and 15-fold increases in symptoms. A nested case-control study suggested emphysematous-like disease in individuals meeting questionnaire definitions for cases. Replication of analysis strategies used in similar previous investigations suggested an association between worsening symptoms and decreased diffusing capacity of the lung. Performance on neuropsychological measures was similar for both cases and controls, although workers with symptoms reported increased levels of current but not past psychiatric symptomatology. Chemical analyses demonstrated the presence of satratoxins G and H. Cytotoxic laboratory analyses demonstrated the presence of agents with biological effectiveness in bulk materials. No association was seen between IgE or IgG antibodies and the presence of disease. This outbreak represents a likely human response to inhaled fungal toxins in indoor environments. Moisture indoors represents a public health issue currently inadequately addressed by building, health, or housing codes.


(1998) **Cognitive behavioural therapy for patients with electric sensitivity - a multidisciplinary approach in a controlled study.**

**BACKGROUND:** Electric sensitivity is a syndrome that still lacks diagnostic criteria and proven aetiology. The suffering of afflicted persons motivates development and
evaluation of effective handling and treatments. The aim of the study was to evaluate the effect of cognitive behavioural therapy in patients with electric sensitivity.

METHODS: Cognitive behavioural treatment, as part of a multidisciplinary treatment package for patients with electric sensitivity, was evaluated in a controlled trial. Ten patients who received treatment were compared to 12 controls. Outcome measures included different dimensions such as symptoms, beliefs, behaviour, and biochemical measurements of stress-related variables. All outcome measures were collected prior to the study, post-treatment, and after an additional 6-month follow-up. RESULTS: The therapy group rated their electric sensitivity as significantly lower than did the control group at the 6-month follow-up, and reduction of self-rated discomforts from triggering factors was significant in the therapy group. There were no systematic changes in the biochemical variables. The symptom indices were significantly reduced over time, and ability to work continued to be good in both groups. CONCLUSION: The prognosis for this syndrome is good with early intervention and cognitive therapy may further reduce the perceived hypersensitivity. This may have important implications on handling of patients with electric sensitivity.


Patients who had experienced well-documented neurotoxic exposure months or years earlier were evaluated. Seventy-two right-handed adults who claimed continuing abnormalities of cognitive and memory function were examined after Xenon-133 inhalation and i.v. HMPAO. Single photon emission computed tomography (SPECT) results were statistically compared with age-matched controls. Bilateral, often asymmetrical, impairment of perfusion was found, mostly in the frontal, temporal, and parietal lobes. This hypoperfusion was predominantly left-sided in young patients and predominantly right-sided in the elderly. Abnormalities were found months and years after neurotoxic exposure had ceased. Our findings suggest that NeuroSPECT can provide evidence of impaired cerebral function and may therefore help to further define neurotoxic exposure and its chronic effects.

(1998) [Environmental-medical diagnosis and therapy. Hasty diagnosis of unspecified environmental syndromes should be avoided].

In the past ten years environmental medicine has virtually exploded. Major instruments for the interdisciplinary environmental-medical diagnosis are history, on-site inspection, biomonitoring and ambient monitoring. Since the definitive diagnosis of an
environment-related disease usually requires a joint evaluation of toxicological, somatic and psychosomatic findings, it is recommended that cooperation with an experienced center for environment medicine should be established early on. By doing so, an inappropriate diagnosis of unspecific environment-medical symptom complexes such as, e.g., multiple chemical sensitivity may be avoided. Such "diagnoses" may result in drastic, and for the patient and his family, often stressful, consequences.

(1998) [Neurological problems in environmental medicine].

It has been tried to demonstrate the role of neurology in the new medical discipline "environmental medicine" or "clinical ecology". Encephalopathy and polyneuropathy are the most common diseases related to neurology following the exposure to low levels of environmental substances. The problems of measuring are discussed, also the difference to other causes of illness. Important are also psychological aspects in the whole context of environmental medicine. The importance of amalgam, organic solvents and ozone is explained in their relation to neurology and clinical ecology. Mentioned is also the difficult concept of "multiple chemical sensitivity". Referring to the environmental consultation an open and evaluating attitude is recommended to avoid damage as a result of environmental poisoning equally to exaggerated medical activities.


Toxins such as carbon monoxide, lead, and mercury that present occasionally with primarily psychiatric symptoms can pose some of the most difficult diagnoses. This article reviews the clues that can allow the diagnostician to identify the role of one of these substances. Equally important, the article discusses the contentious issues that surround the phenomenon known as multiple chemical sensitivity. Viewed primarily as a functional illness, often with legal overtones, this putative disorder is critically reviewed to see if it meets the same demanding standard of validity that is found in the psychiatric symptoms associated with other toxic disorders. Although questioning the strict medical origin of medical chemical sensitivity, the article outlines some treatment hints that may helpful in the management of this difficult group of patients.
A case-control study was conducted to determine whether menstrual and gynecologic abnormalities precede the onset of chronic fatigue syndrome (CFS) in women with this disorder to a greater extent than that observed among healthy controls. We identified 150 women who met the 1988 Centers for Disease Control criteria for CFS from the Brigham and Women’s Hospital Cooperative CFS Research Center. A comparison group of 149 women being seen for nongynecologic conditions were selected from the waiting area of the Brigham and Women’s Hospital Internal Medicine outpatient department. Women with and without CFS completed self-administered questionnaires on menstrual, reproductive, and medical history. Women with CFS reported increased gynecologic complications and a lower incidence of premenstrual symptomatology. After adjustment for age, a somewhat greater number of cases compared with controls self-reported irregular cycles, periods of amenorrhea, and sporadic bleeding between menstrual periods. Factors suggestive of abnormal ovarian function--such as a history of polycystic ovarian syndrome, hirsutism, and ovarian cysts--were reported more often in CFS cases compared with controls. Frequent anovulatory cycles due to ovarian hyperandrogenism (PCOS) or hyperprolactinemia may increase risk for CFS through loss of the potential immunomodulatory effects of progesterone in the presence of continued estrogen production. We hypothesize that frequent anovulatory cycles due to PCOS and/or hyperprolactinemia may explain the increased reporting of gynecologic complications and the lower reported premenstrual symptomatology observed in women with CFS.
receiver. TYPICAL NOCEBO PHENOMENA: Here some epidemiological examples of nocebo phenomena will be presented. Each society selects the matching nocebos, today mainly as chemical exposures from oecological sources such as environment, buildings, emissions and industrial products. THERAPEUTICAL APPROACH: Suspicion of nocebo should not hamper the search for chemical poisons. Anxiety and fear furnish the neurobiological and evolutionary basis of the nocebo phenomena. Hence behavioural and conversational therapy, supported by antidepressants if needed, should be tried. Unfortunately, most patients expect their psychosocial problems instead to be declared as chemical.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9545711

---------------------------------------------------------------


Diisopropyl phosphorofluoridate (DFP) produces delayed neurotoxicity, known as organophosphorus ester-induced delayed neurotoxicity (OPIDN), in hen, human, and other sensitive species. A single dose of DFP (1.7 mg/kg, se.) produces first mild ataxia followed by paralysis in 7-14 days in hens. DFP treatment also increases in vitro autophosphorylation of Ca2+ calmodulin-dependent protein kinase II (CaM kinase II) and the phosphorylation of several cytoskeletal proteins in the hen brain. To investigate whether increase in CaM kinase II activity is associated with increased expression of its mRNA, we cloned and sequenced CaM kinase II alpha subunit cDNA, and used it to study CaM kinase II expression in brain regions and spinal cord. Hen CaM kinase II alpha subunit differs in 7 amino acids from that of rat CaM kinase II. Its mRNA occurs predominantly as a 6.7 kb message, which is very close to that of human CaM kinase II alpha subunit. Northern blot analysis showed a transient increase in CaM kinase II alpha subunit mRNA in the cerebellum and spinal cord of DFP-treated chickens. The increase in CaM kinase II mRNA expression is consistent with the previously reported increase in its activity in brain and spinal cord, and its increased expression only in cerebellum and spinal cord, which are sensitive to the Wallerian-type degeneration characteristic of OPIDN, suggests the probable role of this enzyme in delayed neurotoxicity.

---------------------------------------------------------------

(1998) Tau proteins-enhanced Ca2+/calmodulin (CaM)-dependent phosphorylation by the brain supernatant of diisopropyl phosphorofluoridate
(DFP)-treated hen: tau mutants indicate phosphorylation of more amino acids in tau by CaM kinase II.
Gupta, RP and Abou-Donia, MB Journal/Brain Res. 813: 32-43.

Diisopropyl phosphorofluoridate (DFP) produces organophosphorus ester-induced delayed neurotoxicity (OPIDN) in hen, human, and other sensitive species. A single dose of DFP (1.7 mg/kg, s.c.) produces mild ataxia in 7-14 days in hens, followed by progression to severe ataxia or paralysis. We studied the effect of DFP administration on Ca2+/calmodulin-dependent phosphorylation of tau proteins by the brain supernatants of control and DFP-treated hens. Brain supernatants from DFP-treated hens showed enhanced in vitro phosphorylation of htau40 and its various mutants, but no change in the two-dimensional phosphopeptide pattern, when compared to control hen brain supernatants. Analysis of tau mutants phosphorylated by brain supernatant and recombinant CaM kinase II alpha-subunit showed that (1) brain supernatant CaM kinase II is mainly responsible for the phosphorylation of Ser416, (2) Ser356, but probably not Ser262, is phosphorylated by CaM kinase II, (3) no amino acid between Lys395-Ala437 except Ser416 is phosphorylated by CaM kinase II, (4) a number of amino acids in the tau molecule, which are phosphorylated by the brain supernatant in the absence of Ca2+/calmodulin are also mildly phosphorylated by CaM kinase II. The enhanced Ca2+/calmodulin-dependent phosphorylation of tau proteins by brain supernatant of DFP-treated hens that includes phosphorylation of a number of amino acids is likely to alter the functional properties of tau proteins in OPIDN. The hyperphosphorylated tau may destabilize microtubules, alter axonal transport, and result in degeneration of axons in OPIDN.


(1998) The role of the T lymphocytic cell cycle and an autogenous lymphocytic factor in clinical medicine.

In this study 315 individuals (25 controls, 290 chemically sensitive immunocompromised patients) were investigated. Each patient had been on a standard therapy of avoidance of pollutants, nutritional supplementation, and injections of antigens for foods, and biological inhalants, but did not attain their immunological competence. Peripheral lymphocytes were collected and DNA histograms were
constructed. The flow cytometer was used to evaluate the cell cycle, haematological, and other immunological profiles. From the other portion of the blood specimen, lymphocytes were propagated in vitro, harvested, and a lysate, termed the autogenous lymphocytic factor (ALF), was prepared. When treated with ALF, 88% of these individuals showed a significant (p < 0.001) clinical improvement which correlated with laboratory findings, involving regulation of abnormal cell cycles, increase in total lymphocytes and subsets T4, T8, (p < 0.05) and cell mediated immunity (CMI) response (p < 0.001). The ALF presumably acts as a biological response modifier. The cell cycle and ALF provide clinical tools for diagnosis and regulation of immunological incompetence.

Green, BG Journal/Crisp Data Base National Institutes Of Health.
RPROJ The long-term goal of this project is to provide an integrated psychophysical description of the human ability to sense chemical irritants via she trigeminal nerve. Guided by the view that the sensitivity to irritants derives from elements of the nociceptive and thermal senses present in all types of skin, the proposed research will investigate the extent to which this common neural basis influences chemosensory perception throughout the trigeminal system. This objective will be pursued by (1) measuring the sensitivity to irritants across the full diversity of trigeminal regions--the oral cavity, nasal cavity, face and eyes--on a large number of subjects, and inferring from those data the-contributions of local and systemic factors to individual differences; (2) measuring individual differences in sensitization and desensitization produced by two different irritants on two kinds of skin, thus determining whether these phenomena vary locally or systemically; (3) providing the first quantitative investigation of long-term capsaicin desensitization in the trigeminal region and determining if menthol, which was recently found to produce short-term desensitization, has similar long-term hyperalgesic effects; and (4) investigating the role of counterirritation, a form of masking intrinsic to the nociceptive system, on the perception of multiple and/or spatially complex irritant stimuli within the trigeminal field. As well as providing new information about trigeminal chemoreception and the extent to which it may be influenced by systemic (nociceptive) factors, the proposed research will employ a battery of new psychophysical procedures that could prove useful for assessing the incidence, and nature of apparent hypersensitivity syndromes such as contact dermatitis and multiple chemical sensitivities. In addition, studies of long-term desensitization and counterirritation will provide basic information about how these two phenomena may impact on applied issues ranging from the perception and liking of hot and spicy foods to the use of chemical irritants as topical analgesics.

(1998) [Multiple chemical sensitivity: a new type of toxicity?].
Multiple chemical sensitivity (MCS) is a chronic condition manifested by the appearance of variable symptoms, involving many systems and organs, after exposure to extremely low levels of chemicals, mainly pesticides and solvents. The paper discusses briefly the main hypotheses concerning causes and mechanisms of MCS development. It was emphasized that during neurotoxicity assessment is necessary to pay more attention to these aspects of toxic effects of chemicals likely to generate MCS.


(1998) Treating chronic fatigue with exercise. Exercise, and rest, should be tailored to individual needs.
Goudsmit, E Journal/Bmj. 317: 599; author reply 600.

(1998) [Long-term ecological and genetic consequences of use of dioxin-containing environmental agents].

The long-term consequences of the use of dioxine-containing ecotoxic agents in the USA in 1961-1972 are ecologically and genetically characterized. There were increases in the incidence of pathological reproductive events in the contaminated region. It is concluded that there will be higher probability of abnormalities in the families of individuals born at war or just thereof. An association of impaired reproduction with functional disorders and women's poorer health, with higher incidence of somatic and gynecological diseases (chronic ones in particular) is shown. Cytogenetic changes in the lymphocytes were found in individuals from exposure risk groups. The contribution of chromosomal alterations observed in the contaminated area to immunodeficiency is appreciated. The systemic pattern of the action of biologically active properties of dioxine was demonstrated from the morphofunctional changes of different cell types. Cluster analysis revealed associations of cytogenetic parameters with the integrated index of health status in individuals from different contaminated areas. The ecological and genetic consequences may be regarded as part of homeostatic changes at many levels, as suggested by a correlation between the genetic instability and the changes occurring in other tissues, organs, and systems.

BIOSIS COPYRIGHT: BIOL ABS. A survey of the toxicity of soils from the several industrial zones of the Spanish Basque Country was undertaken in order to identify the relationship between chemical contamination and toxicity. The measured effect in the solid and liquid-phase Microtox toxicity test was correlated with the chemical parameters to determine the origin of the toxicity effect. Results indicate the higher sensitivity of solid-phase bioassay. In a comparative study with the liquid-phase assay it was found that due to different solubility of each contaminant in water the test on the extracts represents only a part of multiple contamination. Moreover water elutriation could underestimate the types and concentrations of organic contaminants present.


The frequent association of an active viral infection with the symptoms of CFS led researchers to hypothesize that chronic fatigue syndrome (CFS) is induced by a virus. Results of these studies indicated that despite clinical support for this hypothesis, there were no clear data linking viruses to CFS. In this overview, we will explore the interrelation of the immune, endocrine, and central nervous systems, and the possibility that stress and/or the reactivation/replication of a latent virus (such as Epstein Barr virus) could modulate the immune system to induce CFS. Relevant research conducted in the developing field of psychoneuroimmunology will be reviewed, with a particular focus on cytokine synthesis, natural killer (NK) cell activity, and T-lymphocyte function, as they relate to CFS.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-8/2bc54aaf865dc948903e0f0632de744


Social support was examined in 305 persons with multiple chemical sensitivity using the Personal Resource Questionnaire 85 (PRQ85; Weinert, 1987) and qualitative descriptions of respondents’ social interactions. PRQ85 scores were lower than those
of healthy populations, but similar to samples with chronic illness. Participants needed but were prevented from receiving support for personal difficulties due to their limited public access, their need for chemical avoidance including fragrances, and others' lack of information and negative attitudes regarding chemical sensitivities. Respondents drew some support and validation from support groups and from romantic relationships. Fatigue level, being in a romantic relationship, contact with a support group on a monthly or more frequent basis, chemical avoidance in the home, gender, and an improved course of illness predicted 19% of the variance for perceived social support. Qualitative data are used to illustrate particular problems of persons in this sample, and suggestions are made for practitioners who encounter this population.


PURPOSE: The effects of the anti-cholinesterase organophosphate pesticide chlorpyrifos (CPF) on the refractive development of the eye were examined. Form deprivation was used to induce eye growth to address the previously reported relationship between organophosphate pesticide use and the incidence of myopia. METHODS: Chickens, a well-established animal model for experimental myopia and organophosphate neurotoxicity, were dosed with chlorpyrifos (3 mg/kg per day, orally, from day 2 to day 9 after hatching) or corn oil vehicle (VEH) with or without monocular form deprivation (MFD) over the same period. The set of dependent measures included the refractive state of each eye measured using retinoscopy, axial dimensions determined with A-scan ultrasound, and intraocular pressure. RESULTS: Dosing with CPF yielded an inhibition of 35% butyrylcholinesterase in plasma and 45% acetylcholinesterase in brain. MFD resulted in a significant degree of myopia in form-deprived eyes resulting from significant lengthening of the vitreal chamber of the eye. CPF significantly reduced the effect of MFD, resulting in less myopic eyes (mean refraction: VEH-MFD = -16.2 +/- 2.3 diopters; CPF-MFD = -11.1 +/- 1.8 diopters) with significantly shorter vitreal chambers. Nonoccluded eyes were, on average, slightly hyperopic. Treatment with CPF for 1 week in the absence of MFD led to no significant change in ocular dimensions or refraction relative to controls. CONCLUSIONS: The use of form deprivation as a challenge suggests that CPF treatment interferes with the visual regulation of eye growth.
Genetically determined susceptibility to organophosphorus insecticides and nerve agents: developing a mouse model for the human PON1 polymorphism.

Several organophosphorus insecticides and nerve agents are detoxified through the cytochrome P450/paraoxonase (PON1) pathway. PON1 is an HDL-associated enzyme encoded as a 355 amino acid protein in humans. The PON1 Arg192 isoform hydrolyzes paraoxon rapidly while the Gln192 isoform hydrolyzes this compound slowly. Both isoforms hydrolyze phenylacetate and chlorpyrifos oxon at approximately the same rate. We recently found that the effect of this polymorphism is dramatically reversed for sarin hydrolysis. The PON1 Arg192 isoform has virtually no sarinase activity while the Gln192 isoform has substantial activity. The Gln192 isoform also hydrolyzes diazoxon and soman faster than the Arg192 isoform. In addition to the large differences in rates of hydrolysis observed for some OP substrates by the two PON1 isoforms, there is also a large variability in serum PON1 concentrations that is stable over time between individuals. Thus, two factors govern the PON1 status of a given individual, the PON1 genotype as well as the amount of protein expressed from each allele. A two-dimensional enzyme analysis provides an excellent assessment of an individual's PON1 status, i.e. the position 192 genotype as well as phenotype, or level of serum PON1 (Nature Genet 14:334-336). Do these interindividual differences in rates of substrate hydrolysis by PON1 reflect an individual's sensitivity or resistance to OP compounds processed through the P450/PON1 pathway? Injection of purified PON1 into mice clearly demonstrates the protective effect of having high serum levels of PON1 against toxicity by chlorpyrifos oxon or chlorpyrifos. Preliminary experiments with PON1 knockout mice, on the other hand, clearly demonstrate that low PON1 levels result in dramatically increased sensitivity to chlorpyrifos oxon. Attempts to express human PON1 in mice from constructs containing either of the human PON1 cDNA sequences were unsuccessful, despite the generation of the respective transgenic mice.

Scents and sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9831547

Private-public sector co-operation to improve pesticide safety standards in developing countries.
Ellis, WW Journal/Med Lav.  89 Suppl 2: S112-22.

This paper draws on the author's experiences of the pilot phase of the Safe Use Project (SUP) in Thailand; this project is a part of a major GIFAP initiative carried out in some developing countries. The SUP's objectives were; i) to raise awareness and compliance in the safe handling and storage of pesticides within the industry, the medical profession and the end-users; ii) to reduce the incidence of pesticide poisoning; iii) to protect the environment; iii) to help relevant government agencies with resources, expertise and training. To achieve those objectives, the SUP used local-language training resources, provided basic training, lobbied for changes in governmental policies and regulations, and acted as a focal point for pesticide safety-related information. The SUP targeted the whole distribution chain, from importer/formulator, through to the endusers. Also medical profession, teachers and school students were targeted. On the base of independent audit and surveys, a general improvement in awareness has been shown within targeted groups; a longer time frame is required to detect meaningful changes in farmer practice. The SUP key programmes have been: I) training of trainers, retailers and farmers; II) schools programme; III) medical training; IV) protective clothing; V) industry standards; VI) model farm. The main conclusions of the pilot phase were: i) pesticide safety needs to be addressed by all concerned agencies in a joint effort; ii) a rural development perspective must be adopted in improving pesticide safety; iii) integrated pest management training programmes must include precautionary advice for proper handling, use and disposal of pesticides, wherever these are necessary.

(1998)  [Interpretation of toxicologic data in clinical environmental medicine].


A culture-independent molecular phylogenetic approach was used to survey constituents of microbial communities associated with an aquifer contaminated with hydrocarbons (mainly jet fuel) and chlorinated solvents undergoing intrinsic bioremediation. Samples were obtained from three redox zones: methanogenic, methanogenic-sulfate reducing, and iron or sulfate reducing. Small-subunit rRNA genes were amplified directly from aquifer material DNA by PCR with universally conserved or Bacteria- or Archaea-specific primers and were cloned. A total of 812
clones were screened by restriction fragment length polymorphisms (RFLP), approximately 50% of which were unique. All RFLP types that occurred more than once in the libraries, as well as many of the unique types, were sequenced. A total of 104 (94 bacterial and 10 archaeal) sequence types were determined. Of the 94 bacterial sequence types, 10 have no phylogenetic association with known taxonomic divisions and are phylogenetically grouped in six novel division level groups (candidate divisions WS1 to WS6); 21 belong to four recently described candidate divisions with no cultivated representatives (OP5, OP8, OP10, and OP11); and 63 are phylogenetically associated with 10 well-recognized divisions. The physiology of two particularly abundant sequence types obtained from the methanogenic zone could be inferred from their phylogenetic association with groups of microorganisms with a consistent phenotype. One of these sequence types is associated with the genus Syntrophus; Syntrophus spp. produce energy from the anaerobic oxidation of organic acids, with the production of acetate and hydrogen. The organism represented by the other sequence type is closely related to Methanoseta spp., which are known to be capable of energy generation only through aceticlastic methanogenesis. We hypothesize, therefore, that the terminal step of hydrocarbon degradation in the methanogenic zone of the aquifer is aceticlastic methanogenesis and that the microorganisms represented by these two sequence types occur in syntrophic association.


This paper approaches the issue of chemical sensitivity and the immune system through a consideration of established environmentally-induced immune alterations which have particular relevance to the broader topic of chemical sensitivity. Additionally, the report discusses the potential problems associated with prior narrow evaluation strategies for the assessment of environmentally-induced inflammation. A combined approach to assessment drawing upon biomarkers of both the immune and neurological systems is suggested. Such an approach recognizes the key roles which mediators of these two systems play in facilitating host inflammatory responses. The paper concludes with a discussion of the types of specific immune alterations which, from a mechanistic perspective, are likely to be involved with any linkage of chemical sensitivity to the immune system.


Compared with normal individuals, subjects with asthma have elevated levels of expired nitric oxide (NO). These levels are hypothesized to reflect the degree of airway inflammation. Expired NO levels rise during the late phase of allergen challenge and decrease in asthmatics after steroid treatment. Isocapnic cold air hyperventilation (ISH) is believed to cause airway narrowing through noninflammatory mechanisms. We measured mixed expired NO in 10 individuals with atopic asthma who underwent both ISH challenge and allergen challenge, and compared these measurements with the change in expired NO that occurred after serial spirometry alone. We found that ambient NO levels affected mixed expired NO. Controlling for inspired NO, we found that repeated spirometry alone produced a significant fall in mixed expired NO (p < 0.01) that was maximal after 30 min (36.6 +/- 8.5% fall). After allergen and ISH challenges, expired NO was elevated relative to levels after repeated spirometry (p < 0.01 and p = 0.065, respectively). In addition, we found that prechallenge expired NO levels were significantly correlated with the magnitude of the late fall in FEV1 following allergen challenge (r = 0.80, p < 0.01). These data demonstrate that repeated spirometry results in reduced mixed expired NO and suggest that both ISH and allergen-induced bronchoconstriction share pathobiologic mechanisms that produce increases in mixed expired NO.


Demitrack, MA Journal/The American Journal of Medicine. 105: 11S-14S.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-4/24aae6d970d103bb49a3ca65988ceb333


De Becker, P, Dendale, P, De Meirleir, K, Campine, I, Vandenborne, K and Hagers, Y
Journal/The American Journal of Medicine. 105: 22S-26S.

The purpose of this study was to determine whether chronic fatigue syndrome (CFS) patients show autonomic dysfunction at the cardiac level and if so, to discover whether these abnormalities explain the fatiguability and/or other symptoms in CFS. The study population consisted of 21 CFS patients (Centers for Disease Control and Prevention [CDC] criteria, 1988) and 13 age- and sex-matched healthy controls. The autonomic testing consisted of: (1) postural challenge: registration of heart rate and blood pressure (BP) and heart rate variability in supine and in upright position (tilted to 70[deg]); (2) Valsalva maneuver; (3) handgrip test; (4) cold pressor test; and (5) heart rate response to deep breathing. Statistical analysis was performed using the Mann Whitney rank sum test; results of the test were considered significant at the 0.05 level. After tilting heart rate was significantly higher in CFS patients compared with healthy controls (mean CFS = 88.9 beats/min vs control = 77.9 beats/min; P P = 0.02). There was a trend toward an increased heart rate during the cold pressor test. Other parameters did not differ between the CFS and control populations. The observed changes point toward a sympathetic overactivity in CFS patients when they are exposed to stress. Parasympathetic abnormalities could not be observed. Therefore, our findings provide no real explanation for the fatigue and intolerance to physical exertion in these patients.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-6/2
dd9f70f1d0a260a1ae334cb2515ffde3


The World Health Organization recently reported that breast cancer has become the most common cancer in women throughout the world. Known risk factors account for less than half of all cases of breast cancer, and inherited germ line mutations occur in at most only 10% of all cases. Cumulative exposure to estradiol and other hormones links many of the established risk factors for breast cancer. This paper reviews epidemiologic and toxicologic evidence on breast cancer risks and presents a comprehensive construct of risk factors intended to focus on the identification of those factors that can be controlled or modified. We attempt to provide a framework for interpreting the etiologic interplay of endogenous metabolic changes and environmental changes in the etiology of breast cancer. The construct we develop distinguishes between those risk factors that are directly causal, such as ionizing radiation and inherited germ cell defects, those vulnerability factors that extend the
time period during which the breast undergoes development, and those contributing factors that increase total hormonal stimulation of the breast. Some hormonally active compounds, such as those in soy and broccoli and other phytoestrogen-containing foods, can be protective against breast cancer, while others, such as some environmental contaminants, appear to increase the risk of the disease by increasing levels of harmful hormones. Efforts to explain patterns of breast cancer should distinguish between these different risk factors. Identification of vulnerability and contributing risk factors can foster the development of public policy to reduce the burden of this prevalent cancer. Prudent precautionary principles suggest that reducing exposure to avoidable or modifiable risk factors should receive high priority from the public and private sectors.

----------------------------------------------------------------------


In this article, investigators report on the presence and nature of chemical sensitivities and other indices of illness in a cohort of workers excavating a new subway tunnel located under a former gasoline station. The workers were exposed to gasoline fumes for up to approximately 2 mo when they inadvertently dug into soil contaminated by gasoline. The cohort was unique in several ways: (a) contact with gasoline was made by the workers at a time when no one had complained of multiple chemical sensitivities syndrome; (b) all were males of low socioeconomic status; (c) the exposure was well documented; (d) the cohort could be considered "naive" because, at the time of the study, the men were not members of support groups and were not being seen by clinical ecologists, and they were not labeled, either by self or others, as having multiple chemical sensitivities syndrome or any related diagnosis; and (e) at the time of interview, all workers we contacted appeared to be either gainfully employed or laid off temporarily and seeking gainful employment. We explored the health status of the workers at two different times: (1) soon after the tunnel was closed as a result of high, measured benzene-exposure levels and (2) 10-13 mo after the tunnel was closed. The workers were chronically overexposed to gasoline fumes, after which approximately one-fourth (26.7%) of our random sample of relatively naive, low-socioeconomic-status male laborers-although neither disabled nor generally litigious-reported the new onset of chemical hypersensitivities and other characteristics that fit conservative criteria for multiple chemical sensitivities syndrome.


----------------------------------------------------------------------


It is generally believed that the neuronal form of nitric oxide synthase (nNOS) is constitutively expressed and that regulation of this enzyme's activity is mediated solely by changes in cytosolic calcium concentration. Serendipitously, however, we observed that pretreatment of Chinese hamster ovary (CHO) cells, which coexpress muscarinic M1 receptors and nNOS, with 3.3 microM or 1 mM carbachol (CCh) for 48 h resulted in marked enhancement of maximal muscarinic receptor-stimulated nNOS activity as determined by L-[3H]citrulline and cyclic [3H]GMP production. This was accompanied by a decrease in the potency of CCh. Muscarinic receptor density was reduced in the agonist-pretreated cells, as determined by specific [N-methyl-3H]scopolamine methyl chloride binding, whereas competition binding studies revealed no changes in agonist affinity. Both receptor-stimulated inositol phosphate formation and elevation of intracellular calcium concentrations were found to be desensitized in agonist-pretreated cells in a manner dependent on CCh pretreatment concentration. It is interesting that ionomycin-stimulated nNOS activity was greater in CCh-pretreated cells. Also, western analysis revealed increased nNOS immunoreactivity in pretreated cells. A similar increase in nNOS immunoreactivity following agonist treatment was demonstrated in N1E-115 neuroblastoma cells, which endogenously express nNOS and muscarinic M1 receptors. Thus, the enhancement of maximal receptor-stimulated nNOS activity following agonist pretreatment can be attributed to up-regulation of nNOS. It is interesting that this augmentation of the response takes place in spite of receptor down-regulation and desensitization of multiple steps involved in nNOS activation.

(1998) [The non-specific environmental syndromes MCS (Multiple Chemical Sensitivity), IEI (Idiopathic Environmental Intolerance) and SBS (Sick Building Syndrome)].

This review starts with a clinical description of the most common unspecific environmental diseases, such as Multiple Chemical Sensitivities (MCS), Idiopathic Environmental Intolerances (IEI) and Sick Building Syndrome (SBS). These syndromes are very controversial discussed between scientific medicine and "clinical ecology". In addition, they have fundamental similarities to Chronic Fatigue Syndrome (CFS) and Fibromyalgia. Finally the spectrum of therapeutic approaches is discussed.
Couper, D, Ponsonby, AL and Dwyer, T Journal/Clin Exp Allergy. 28: 715-23.

BACKGROUND: High exposure to house dust mite allergen during the first year of life has been found to increase the risk of subsequent asthma and mite sensitization. Environmental factors, home construction and cleaning methods used are associated with levels of dust mites in the home. OBJECTIVE: To investigate determinants of levels of Der p 1 and Der f 1 mite allergens in homes of infants in southern Tasmania. METHODS: Dust samples were collected from 72 homes of infants participating in the Tasmanian Infant Health Survey (TIHS). The Der p 1 and Der f 1 allergen concentrations in these samples were measured. The TIHS interviewers obtained information from the mothers of the infants via a questionnaire, observed specified aspects of the home environment, and took readings of bedroom temperature and humidity. The effect of each item on allergen concentration in dust from bedroom floors was examined in a variety of ways. Those items which in this study appeared to be significantly related to allergen concentrations plus items which in other studies have been found to be related to allergen concentrations were then investigated further in multivariate models. RESULTS: Der p 1 allergen concentration (microg/g) and density (microg/m2) in dust from bedroom floors were found to be related to several home environment factors. In the univariate analyses, indoor humidity, 24 h maximum temperature, number of residents and a combination of floor covering and cleaning methods appeared to have a significant effect on allergen levels. These factors remained important in the multivariate model except that indicators for mould in the bathroom and drying washing on an outside line replaced indoor humidity. CONCLUSION: Features related to home dampness, the number of residents and floor covering and cleaning were major determinants of Der p 1 levels in the bedrooms studied.

Cooley, JD, Wong, WC, Jumper, CA and Straus, DC Journal/Occup Environ Med. 55: 579-84.

OBJECTIVE: To examine the role of fungi in the production of sick building syndrome. METHODS: A 22 month study in the United States of 48 schools (in which there had been concerns about health and indoor air quality (IAQ). Building indoor air and surface samples, as well as outdoor air samples were taken at all sites to look for the presence of fungi or their viable propagules. RESULTS: Five fungal genera were
consistently found in the outdoor air and comprised over 95% of the outdoor fungi. These genera were Cladosporium (81.5%), Penicillium (5.2%), Chrysosporium (4.9%), Alternaria (2.8%), and Aspergillus (1.1%). At 20 schools, there were significantly more colony forming units per cubic metre (CFU/m³) (p < 0.0001) of propagules of Penicillium species in the air samples from complaint areas when compared with the outdoor air samples and the indoor air samples from noncomplaint areas. At five schools, there were more, although not significant (p = 0.10), Penicillium propagules in the air samples from complaint areas when compared with the outdoor air samples and the indoor air samples from noncomplaint areas. In 11 schools, the indoor air (complaint areas) fungal ratios were similar to that in the outdoor air. In these 11 schools Stachybotrys atra was isolated from swab samples of visible growth under wetted carpets, on wetted walls, or behind vinyl wall coverings. In the remaining 11 schools, the fungal ratios and CFU/m³ of air were not significantly different in different areas. Many of the schools took remedial action that resulted in an indoor air fungal profile that was similar to that outdoors. CONCLUSIONS: Propagules of Penicillium and Stachybotrys species may be associated with sick building syndrome.


Although oxidants such as superoxide (O2.) and hydrogen peroxide (H2O2) play a role in host-mediated destruction of foreign pathogens yet excessive generation of oxidants may lead to a variety of pathological complications in the cardiovascular system. An important mechanism by which oxidants cause dysfunction of the cardiovascular system appears to be due to the increase in intracellular free Ca2+ concentration. Oxidants cause cellular Ca2+ mobilization by modulating activities of a variety of regulators such as Na+/H+ and Na+/Ca2+ exchangers, Na+/K+ ATPase and Ca2+ ATPase and Ca2+ channels that are associated with Ca2+ transport in the plasma membrane and the sarco(endo)plasmic reticular membrane of myocardial cells. Recent research have suggested that the increase in Ca2+ level by oxidants plays a pivotal role in inducing several protein kinases such as protein kinase C, tyrosine kinase and mitogen activated protein kinases. Oxidant-mediated alteration of different signal transduction systems and their interactions eventually regulate a variety of pathological conditions such as atherosclerosis, apoptosis and necrosis in the myocardium.

Parallels between post-polio fatigue and chronic fatigue syndrome: a common pathophysiology?

Fatigue is the most commonly reported and most debilitating of post-polio sequelae affecting the >1.8 million North American polio survivors. Post-polio fatigue is characterized by subjective reports of difficulty with attention, cognition, and maintaining wakefulness. These symptoms resemble those reported in nearly 2 dozen outbreaks of post-viral fatigue syndromes (PVFS) that have recurred during this century and that are related clinically, historically, anatomically, or physiologically to poliovirus infections. This article reviews recent studies that relate the symptoms of post-polio fatigue and chronic fatigue syndrome (CFS) to clinically significant deficits on neuropsychologic tests of attention, histopathologic and neuroradiologic evidence of brain lesions, impaired activation of the hypothalamic-pituitary-adrenal axis, increased prolactin secretion, and electroencephalogram (EEG) slow-wave activity. A possible common pathophysiology for post-polio fatigue and CFS, based on the Brain Fatigue Generator Model of PVFS, and a possible pharmacotherapy for PVFS based on replacement of depleted brain dopamine, will be described.

http://www.sciencedirect.com/science/article/B6TDC-3VF94GM-F/2701d7b8d843f5acd1e0db6c30715fb7

Somatic complaints disproportionately contribute to Beck Depression Inventory estimates of depression severity in individuals with multiple chemical sensitivity.

A number of individuals with multiple chemical sensitivity (MCS) are also diagnosed with depression. However, there is content overlap in MCS and symptoms of depression with respect to somatic complaints. The Beck Depression Inventory (BDI) was used to document severity of depressive symptomatology in 42 individuals with MCS. The purpose was to determine the extent to which somatic complaints contributed to the total BDI score. Analysis of cognitive-affective and somatic-performance complaints subscale indicated a significantly higher mean item score on somatic-performance items, relative to cognitive-affective items (t = 6.43, P < 0.05). Consequently, the total BDI score classified a greater percentage (43%) of the sample as moderately depressed than did the cognitive-affective subscale score (29%). An item analysis of the BDI revealed that individuals with MCS tended to endorse more somatic-performance items than did a sample of depressed outpatients. Two alternative interpretations are possible: (a) the BDI total score overestimated severity of depressive symptomatology in this sample, and/or (b) individuals with MCS tended to express depressive symptomatology in terms of somatic complaints. It was
recommended that until the etiology of MCS is better understood, caution be used when estimating severity of depressive symptomatology in individuals with MCS when measures include somatic items.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9800170

(1998) Prenatal exposure to neurotoxicants dieldrin or lindane alters tert-butylbicyclopophosphorothionate binding to GABA(A) receptors in fetal rat brainstem.

GABA acts as a trophic signal for cultured embryonic rat monoamine neurons by activating GABA(A) receptors. These effects are blocked by the organochlorine insecticide dieldrin and the classic GABA(A) antagonist bicuculline. Both dieldrin and another organochlorine insecticide, lindane, block the effects of GABA on the GABA(A) receptor by binding directly to the Cl- channel. Therefore, prenatal exposure to these chemicals could lead to disturbances in the trophic actions of GABA on monoamine neurotransmitter systems in the embryonic brain and produce alterations in GABA(A) receptor expression and function. Effects of daily prenatal exposure to organochlorine insecticide (dieldrin or lindane) or bicuculline from embryonic day (E)12-17 were determined in brains of E17 fetal rats using t-[35S]butyl-bicyclophosphorothionate ([35S]TBPS) binding. This radioligand was chosen because, like organochlorine insecticides, it binds directly to GABA(A) receptor/Cl- channels. [35S]TBPS binding was analyzed in extensively washed membranes from E17 brainstem and whole brain with the brainstem removed ('rest of brain') at a TBPS concentration that approximated the KD determined in [35S]TBPS saturation binding experiments performed on normal E17 rat brainstem. In utero exposure to dieldrin, lindane, or bicuculline from E12-E17 caused a significant reduction in the amount of [35S]TBPS binding in E17 brainstem compared to vehicle-injected controls, but had no significant effect on 'rest of brain'. These data suggest that in utero exposure to organochlorine insecticides that act as GABA(A) antagonists negatively regulate expression of GABAA receptors in fetal brainstem. If these effects persist, they could lead to disturbances in postnatal functions of the ascending GABAergic system, possibly with behavioral consequences.


The present state of knowledge and controversies about the etiopathogenesis of type 1 diabetes can be summarized as follows: GENETICS: MHC class II genes (IDDM1)
confer the strongest susceptibility with a hierarchy DQ > DR; more than ten other chromosome regions (IDDM2 to IDDM13) have been identified as candidates for linkage with type 1 diabetes: currently, there is consensus for insulin (IDDM2) and a few other loci, while the remainder await confirmation. ENVIRONMENT: The role of milk as a trigger is debated. In fact, the protective effect of breast feeding is marginal, while the immune response to milk proteins in type 1 diabetics is very heterogeneous; moreover, the putative autoantigens showing sequence homology with milk proteins have been questioned. With regard to viruses, seasonal variations of incidence have been confirmed, although not uniform across countries; serological studies are controversial, while isolation of viruses from diabetic pancreases remains anecdotal; very interesting is the demonstration of enteroviral infection in pregnant mothers of future diabetic children, although this does not prove a causal role; a new frontier of investigation could be that of endogenous retroviruses acting either as autoimmune genes or infectious agents. AUTOIMMUNITY: GAD65, IA2 and insulin are at present the only established autoantigens; autoantibodies to these molecules, used in combination with ICA, can accurately predict type 1 diabetes; B-lymphocytes and autoantibodies might play a pathogenetic role; autoantigen targets of T-lymphocytes are yet to be characterized; assays for measuring autoreactive T-lymphocytes require standardization; antigen-specific Th1/Th2 relationship in type 1 diabetes remains controversial.


Long-acting somatostatin analogs have recently become supplemental drugs in the treatment of neurofibroma because of their marked tumor growth inhibitory effect. Somatostatin is currently under extended evaluation in other cancers as a possible supplemental drug to the treatment protocols in use. The mode of action is not known. Somatostatin has been shown to cause glucose intolerance by inhibiting glucose-6-phosphate dehydrogenase (G6PD) in fish liver. Recent data generated in our laboratory indicate that it is this pathway and the transketolase reactions of the pentose cycle (PC) which are directly involved in the ribose synthesis process of pancreatic adenocarcinoma cells. In cell culture, somatostatin alone inhibited glucose carbon recycling through the PC by 5.7%, which was increased to 19.8% in combination with oxythiamine, a competitive inhibitor of transketolase. Oxythiamine produced strong apoptosis in in-vitro hosted tumor cells. We hypothesize that somatostatin- and oxythiamine-induced antiproliferative action is mediated by the inhibition of G6PD, transketolase, or both.
(1998) **Involvement of endogenous nitric oxide signalling system in brain muscarinic acetylcholine receptor activation.**

Biochemical signalling events coupled to muscarinic cholinergic receptors (mAChR), specifically those related to nitric oxide (NO) production, were studied on rat cerebral frontal cortex. The mAChR agonist carbachol was found to exert a specific biphasic action on NO synthase (NOS) activity: low doses ranging between 10(-9) M to 10(-7) M lead to NOS activation while higher doses (>10(-6) M) inhibited enzymatic activity. Carbachol stimulatory action was blunted by agents that interfere with calcium-calmodulin while a protein kinase (PKC) inhibitor, staurosporine was able to abrogate the inhibitory effect. Moreover, PKC activity showed maximum translocation to cerebral frontal cortex membranes with carbachol concentrations that inhibited NO production. Products from phosphoinosite (PI) hydrolysis are involved in these actions as carbachol was found to increase PI turnover in a dose dependent manner. These results would serve as an example of cross-talk between both enzymatic pathways.

(1998) **Excitatory amino acid antagonists alleviate convulsive and toxic properties of lindane in mice.**
Blaszczak, P and Turski, WA Journal/Pharmacol Toxicol. 82: 137-41.

Pesticides acting at GABAA receptors may induce convulsions in man and animals, but the mechanisms responsible for their convulsant activity are not fully explained. The following excitatory amino acid antagonists were studied for their protective action in mice intoxicated with chlorinated hydrocarbon insecticide lindane (gamma-hexachlorocyclohexane): the competitive NMDA antagonist: 3-(2-carboxypiperazine-4-yl)propenyl-1-phosphonic acid (D-CPPene, 20 mg/kg), the non-competitive NMDA antagonist: dizocilpine (MK-801, 0.4 mg/kg), the glycine site antagonist of NMDA receptor: 2-phenyl-1,3-propane-diol dicarbamate (felbamate, 400 mg/kg) and the competitive AMPA antagonist: 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)quinoxaline (NBQX, 100 mg/kg). Systemic administration of an antagonist prior to lindane resulted in a strong anticonvulsant effect. D-CPPene, MK-801 and NBQX produced a marked increase of CD50 values of lindane for clonic convulsions. All the antagonists protected animals against tonic convulsions. Toxicity of lindane was potently reduced, as assessed 2, 24 and 120 hr after administration of the pesticide. Our results demonstrate that excitatory amino acid antagonists reduce convulsant properties and toxicity of lindane, suggesting that excitatory amino acid neurotransmission may be involved in its central action.
(1998) **Self-reported chemical sensitivity and wartime chemical exposures in Gulf War veterans with and without decreased global health ratings.**

This cross-sectional telephone survey study assessed prevalence rates of current chemical sensitivity, frequency of chemical odor intolerance, and self-reported Persian Gulf chemical exposures among 41 randomly sampled Department of Veterans Affairs outpatients who were Persian Gulf War (PGW) and PGW-era veterans. The participants were drawn from an initial random list of 100 veterans, of whom 28 PGW and 20 era veterans had correct telephone data on file. Of those contacted, 86% of PGW veterans (24/28) and 85% of era veterans (17/20) agreed to participate. Significantly more PGW veterans with poorer global health after military service reported considering themselves now "especially sensitive to certain chemicals" (86%, 12/14) than did the PGW veterans or era veterans in stable health (both comparison groups 30%, 3/10). Among PGW veterans, the subset with worse health associated with marked increases in chemical odor intolerance since their military service had a significantly higher odds ratio for exposure to multiple chemicals, notably wartime pesticides and insect repellent, than did comparison groups. The high rate of chemical sensitivity of PGW veterans with deteriorated health is almost three times that in PGW-era veterans and in elderly primary care outpatient veterans at the same Department of Veterans Affairs medical center and in community-based civilian samples (i.e., 30%). These preliminary findings suggest the need for further study of chemical sensitivity, including tests for acquired increases in neural sensitizability to multiple low-level chemicals, in ill PGW veterans.


---------------------------------------------------------------

(1998) **Differential resting quantitative electroencephalographic alpha patterns in women with environmental chemical intolerance, depressives, and normals.**

BACKGROUND: Previous research suggests that a subset of individuals with intolerance to low levels of environmental chemicals have increased levels of premorbid and/or comorbid psychiatric disorders such as depression, anxiety, and somatization. The purpose of this study was to evaluate the psychological profiles and quantitative electroencephalographic (qEEG) profiles at baseline of women with and without chemical intolerance (CI). METHODS: Participants were middle-aged women who reported illness from the odor of common chemicals (CI, n = 14), depressives without such intolerances (D, n = 10), and normal controls (N, n = 11). They completed a set of psychological scales and underwent two separate qEEG recording laboratory...
sessions spaced 1 week apart, at the same time of day for each subject. RESULTS: CI were similar to D with increased lifetime histories of physician-diagnosed depression (71% vs. 100%), Symptom Checklist 90 (revised) (SCL-90-R) somatization scores, Barsky Somatic Symptom Amplification, and perceived life stressfulness, although D had more distress than either CI or N on several other SCL-90-R subscales. CI scored significantly higher on the McLean Limbic Symptom Checklist somatic symptom subscale than did either D or N. On qEEG, CI exhibited significantly greater overall resting absolute alpha activity with eyes closed, especially at the parietal midline site (Pz), and increased (sensitized) frontal alpha from session 1 to 2, in contrast with the D and N groups. D showed right frontal asymmetry in both sessions, in comparison with CI. CONCLUSIONS: The data indicate that CI with affective distress diverge from both D without chemical intolerance and N in qEEG alpha patterns at resting baseline. Although CI descriptively resemble D with increased psychological distress, the CI's greater alpha suggests the possibility of a) central nervous system hypo-, not hyper-, activation; and/or b) an overlap with EEG alpha patterns of persons with positive family histories of alcoholism.

(1998) Serum neopterin and somatization in women with chemical intolerance, depressives, and normals.

The symptom of intolerance to low levels of environmental chemicals (CI, chemical intolerance) is a feature of several controversial polysymptomatic conditions that overlap symptomatically with depression and somatization, i.e., chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity, and Persian Gulf syndrome. These syndromes can involve many somatic symptoms consistent with possible inflammation. Immunological or neurogenic triggering might account for such inflammation. Serum neopterin, which has an inverse relationship with l-tryptophan availability, may offer a marker of inflammation and macrophage/monocyte activation. This study compared middle-aged women with CI (who had high levels of affective distress; n = 14), depressives without CI (n = 10), and normals (n = 11). Groups did not differ in 4 p.m. resting levels of serum neopterin. However, the CI alone had strong positive correlations between neopterin and all of the scales measuring somatization. These preliminary findings suggest the need for additional research on biological correlates of 'unexplained' multiple somatic symptoms in subtypes of apparent somatizing disorders.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9701717
(1998) Quantitative EEG patterns during nose versus mouth inhalation of filtered room air in young adults with and without self-reported chemical odor intolerances.

Individuals who report illness (e.g. nausea, headache) from common chemical odors tend to report CNS symptoms suggestive of olfactory-limbic system involvement. This study compared the resting quantitative electroencephalographic (qEEG) patterns of young adult college students reporting subjectively elevated chemical odor intolerance ratings (HICI) with those of controls reporting little or no odor intolerance (LOCI). Each group was subdivided into those with higher (HIDEP) vs. lower (LODEP) ratings of concomitant depression. Nineteen channels of EEG were recorded during a single session over four separate rest periods, respectively, following baseline, cognitive, chemical exposure and olfactory identification tests. Each recording involved two 30-s, eyes-closed, filtered room air breathing conditions: (1) nose inhalation followed by mouth exhalation and (2) mouth inhalation followed by mouth exhalation. HICI showed significantly less beta 1 (beta 1) over the temporal-central region during nose than during mouth inhalation. Over some temporal and central leads, task, DEP and CI interacted to influence beta 1 as well. For theta (theta), CI differences emerged during nose inhalation after the cognitive task at Cz, after chemical exposures at C3, Cz and C4 and after the olfactory ID task at C4. Cz differences emerged during mouth breathing after the olfactory ID task at Cz, C4 and T4. The T5-T6 coronal array showed significant CI differences after chemical exposures during nose breathing and during mouth breathing after the cognitive and olfactory ID tasks. The theta findings in the HICI may be related to reports of disturbed attention in CI.

(1998) Illness from low levels of environmental chemicals: relevance to chronic fatigue syndrome and fibromyalgia.
Bell, IR, Baldwin, CM and Schwartz, GE Journal/Am J Med. 105: 74S-82S.

This article summarizes (1) epidemiologic and clinical data on the symptoms of maladies in association with low-level chemicals in the environment, i.e., environmental chemical intolerance (CI), as it may relate to chronic fatigue syndrome (CFS) and fibromyalgia; and (2) the olfactory-limbic neural sensitization model for CI, a neurobehavioral synthesis of basic and clinical research. Severe CI is a characteristic of 20-47% of individuals with apparent CFS and/or fibromyalgia, all patients with multiple chemical sensitivity (MCS), and approximately 4-6% of the general population. In the general population, 15-30% report at least minor problems with CI. The levels of chemicals reported to trigger CI would normally be considered nontoxic or subtoxic. However, host factors--e.g., individual differences in susceptibility to neurohormonal sensitization (amplification) of endogenous responses--may contribute to generating a disabling intensity to the resultant multisystem dysfunctions in CI. One site for this
amplification may be the limbic system of the brain, which receives input from the olfactory pathways and sends efferents to the hypothalamus and the mesolimbic dopaminergic [reward] pathway. Chemical, biologic, and psychological stimuli can initiate and elicit sensitization. In turn, subsequent activation of the sensitized limbic and mesolimbic pathways can then facilitate dysregulation of behavioral, autonomic, endocrine, and immune system functions. Research to date has demonstrated the initiation of neurobehavioral sensitization by volatile organic compounds and pesticides in animals, as well as sensitizability of cardiovascular parameters, beta-endorphin levels, resting EEG alpha-wave activity, and divided-attention task performance in persons with CI. The ability of multiple types of widely divergent stimuli to initiate and elicit sensitization offers a new perspective on the search for mechanisms of illness in CFS and fibromyalgia with CI.

Bell, IR, Baldwin, CM, Russek, LG, Schwartz, GE and Hardin, EE Journal/J Womens Health. 7: 1135-47.

This study (ntotal = 35) compared early life stress ratings, parental relationships, and health status, notably orthostatic blood pressures, of middle-aged women with low-level chemical intolerance (CI group) and depression, depressives without CI (DEP group), and normals. Environmental chemical intolerance is a symptom of several controversial conditions in which women are overrepresented, that is, sick building syndrome, multiple chemical sensitivity, chronic fatigue syndrome, and fibromyalgia. Previous investigators have postulated that people with CI have variants of somatization disorder, depression, posttraumatic stress disorder (PTSD) initiated by childhood abuse or a toxic exposure event. One neurobehavioral model for CI, somatization disorder, recurrent depression, and PTSD is neural sensitization, that is, the progressive amplification of host responses (e.g., behavioral, neurochemical) to repeated intermittent stimuli (e.g., drugs, chemicals, endogenous mediators, stressors). Females are more vulnerable to sensitization than are males. Limbic and mesolimbic pathways mediate central nervous system sensitization. Although both CI and DEP groups had high levels of life stress and past abuse, the CI group had the most distant and weak paternal relationships and highest limbic somatic dysfunction subscale scores. Only the CI group showed sensitization of sitting blood pressures over sessions. Together with prior evidence, these data are consistent with a neural sensitization model for CI in certain women. The findings may have implications for poorer long-term medical as well as neuropsychiatric health outcomes of a subset of women with CI. Subsequent research should test this model in specific clinical diagnostic groups with CI.


The production of nitric oxide (NO) by rat adherent peritoneal cells stimulated with preformed IgE/Dinitrophenyl-BSA (DNP-BSA) complexes and its dependence on the activation of the transcription factor NF-kappa B were studied. Stimulation with IgE DNP-BSA complexes at equivalence induced both the production of NO and an increased expression of the inducible isoform of NO synthase (iNOS) protein. Both events were also elicited by a rabbit polyclonal F(ab')2 anti-CD23 cross-reacting with rat CD23, thus suggesting Fc epsilon RII/CD23 antigen as the IgE-binding structure involved in the triggering of the response and ruling out an interaction of the antibody via its Fc portion. Inhibition of redox-sensitive signaling mechanisms by the antioxidant pyrrolidine dithiocarbamate (PDTC) blocked NO production, iNOS expression, and NF-kappa B activation elicited by both IgE/DNP-BSA complexes and anti-CD23 F(ab')2, thus suggesting the involvement of NF-kappa B in the signaling pathway leading to the transcriptional activation of iNOS. These results show the existence in rat peritoneal macrophages of a signaling pathway triggered by CD23 engagement that promotes nuclear translocation of NF-kappa B and transcriptional activation of the inducible isoform of NO synthase.


Baldwin, CM and Bell, IR Journal/Arch Environ Health. 53: 347-53.

Chemical intolerance, or reported illness from odors of common environmental chemicals (e.g., car exhaust, pesticides), is emerging as an important environmental and public health-care issue. Epidemiologic methods provide relevant heuristic devices
for studies of complex disorders, such as chemical intolerance. The authors examined personal and reported parental cardiopulmonary disease prevalence rates in a community sample of chemically intolerant and control individuals. A county government (Tucson, Arizona) employee and kin subset (N = 181; 113 households) completed standard health questionnaires. Investigators determined chemical intolerance (n = 41/181) from self-reports of individuals who felt "moderately" to "severely" ill from exposure to at least three of five chemicals (i.e., car exhaust, pesticides, paint, new carpet, and perfume) on a Chemical Odor Intolerance Index. The authors chose the control group (n = 57/181) on the basis of self-reports of "never" feeling ill on the Chemical Odor Intolerance Index. The chemically intolerant group, which primarily comprised women (78% versus 51% of controls, p < .05), was significantly more likely to report-and to have sought--medical attention for heart problems, bronchitis, asthma, and pneumonia. Reports of heart problems in the chemically intolerant index cases and the occurrence of heart disease in both of their parents were significant (Fisher's p < .05). The chemically intolerant individuals were also significantly more likely to report maternal histories of chest problems (e.g., inhalant allergens, tuberculosis) than controls. The findings of the study suggested that the chemically intolerant individuals (a preponderance of whom were women [sex-related risk]) were more likely to have (a) reported cardiopulmonary problems (i.e., greater health risk); (b) actively sought medical care for these problems (i.e., increased medical utilization); and (c) reported more parental illnesses—particularly heart disease, asthma, and diabetes (i.e., genetic risk). Additional community-based studies of chemical intolerance are needed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9766480

Ashford, N and Miller, C John Wiley & Sons, Inc.


BACKGROUND: Multiple drug allergy syndrome (MDAS) caused by antibiotics is frequently observed in allergy departments; however, risk factors for such a condition as well as the means to detect patients prone to MDAS are poorly defined.

OBJECTIVE: The identification of patients prone to MDAS and the detection of risk factors for multiple antibiotic sensitivity. METHODS: Two hundred fifty-three elective oral challenges with alternative antimicrobial drugs were performed in 120 patients with histories of recent allergic reactions to antibiotics. RESULTS: Twenty-three (19%)
subjects reacted to at least one antibiotic class. All reactions were mild and easily controlled by conventional therapy. Female sex, history of multiple antibiotic reactions, and reactions to nonsteroidal antinflammatory drugs were the main risk factors for reactions to alternative antibiotics. To date, no patient has reported immediate adverse reactions to drugs negative on oral challenge tests but one had urticaria/angioedema on the fifth day of full dose treatment with ofloxacin. CONCLUSIONS: Elective oral challenges with alternative antibiotics are a sensitive, specific, and safe means to detect patients with MDAS, thus sparing them more severe adverse reactions caused by full dose therapies. The recommendation to perform oral challenge tests with antibiotics just before their therapeutic use seems unnecessary and should be reconsidered.


Diaphragmatic fatigue has been associated with increased production of reactive oxygen species. Among the defenses against reactive oxygen species is the glutathione redox system. The selenium-dependent enzyme glutathione peroxidase is an important component of this system. Thus, we hypothesized that selenium deficiency would lower glutathione peroxidase activity and render the diaphragm more susceptible to a mild exertional protocol. Sprague-Dawley rats were fed a selenium-deficient or control diet for 12 weeks then divided into four experimental groups: (1) unloaded, basic diet with selenium supplementation (control); (2) unloaded, selenium-deficient diet; (3) loaded, basic diet with selenium supplementation; and (4) loaded, selenium-deficient diet. Diaphragmatic in vitro contractile properties, glutathione peroxidase activity and glutathione content were measured. During inspiratory resistive loading, the animals breathed against an inspiratory resistor at 70% of maximal airway pressure until the target pressure was not achieved for five consecutive breaths. Selenium deficiency resulted in a significant decrease in diaphragmatic glutathione peroxidase activity, without changes in total glutathione content. Neither selenium deficiency nor inspiratory resistive loading alone impaired diaphragmatic contractility. Selenium deficiency in conjunction with inspiratory resistive loading resulted in a significant decrease in diaphragmatic twitch and tetanic force, with a downward shift in the force/frequency curve. These data suggest that selenium deficiency lowers diaphragmatic glutathione peroxidase activity, and when these animals are subjected to the oxidative stress of resistive loading, there is an impairment in muscle function. We conclude that a functional glutathione peroxidase is necessary to protect the diaphragm against the effects of resistive loading.

Various environmental triggers, e.g. certain viruses and dietary factors, are thought to initiate the autoimmune process, leading to the destruction of pancreatic beta-cells and consequent Type 1 diabetes. A genetic predisposition is another prerequisite allowing the autoimmune process to progress. Twin studies, major geographical variations in incidence rates, temporal trends in the incidence and findings in migrant studies indicate that environmental factors play a crucial role in the development of Type 1 diabetes. In the present review the major focus is on dietary factors, and among them particularly the possible role of cow's milk proteins. The cow's milk and Type 1 diabetes hypothesis was developed more than 10 years ago, and the issue is still not settled. Among viral infections, enteroviruses are today the most interesting group of viruses in this respect, as recent prospective studies indicate that these viruses may trigger and potentiate existing beta-cell autoimmunity. Among toxins, particularly N-nitroso compounds are of potential interest, as they are probably involved in the aetiology of some cases. Finally, psychosocial factors and the interaction between genetic predisposition and environmental factors are briefly discussed.


Patients with organic solvent-induced toxic encephalopathy (TE) (n = 13) were followed up seven years after the application of an intervention program. They were also compared with untreated TE patients diagnosed at the same time (n = 26) and with unexposed referents (n = 39). Psychological distress, social function, and coping ability and style were measured with the Symptom Checklist-90, Interview Schedule of Social Interaction, and Sense of Coherence and Strategies to Handle Stress questionnaires. Both TE groups had unchanged function in neuropsychological tests. Members of the treated group had improved their social functioning and reduced their mental stress but were not any better than the untreated patients. Compared with referents, the TE patients continued to live with increased psychological distress and used predominantly emotionally focused strategies to cope with their problems. This can be a cause for concern in family life and can also make gainful work impossible.
(1998) Chronic toxic encephalopathy: social consequences and experiences from a rehabilitation program.

This study evaluates a rehabilitation program designed to address the social function issues of patients with solvent-induced chronic toxic encephalopathy (TE) and their families. Fourteen newly diagnosed men and their spouses participated in group sessions. The patients were given cognitive training, and crisis intervention measures were implemented. Their spouses were given information about the disease and had an opportunity to talk about their emotions and the disease's impact on the family's functioning. Interviews after the program showed that patients and their spouses were experiencing less psychological distress and increased social activity and had begun reestablishing contacts with friends. Their psychiatric symptoms, measured during a structured interview by a nurse, decreased significantly immediately after the treatment period but increased again after 6 months. Only a long-term follow-up study comparing the experiences of these patients with those of untreated TE patients can determine whether improvement can be sustained over the long term.

(1998) NIEHS seeks data on multiple chemical sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9647890


One of the national health objectives for 2000 (HP2000) is to establish and monitor nonoccupational "sentinel" environmental diseases, including asthma, heatstroke, hypothermia, heavy metal poisoning, pesticide poisoning, carbon monoxide poisoning, acute chemical poisoning, and methemoglobinemia, in at least 35 states (baseline: 0 states in 1990) (objective 11.16). To assess progress toward this objective, the Council of State and Territorial Epidemiologists (CSTE), the Association of Schools of Public Health, and CDC conducted a telephone survey of environmental epidemiologists in each of the 50 states, the District of Columbia, and Puerto Rico during June-August 1997. This report summarizes the results of that survey, which indicate that progress is being made toward the HP2000 objective.


Patients reporting sensitivity to multiple chemicals at levels usually tolerated by the healthy population were administered standardized questionnaires to evaluate their symptoms and the exposures that aggravated these symptoms. Many patients were referred for medical tests. It is thought that patients with chemical sensitivity have organ abnormalities involving the liver, nervous system (brain, including limbic, peripheral, autonomic), immune system, and porphyrin metabolism, probably reflecting chemical injury to these systems. Laboratory results are not consistent with a psychologic origin of chemical sensitivity. Substantial overlap between chemical sensitivity, fibromyalgia, and chronic fatigue syndrome exists: the latter two conditions often involve chemical sensitivity and may even be the same disorder. Other disorders commonly seen in chemical sensitivity patients include headache (often migraine), chronic fatigue, musculoskeletal aching, chronic respiratory inflammation (rhinitis, sinusitis, laryngitis, asthma), attention deficit, and hyperactivity (affected younger children). Less common disorders include tremor, seizures, and mitral valve prolapse. Patients with these overlapping disorders should be evaluated for chemical sensitivity and excluded from control groups in future research. Agents whose exposures are associated with symptoms and suspected of causing onset of chemical sensitivity with chronic illness include gasoline, kerosene, natural gas, pesticides (especially chlordane and chlorpyrifos), solvents, new carpet and other renovation materials, adhesives, glues, fiberglass, carbonless copy paper, fabric softener, formaldehyde and glutaraldehyde, carpet shampoos (lauryl sulfate) and other cleaning agents, isocyanates, combustion products (poorly vented gas heaters, overheated batteries), and medications (dinitrochlorobenzene for warts, intranasally packed neosynephrine, prolonged antibiotics, and general anesthesia with petrochemicals). Multiple mechanisms of chemical injury that magnify response to exposures in chemically sensitive patients can include neurogenic inflammation (respiratory, gastrointestinal, genitourinary), kindling and time-dependent sensitization (neurologic), impaired porphyrin metabolism (multiple organs), and immune activation.
White, RF Journal/Govt Reports Announcements & Index. NTIS/AD-A327 679/7, Product re.

TD3: Persian Gulf War (PGW) veterans have reported a constellation of health symptoms referred to as Gulf War Syndrome. Suggested causes of these symptoms include exposure to environmental hazards and biological or chemical warfare agents. Some of the symptoms reported overlap with those of post traumatic stress disorder (PTSD), multiple chemical sensitivity (MCS) or chronic fatigue syndrome (CFS). Both exposure to neurotoxicants and the disorders noted above are known to produce cognitive impairments. This study evaluates the neuropsychological functioning of PGW era veterans who are seeking treatment or evaluation for any type of health or adjustment complaint. PGW deployed patients will be compared with non-deployed patients. These subjects will also be compared with subjects from a (non-treatment seeking) research sample of PGW veterans. All patients and research subjects will additionally be administered a standardized set of questionnaires and interviews to identify their health symptoms includ

---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------


People suffering from multiple chemical sensitivity (MCS) complain of a variety of symptoms that could impair cognitive and psychomotor function either directly or indirectly. This paper discusses the use of cognitive and psychomotor performance tests together with some experiment designs that could be considered for use to assess fitness of MCS sufferers for work or the efficacy of diagnostic, preventative, or therapeutic measures. The tests could also contribute to the body of objective information on MCS and help sway the opinion of those who are dubious of its authenticity. The credentials of cognitive and psychomotor performance tests are derived from their successful use in studying the effects of drugs, and the types of tests are illustrated by describing those used by the United Kingdom Defence Evaluation and Research Agency Chemical and Biological Defence Human Studies Group, which has been involved in the assessment of drugs and chemicals on work performance for many years. The tests include mathematical, verbal and spatial processing, tracking, reaction time, attention and vigilance, and memory tests. The discussion of experiment designs includes both repeated measures and parallel groups designs together with their advantages and disadvantages and some suggested modifications to accommodate the particular problems posed by MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167986

Skepticism about the validity of the multiple chemical sensitivity (MCS) syndrome stems in part from the lack of supporting experimental data. Performing the relevant experiments requires investigators to take account of broad variations in sensitivity and the need to establish reproducibility. The research approach best suited for MCS studies is the single-subject design. In contrast with conventional group designs, such designs emphasize repeated observations on individual subjects. Repeated observations of this kind constitute a time series in which successive measurements are serially or autocorrelated. One statistical method that bypasses the serial correlation problem is randomization tests. Explicit time series analyses take account of this aspect and can correct for it to determine the impact of an intervention such as a chemical exposure.


(1997) Activation of neuronal nitric oxide synthase by M2 muscarinic receptors associated with a small increase in intracellular calcium.

We investigated the coupling of the M2 muscarinic acetylcholine receptors expressed in Chinese hamster ovary cells to activation of neuronal nitric oxide (NO) synthase. Stimulation of guanylate cyclase activity in detector neuroblastoma cells was used as an indirect measure of the generation of NO in Chinese hamster ovary cells. The muscarinic agonist carbachol induced marked time- and concentration-dependent enhancement of the activity of NO synthase. Activation of neuronal NO synthase by M2 muscarinic receptors was associated with a small increase in the concentration of intracellular Ca2+. These data suggest the presence of alternate mechanisms of activation of neuronal NO synthase which might be operative in the absence of large changes in the concentration of cellular Ca2+. These findings help to understand the mechanisms of activation of NO synthase.

The term fibromyalgia describes a complex syndrome characterized by pain amplification, musculoskeletal discomfort, and systemic symptoms. Although its existence has been controversial, nearly all rheumatologists now accept fibromyalgia as a distinct diagnostic entity. In fact, in the United States it is the third or fourth most common reason for rheumatology referral. Exciting new insights into the aetiology, pathogenesis, diagnosis and treatment of fibromyalgia will be reviewed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9073320

(1997) Genome study maps chemical sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9208251

(1997) Multiple chemical sensitivity. A view from under the grassroots.

(1997) Multiple chemical sensitivity a view from under the grassroots.

Biosis copyright: biol abs. rrm journal article human patient multiple chemical sensitivity environmental hazards toxicology public health pollution EPA pathogenesis immune system disease diagnosis

VanEenwyk, J Journal/Public Health. 111: 405-10.

Public health workers are challenged to address community health concerns believed to be related to environmental exposures. The challenge is heightened when there are multiple potential exposures and numerous health concerns. In a community in Washington State, we employed different approaches depending on the specificity of diagnosis and the relation of the disease to environmental exposures. For diseases
with specific diagnoses and questionable associations with environmental exposures, we began by determining whether rates of disease were higher than expected. Different approaches were needed for three different health concerns. Major limitations were estimating community population counts and obtaining comparison rates from published literature. Despite limitations, epidemiologic data developed at a relatively low cost were useful in assisting the community in understanding its health status.


(1997) Learning to have psychosomatic complaints: conditioning of respiratory behavior and somatic complaints in psychosomatic patients.

OBJECTIVE: Assuming a subjective similarity between the experience of a hyperventilation episode and inhaling CO2-enriched air, we tested whether a respiratory challenge in association with a particular stimulus could result in altered respiratory behavior and associated somatic complaints upon presenting the stimulus only. METHOD: Psychosomatic patients (N = 28) reporting hyperventilation complaints participated in a differential conditioning paradigm using odors with a positive or negative valence as conditioned stimuli (CS+ or CS-) and 7.4% CO2-enriched air as the unconditioned stimulus (US). Three CS+ and three CS-acquisition trials were run. During the test phase, two CS(+) - and two CS(-)-only trials were run, followed by two new test odors (with a positive or negative valence). Respiratory frequency, tidal volume, end-tidal fractional concentration of CO2, and heart rate were measured throughout the experiment. Somatic complaints were registered after each trial.

RESULTS: We observed a) increased respiratory frequency and an elevated level of somatic complaints upon presenting the CS+ only; b) a selective association effect: conditioning was only apparent with the negatively valenced CS+ odor; c) no generalization of respiratory responses and complaints to the new odors; d) no conditioning effect on dummy complaints that are usually not reported when inhaling CO2; e) in exploratory comparisons with normal subjects, stronger conditioning effects on typical hyperventilation complaints in patients, and, in female subjects, on respiratory frequency. CONCLUSION: Respiratory responses and psychosomatic complaints can be elicited by conditioned stimuli in a highly specific way. The findings are relevant for disorders in which respiratory abnormalities and/or psychosomatic complaints may play a role and for multiple chemical sensitivity.


http://www.sciencedirect.com/science/article/B6T4S-3RTS11X-P/2362c4f09937e6dca33d40217f7112327

(1997) Multiple chemical sensitivities or idiopathic environmental intolerances: psychophysiologic foundation of knowledge for a psychogenic explanation.  


The Washington State Managed Care Pilot Project (MCP) tested the effects of experience-rated capitation on medical and disability costs, quality of care, worker satisfaction with medical care, and employer satisfaction in MCP-covered workers, compared with matched fee-for-service controls. In the MCP, medical costs were reduced by approximately 27%, functional outcomes remained the same, workers were less satisfied with their treatment and access to care initially, and employers were much more satisfied with the quality and speed of the information received from the providers. The authors believe that it was the occupational medicine-based delivery model, working in conjunction with the method of reimbursement and the cultural context of managed care, that was the most significant innovation leading to the MCP.
successes. This article describes the occupational medicine-based delivery model implemented for the MCP.


Chemical sensitivity in humans may be an acquired disorder in which individuals become increasingly sensitive to chemicals in the environment. It is hypothesized that in individuals with multiple chemical sensitivity (MCS), a sensitization process has occurred that is akin to behavioral sensitization and kindling observed in rodents. In the rodent sensitization model, repeated exposure to stress or drugs of abuse enhances behavioral and neurochemical responses to subsequent stimuli (stress or drugs of abuse). Kindling is a form of sensitization in which repeated application of electrical stimuli applied to the brain at low levels culminates in the induction of full-blown seizures when the same stimulus is applied at a later time. A similar sensitization of specific limbic pathways in the brain may occur in individuals with MCS. The time-dependent nature of sensitization and kindling and the role of stress in the development of sensitization are discussed in the context of rodent models, with an emphasis on application of these models to human studies of MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167981

Smith, CW Journal/Complement Ther Nurs Midwifery. 3: 111-6.

Sensitivity to the environment is one of the pleasures of life. Unfortunately, for certain individuals this gets out of control. They become hypersensitive to something around them: pollens, moulds, man-made chemicals or to certain foods or drinks. If this is allowed to develop, sensitivity to the electrical environment may also appear as a part of the overall package of sensitivities. The same symptoms will then appear when the individual is in proximity to computers, televisions, telephones, supermarket check-outs, fluorescent lighting and even weather fronts and sunlight. The author has been involved in the diagnosis and treatment of electromagnetic sensitivities with complementary therapy since 1982, and considers here the nursing problems these patients present.

Fibromyalgia (FM) patients often report a high frequency of non-musculoskeletal symptoms, including those suggestive of multiple chemical sensitivity (MCS) syndrome. The objective of this pilot study was to determine the prevalence of MCS in FM patients from a university-based rheumatology practice. Self-report questionnaires were administered to determine the presence of MCS, utilizing the criteria from a recent study of the immunologic profile of patients with this disorder. Patients also responded "yes" or "no" to the presence of 48 FM-related symptoms. Thirty-three of 60 patients with FM met the criteria for MCS. Eleven of these patients also fulfilled more restrictive criteria, requiring a "higher degree" of chemical sensitivity. The symptoms and substances most frequently cited were similar to those reported in other studies of MCS. FM patients with and without MCS did not differ in other symptomatology. MCS may represent an additional symptom complex within the spectrum of FM.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9385348


Pavlovian conditioning processes may contribute to some symptoms of multiple chemical sensitivity (MCS). This review summarizes the potential relevance of the literature on conditional taste and olfactory aversions, conditional sensitization, and conditional immunomodulation to understanding MCS. A conditioning-based perspective on MCS suggests novel research and treatment strategies.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167990


Multiple chemical sensitivity as a "disease" has emerged as a descendant of food allergy, which, in the 1920s and 1930s, was considered to be responsible for much human suffering and symptoms of disease. After the onmarch of the clinical ecological movement in the 1950s, interest has been focused on the environment, and concern about food allergies and chemical sensitivity has reached epidemic proportions. "Active hazardous waste sites" and "workers exposed to toxic chemicals" are at the top of the list of public worries. The public believes manufactured chemicals to be more
dangerous than natural ones, although toxicologists regard the risks as equal. Originally, symptoms of patients were explained as "allergies", but since the 1960s the concept of "chemical sensitivities" has become a big-time diagnosis. The ideas of the clinical ecologists diffused rapidly into the community aided by public media. Today organizations like "Chemical Victims" and "National Foundation for the Chemically Hypersensitive" have thousands of members. Although the diagnosis of the disease is very vague, suffering patients believe that the clinical ecologists can offer them something that traditional medicine cannot: sympathy, recognition of pain and suffering, a physical explanation for their suffering, and active participation in medical care. Ecologic medicine thus soared in the patients' esteem, not just because of the content of the objective diagnoses that ecologic practitioners were able to supply, but because of the subjective nature of the doctor-patient relationship they were able to offer.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9456064

(1997) Fatiguing illness among employees in three large state office buildings, California, 1993: was there an outbreak?

The objective was to determine if a cluster of chronic fatigue syndrome (CFS)-like illness had occurred among employees in two large state office buildings in northern California, and to identify risk factors for and features of fatiguing illness in this population. DESIGN: case-control study. POPULATION AND SETTING: Over 3300 current employees in two state office buildings and employees in a comparable "control" building. Information was collected on demographic and occupational variables, the occurrence of fatiguing illness for at least one month in the previous year, and the presence of 36 symptoms. A total of 3312 (82%) of 4035 employees returned questionnaires. Overall, 618 (18.7%) persons reported fatigue lasting at least one month; including 382 (11.5%) with fatigue of at least six months' duration and 75 (2.3%) with symptoms compatible with a CFS-like illness. Independent risk factors for fatigue lasting one month or longer were found to be Native American ethnicity (OR 2.4, CI 1.1,5.3), Hispanic ethnicity (OR 1.7, CI 1.3,2.3), female sex (OR 1.5, CI 1.2,1.9), gross household incomes of less than $50,000 (OR 1.3, CI 1.1,1.6), and less than a college education (OR 1.3, CI 1.1,1.6). Similar risks were observed for persons who reported fatigue lasting six months or longer. Female sex (OR 3.2, CI 1.7, 6.4) was the only independent risk factor found for those persons classified as having a CFS-like illness. Case prevalence rates for all three categories of fatigue, as determined by multivariate analysis, were not significantly different among buildings. Despite finding a substantial number of employees with fatiguing illness in the two state office buildings, the prevalence was not significantly different than that for a comparable control building. Previously unidentified risk factors for fatigue of at least
one month and at least six months identified in this population included Hispanic ethnicity, not having completed college, and income below $50,000.


An increasing number of people in Sweden are claiming that they are hypersensitive to electricity. These patients suffer from skin as well as neurological symptoms when they are near computer monitors, fluorescent tubes, or other electrical appliances. Provocation studies with electromagnetic fields emitted from these appliances have, with only one exception, all been negative, indicating that there are other factors in the office environment that can effect the autonomic and/or central nervous system, resulting in the symptoms reported. Flickering light is one such factor and was therefore chosen as the exposure parameter in this study. Ten patients complaining of electrical hypersensitivity and the same number of healthy voluntary control subjects were exposed to amplitude-modulated light. The sensitivity of the brain to this type of visual stimulation was tested by means of objective electrophysiological methods such as electroretinography and visual evoked potential. A higher amplitude of brain cortical responses at all frequencies of stimulation was found when comparing patients with the control subjects, whereas no differences in retinal responses were revealed.

Safer, A Journal/Archit Rec. 185: 48.

(1997) Clinical characteristics of chemical sensitivity: an illustrative case history of asthma and MCS.

A case history of the induction of asthma and chemical sensitivity in a 42-year-old registered nurse illustrates several of the characteristic features of multiple chemical sensitivity (MCS). This patient's problems started shortly after moving into a new home under construction, with associated chemical exposures. Other MCS patients report the onset of the condition with other chemical exposures such as those encountered at their places of work or use of pesticides at their residences. Patients often describe a
spreading phenomenon of increasing intolerance to commonly encountered chemicals at concentrations well tolerated by other people. Symptoms usually wax and wane with exposures, and are more likely to occur in patients or families with preexisting histories of migraine or with classical allergies. Idiosyncratic medication reactions (especially to preservative chemicals) are common in MCS patients, as are dysautonomia symptoms (such as vascular instability) and poor temperature regulation. Myalgia and joint pains and food intolerance are common features as well. Contamination with xenobiotic chemicals is frequently found in these patients when they are tested. Reactive airways dysfunction syndrome is a recently identified condition that exhibits features of both asthma and chemical sensitivity. MCS patients frequently have patterns of neurotoxic brain metabolism that can be confirmed on single photo emission computed tomography imaging.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167976


http://www.sciencedirect.com/science/article/B6T4S-3WBPRJ7-T7/2
ad18033c562e75ce055be95800f7cb97


Absence due to illness among children in 24 daycare centres in Copenhagen was registered during two periods of one year each with a five year interval. The results from the first period have been reported earlier. In each period, the physical, environmental, hygienic and social conditions of the institutions were assessed, and the playroom area per child was registered. The total number of children increased from 855 in the first period to 921 in the second because 13 of the 24 institutions had increased their capacity in the intervening period. On average, the playroom area per child decreased with 0.27 square metre per child in the 13 institutions with an increased number of children. All children were less than three years of age. Absence due to sickness constituted 7.6% of the days during which the institutions were open. For the second period, where the childrens age had been exactly registered, the effect of age on absence due to sickness was found to be statistically significant. The direction of the effect was a decrease in illness with increasing age. However, due to a
high correlation between age and time attending the institution, the effect of age could not be separated from the similar effect of length of time that the child had attended the institution. It was found that sickness will decrease with 7.8% per month that the age of the child and time attending the institution is increased. A statistically significant connection was found between the playroom area per child and absence due to sickness after correction for the influence of age in a multivariate analysis. In conclusion, the sickness will decrease with 10.8% per square metre the playroom area per child is increased.

-------------------------------------------------------------------------------------------------------------------------------------


PROBLEM/CONDITION: Although chronic fatigue syndrome (CFS) has been recognized as a cause of morbidity in the United States, the etiology of CFS is unknown. In addition, information is incomplete concerning the clinical spectrum and prevalence of CFS in the United States. REPORTING PERIOD COVERED: This report summarizes CFS surveillance data collected in four U.S. cities from September 1989 through August 1993. DESCRIPTION OF SYSTEM: A physician-based surveillance system for CFS was established in four U.S. metropolitan areas: Atlanta, Georgia; Wichita, Kansas; Grand Rapids, Michigan; and Reno, Nevada. The objectives of this surveillance system were to collect descriptive epidemiologic information from patients who had unexplained chronic fatigue, estimate the prevalence and incidence of CFS in defined populations, and describe the clinical course of CFS. Patients aged > or = 18 years who had had unexplained, debilitating fatigue or chronic unwellness for at least 6 months were referred by their physicians to a designated health professional(s) in their area. Those patients who participated in the surveillance system a) were interviewed by the health professional(s); b) completed a self-administered questionnaire that included their demographic information, medical history, and responses to the Beck Depression Inventory, the Diagnostic Interview Schedule, and the Sickness Impact Profile; c) submitted blood and urine samples for laboratory testing; and d) agreed to a review of their medical records. On the basis of this information, patients were assigned to one of four groups: those whose illnesses met the criteria of the 1988 CFS case definition (Group I); those whose fatigue or symptoms did not meet the criteria for CFS (Group II); those who had had an identifiable psychological disorder before onset of fatigue (Group III); and those who had evidence of other medical conditions that could have caused fatigue (Group IV). Patients assigned to Group III were further evaluated to determine the group to which they would have been assigned had psychological illness not been present, the epidemiologic characteristics of the illness and the frequency of symptoms among patients were evaluated, and the prevalence and incidence of CFS were estimated for each of the areas. RESULTS: Of the 648
patients referred to the CFS surveillance system, 565 (87%) agreed to participate. Of these, 130 (23%) were assigned to Group I; 99 (18%), Group II; 235 (42%), Group III; and 101 (18%), Group IV. Of the 130 CFS patients, 125 (96%) were white and 111 (85%) were women. The mean age of CFS patients at the onset of illness was 30 years, and the mean duration of illness at the time of the interview was 6.7 years. Most (96%) CFS patients had completed high school, and 38% had graduated from college. The median annual household income for CFS patients was $40,000. In the four cities, the age-, sex-, and race-adjusted prevalences of CFS for the 4-year surveillance period ranged from 4.0 to 8.7 per 100,000 population. The age-adjusted 4-year prevalences of CFS among white women ranged from 8.8 to 19.5 per 100,000 population. INTERPRETATION: The results of this surveillance system were similar to those in previously published reports of CFS. Additional studies should be directed toward determining whether the data collected in this surveillance system were subject to selection bias (e.g., education and income levels might have influenced usage of the health-care system, and the populations of these four surveillance sites might not be representative of the U.S. population). ACTIONS TAKEN: In February 1997, CDC began a large-scale, cross-sectional study at one surveillance site (Wichita) to describe more completely the magnitude and epidemiology of unexplained chronic fatigue and CFS.


OBJECTIVE: Patients may have various forms of angioedema and require dental treatment which can cause or contribute to the onset of an episode of angioedema. This paper seeks to highlight the causes and the management of this serious condition. DESIGN: An outline of the different types of angioedema is given here, along with three case reports which illustrate treatment and management. SUBJECTS AND METHODS: Three patients who presented to an Oral Medicine clinic with angioedema are presented to illustrate various types of angioedema and the different contributing factors that precipitated episodes of the condition. MAIN OUTCOME MEASURES: The three patients were all investigated for biochemical and allergic factors which may have caused their disease. RESULTS: Both drugs and dental materials were shown to be involved in the pathogenesis of angioedema in this short series of patients. CONCLUSIONS: Dental treatment or the use of some materials may promote or contribute to the disorder. Referral to hospital for specialist care is indicated for certain groups of patients who require invasive dental treatment. The multi-disciplinary team approach in the investigation and management of patients with angioedema is emphasised.
(1997) **Involvement of mechanisms dependent on NMDA receptors, nitric oxide and protein kinase A in the hippocampus but not in the caudate nucleus in memory.**

The effects of the NMDA receptor antagonist AP5, the nitric oxide synthase (NO) inhibitor NO-arg or the protein kinase A (PKA) inhibitor KT5720 on memory were evaluated. Rats bilaterally implanted in the CA1 region of the dorsal hippocampus were trained and tested in a step-down inhibitory avoidance task, and rats unilaterally implanted in the left posteroventral region of the caudate nucleus were trained and tested in a cued water maze task. Previous findings from this and other laboratories had found that lesions or pharmacological treatments of these sites significantly altered memory of these two tasks. Immediately after training, animals received intrahippocampal or intracaudate 0.5 microliter microinfusions of saline, AP5, NO-arg or KT5720. All three drugs impaired retention of inhibitory avoidance, but did not affect retention of the cued water maze. The findings suggest that NMDA receptor-, NO- and PKA-mediated processes in the dorsal hippocampus, but not in the caudate nucleus, are involved in memory.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9832957

(1997) **Validity of computerized testing in toxic encephalopathy.**
Proctor, SP Journal/Crisp Data Base National Institutes Of Health.
RPROJ The epidemiologic study of neurobehavioral effects due to neurotoxicant exposure is necessary in order to understand the possible effects of chemical exposures in occupational and environmental settings. The computer-administered Neurobehavioral Evaluation System (NES) test battery provides a fuller, more standard method of measuring neurobehavioral effects in population groups, compared to the traditional paper and pencil type of clinical neuropsychological tests. However, traditional tests have been validated and thus, have been shown to measure s-f.c. brain-behavior relationships (Lezak, 1983). The validation process of the NES is ongoing. Studies done to date have not evaluated whether a computerized version of the standard test measures the same level of cognitive functioning, e.g. does pressing a computer key to indicate a positive response to a task presented on the screen involve the same processing 'as verbally responding to a question asked by an examiner? A recent study has been undertaken to evaluate the ability of the NES to detect predicted functional deficits in neurological patients diagnosed with diseases involving cerebral dysfunction, i.e. patients with early Parkinson's disease, multiple sclerosis, and focal strokes. The objective of the proposed study is to validate the use of the NES in patients diagnosed with toxic encephalopathy, i.e. central nervous system (CNS) damage caused by chemical exposure, in order to improve the interpretation of NES test performance in research studies of CNS dysfunction.
secondary to chemical exposures. Performance on the NES by persons diagnosed with solvent and lead encephalopathy will be compared to that of controls to see if the differences reflect a priori brain-behavior relationships. Performance on the NES tests will also be compared to performance on the associated standard tests. This study will be important in examining the sensitivity and specificity of the NES to detect subtle brain damage indicative of neurotoxicant exposures. If the NES is shown to be a valid predictor of toxic encephalopathy, it will provide an important research tool in epidemiologic studies of behavioral neurotoxicology and an important clinical tool in the follow-up care of patients with toxic encephalopathy.

-------------------------------------------------------------------------


In environmental medicine, we frequently see patients who have a very firm, sometimes fixated view of the nature of their disease, and they do not except the correction by the physician but only confirmation. Therefore, we face the task to undertake these patients a careful medical and psychological differential diagnosis. In a major number of cases, the symptoms are caused not by supported environmental effects but by an unknown diagnosis, and recognition and treatment would be impossible in case of an uncritical adoption of the patient's illness theory. Further, psychosomatic syndromes, which are well accessible by treatment procedures of psychosomatic medicine, can be diagnosed in many of those patients. This article demonstrates the different kinds of psychosomatic diseases in the area of environmental medicine and its appropriate therapeutic consequences.

-------------------------------------------------------------------------


Biosis copyright: biol abs. rrm editorial human patient allergy multiple chemical sensitivities toxicity causal agents dizziness headache immune system disease palpitations fatigue

-------------------------------------------------------------------------


Polymorphisms of xenobiotic-metabolizing enzymes, responsible for individual differences in metabolic activation and detoxification reactions, may profoundly modulate the effects of chemical carcinogens. In the case of genotoxic carcinogens, differences in biological effects due to genetic polymorphisms can be evaluated by cytogenetic methods such as the analysis of chromosomal aberrations (CAs), sister chromatid exchanges (SCEs), micronuclei (MN), and changes in chromosome number. These techniques can be applied to any exposure known to induce such alterations, without additional method development for each exposing agent. The influence of polymorphic genes on the cytogenetic effects of a carcinogen can quickly be tested in vitro using metabolically competent cells collected from donors representing different genotypes or phenotypes. For instance, erythrocytes from individuals positive for glutathione S-transferase T1 (GSTT1) express GSTT1, whereas GSTT1-null donors, having a homozygous deletion of the GSTT1 gene, completely lack this detoxification enzyme. This deficiency results in highly increased sensitivity to SCE induction in whole-blood lymphocyte cultures by 1,2;3,4-diepoxybutane, a reactive metabolite of 1,3-butadiene. The same cytogenetic techniques can also be applied as effect biomarkers in studies of human populations exposed to genotoxic carcinogens. For example, elevated rates of chromosome damage have been detected among smokers lacking glutathione S-transferase M1 (GSTM1-null genotype), and the baseline level of SCEs seems to be increased in GSTT1-null individuals. Information obtained from cytogenetic studies of genetic polymorphisms can be used, for example, to recognize the genotoxically relevant substrates of the polymorphic enzymes, to identify genotypes that are susceptible to these genotoxins, to improve in vitro genotoxicity tests utilizing human cells, to increase the sensitivity of cytogenetic endpoints as biomarkers of genotoxic effects in humans, and to direct mechanistic studies and cancer epidemiology.

(1997) Are deficits in the equilibrium system relevant to the clinical investigation of solvent-induced neurotoxicity?
OBJECTIVES: The diagnosis of solvent-induced chronic toxic encephalopathy is commonly based on case histories of exposure to solvents, symptoms, and deficits on psychometric tests. It has previously been demonstrated that long-term solvent-exposed workers have disturbances of the equilibrium system. The correlation between these disturbances and the diagnosis of chronic toxic encephalopathy has been analyzed in the present study. MATERIAL AND METHODS: Sixty men, consecutively admitted due to the suspicion of this syndrome, were investigated and classified into 3 groups—solvent-induced chronic toxic encephalopathy, incipient chronic toxic encephalopathy and nonchronic toxic encephalopathy. They were all examined using an otoneurological test battery, including analysis of saccades, smooth pursuit, visual suppression of the vestibular ocular reflex, and dynamic posturography. RESULTS: Compared with healthy referents several of the subjects, even in the nonchronic toxic encephalopathy group, showed a reduced visual suppression ability, a prolonged latency of saccades, and pathological posturographic results. Some otoneurological tests correlated with the duration of exposure and the results of psychometric tests representing memory and perceptual skills. Nevertheless, there was no significant group correlation between the otoneurological findings and the diagnosis of chronic toxic encephalopathy. CONCLUSION: Disturbances revealed by an otoneurological investigation have so far not been considered in the diagnosis of chronic toxic encephalopathy. Our results indicate that an otoneurological test battery adds worthwhile information about lesions within the brainstem-cerebellar complex not revealed by a psychometric investigation.


Allergic diseases are partly genetically determined, but environmental factors have a strong influence on the expression of allergic symptoms in genetically predisposed subjects. In particular, outdoor air pollution has received widespread attention as a potential manifestation factor. The unification of Germany provided a unique opportunity to study the impact of radically different environmental and social conditions on the development of allergies in two genetically homogeneous populations. A high car density and NO2 exposure were typical for many West German cities. Severe pollution due to heavy industrialization and private coal burning for heating purposes were the main sources of air pollution in East German cities. We assessed the prevalence of asthma and allergic disorders in 9-11 year old children in in East Germany (Leipzig and Halle) and in West Germany (Munich). All fourth grade pupils in Munich (n = 7,445) were compared with those in Leipzig and Halle 1991 (n = 3,105). Hay fever, skin test reactivity to common aeroallergens and asthma were considerably more prevalent in West Germany as compared to East Germany. When atopy was taken into account, there was no longer a significant difference in the prevalence of asthma between the two parts of the country.
(1997) **A behavior-genetic approach to multiple chemical sensitivity.**

This report emphasizes the application of behavior-genetic designs to the study of sensitivity to toxic chemicals, and features of multiple chemical sensitivity and substance abuse that are polar opposites. The implications of these issues for future research are discussed in relation to twin, adoption, and sibling pair studies, as well as in relation to the degree to which genetically selected lines of rodents that have been developed in the alcoholism field are applicable to multiple chemical sensitivity.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167987

(1997) **EDITORIAL: Whither Multiple Chemical Sensitivities.**
Nethercott, JR Journal/Am J Contact Dermat. 8: 199-201.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9074272

(1997) **Expired nitric oxide as a marker for childhood asthma.**

Expression of the inflammatory isoform of the enzyme nitric oxide synthase (NOS) is increased in airway-lining cells of patients with asthma. The NOS product nitric oxide (NO) was measured in the expired gas of children with asthma. Vital capacity expirates from 21 control subjects and 13 subjects with asthma were assayed by chemiluminescence. Measurements were highly reproducible (coefficient of variation, 2.6% +/- 1.1%) and did not vary with age, sex, height, or weight. Patients with asthma had mean NO. levels (16.3 parts per billion) that were more than threefold higher than those of control subjects (5.05 ppb; p < 0.001). Expired NO. decreased as airflow obstruction improved during corticosteroid treatment (r2 = 0.77; n = 7; p < 0.001) but remained higher than normal (13.5 ppb; n = 5; p < 0.01) even after airflow obstruction resolved. We demonstrate the use of a reproducible test for asthma in children that is independent of measures of airflow obstruction. We speculate that expired NO assays may prove to be a more sensitive measure of childhood asthma than spirometry.
query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9063418


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9138648

(1997) [Comment on K. Lohmann, Anke Prohl, E. Schwarz. Multiple chemical sensitivity in patients with neurotoxic illnesses].
Muller-Mohnssen, H Journal/Gesundheitswesen. 59: 56.

(1997) [Environmental diseases, diseases of the 21st century? II. Asthma and atmospheric pollution].

(1997) [Chronic fatigue syndrome: study of the clinical course of 28 cases].

BACKGROUND: Chronic fatigue syndrome (CFS) is an entity of unknown etiopathogenesis without specific markers. The diagnosis is based on clinical criteria. There are few studies evaluating the natural evolution and prognosis-related factors in CFS. OBJECTIVES: a) to evaluate the outcome of patients suffering from CFS, and b) to detect predictive factors associated with a better prognosis. MATERIAL AND METHODS: Clinical records of all patients diagnosed of CFS between January 1986 and December 1992 were retrospectively reviewed. Of these patients, we included those fulfilling the CDC criteria for CFS, with a follow-up period greater than one year. We evaluated epidemiological, clinical and evolutive data recorded by their usual physicians. Moreover, the patients were interviewed in order to know their own appreciation with respect to their current clinical status, as well as their present working situation. RESULTS: Twenty-eight patients were included in the present study. Their
mean age was 38 +/- 7. Seventy-five percent of them were women. The mean time of clinical follow-up was of 3.2 +/- 1.8 years. According to evaluation, 21% of patients improved or became asymptomatic. A similar percentage (28%) of improvement was obtained from the interview. Forty-eight percent of cases had transitory or definitive laboral incapacity. Regarding to prognostic factors, we could not find any statistical differences among the analyzed variables except for marital status. In this variable, married patients had better outcome than unmarried patients. CONCLUSION: CFS is an entity with a poor outcome, since it evolves towards to chronicity in an important number of cases. In addition, strong functional disability may be present, leading frequently to laboral incapacity.


This paper attempts to clarify the nature of chemical sensitivity by proposing a theory of disease that unites the disparate clinical observations associated with the condition. Sensitivity to chemicals appears to be the consequence of a two-step process: loss of tolerance in susceptible persons following exposure to various toxicants, and subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food and drug combinations including caffeine and alcohol. Although chemical sensitivity may be the consequence of this process, a term that may more clearly describe the observed process is toxicant-induced loss of tolerance. Features of this yet-to-be-proven mechanism or theory of disease that affect the design of human exposure studies include the stimulatory and withdrawallike nature (resembling addiction) of symptoms reported by patients and masking. Masking, which may blunt or eliminate responses to chemical challenges, appears to have several components: apposition, which is the overlapping of the effects of closely timed exposures, acclimatization or habituation, and addiction. A number of human challenge studies in this area have concluded that there is no physiological basis for chemical sensitivity. However, these studies have failed to address the role of masking. To ensure reliable and reproducible responses to challenges, future studies in which subjects are evaluated in an environmental medical unit, a hospital-based facility in which background chemical exposures are reduced to the lowest levels practicable, may be necessary. A set of postulates is offered to determine whether there is a causal relationship between low-level chemical exposures and symptoms using an environmental medical unit.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167978

It has been hypothesized that sensitivity to low-level chemical exposures develops in two steps: initiation by an acute or chronic chemical exposure, followed by triggering of symptoms by low levels of previously tolerated chemical inhalants, foods, or drugs. The Working Group on Toxicant-induced Loss of Tolerance has formulate a series of research questions to test this hypothesis: Do some individuals experience sensitivity to chemicals at levels of exposure unexplained by classical toxicological thresholds and dose-response relationships, and outside normally expected variation in the population? Do chemically sensitive subjects exhibit masking that may interfere with the reproducibility of their responses to chemical challenges? Does chemical sensitivity develop because of acute, intermittent, or continuous exposure to certain substances? If so, what substances are most likely to initiate this process? An experimental approach for testing directly the relationship between patients’ reported symptoms and specific exposures was outlined in response to the first question, which was felt to be a key question. Double-blind, placebo-controlled challenges performed in an environmentally controlled hospital facility (environmental medical unit) coupled with rigorous documentation of both objective and subjective responses are necessary to answer this question and to help elucidate the nature and origins of chemical sensitivity.


---------------------------------------------------------------


---------------------------------------------------------------


The reactive airways dysfunction syndrome (RADS), the reactive upper airways dysfunction syndrome (RUDS), the sick building syndrome (SBS), and the multiple chemical sensitivity syndrome (MCS) are overlapping disorders in which there is an intolerance to environmental chemicals. The onset of these illnesses is often associated with an initial acute chemical exposure. To understand the pathophysiology
of these conditions, a study of the nasal pathology of individuals experiencing these syndromes was undertaken. Preliminary data indicate that the nasal pathology of these disorders is characterized by defects in tight junctions between cells, desquamation of the respiratory epithelium, glandular hyperplasia, lymphocytic infiltrates, and peripheral nerve fiber proliferation. These findings suggest a model for a relationship between the chronic inflammation seen in these conditions and an individual's sensitivity to chemicals. A positive feedback loop is set up: the inflammatory response to low levels of chemical irritants is enhanced due to the observed changes in the epithelium, and the epithelial changes are propagated by the inflammatory response to the chemicals. This model, combined with the concept of neurogenic switching, has the potential to explain many aspects of RADS, RUDS, SBS, and MCS in a unified way.

collection.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167982

(1997) Stress, glucocorticoids and the serotonergic system.
McEwen, BS, McKittrick, CR, Blanchard, RJ, Blanchard, DC and Sakai, RR Journal Biological Psychiatry. 42: 60S-61S.

http://www.sciencedirect.com/science/article/B6T4S-3WBPRJ7-TG/2
c88e324fd510677d0b26f31f37bf4f9f


An exploratory case-control study was conducted to assess whether the many reported differences in the immune function of chronic fatigue syndrome (CFS) patients are detectable in rigorously defined cases of CFS. Although many studies have reported differences between cases and controls in various measures of immune function, none of these differences were found in all studies. In this study, no differences were found in white blood cell numbers; immune complex, complement, or serum immunoglobulin levels; delayed type hypersensitivity and allergic responses; NK cell function; and proliferative responses to mitogens and antigens. Marginal differences were detected in cytokine responses and in cell surface markers in the total CFS population. However, when the patients were subgrouped by type of disease onset (gradual or sudden) or by how well they were feeling on the day of testing, more pronounced differences were seen.

Markowitz, A Journal/Crisp Data Base National Institutes Of Health.
RPROJ The laser flash photolysis technique was employed to measure the kinetics of carbon monoxide (CO) binding to cytochrome P450. An apparatus was developed to photolyze CO from P450 and monitor the subsequent recombination reaction. Signal processing techniques in conjunction with a difference kinetic analytical method were applied to define the kinetic behavior of individual P450s. P450s in rat liver microsomes, as well as single expressed human P450s, were examined. The effects of various drugs, carcinogens and inhibitors on these P450s were assessed, and these agents were found to exert a variety of effects on their target P450s. Of particular importance is the finding that single human P450s are composed of multiple species with differential sensitivities to drugs and carcinogens. The objectives were to a) develop an instrument and analytical methodologies based upon CO flash photolysis technique to measure the kinetics of CO binding to P450, b) perform these measurements using turbid biological tissue samples, c) apply the method as a probe of P450 structure and dynamics to elucidate the kinetic behavior of individual P450s, and d) develop analytical methods to distinguish individual P450 forms, kinetically, within a biological tissue containing multiple P450s. The experiments were performed using P450s in natural biological membranes. The results demonstrate that individual P450s can be characterized in a natural environment using differential analytical procedures, whereas previous work in this field mixtures of P450s in microsomes of a single P450 in an artificial reconstitution system.


OBJECTIVE: The physical and mental symptomatology of 99 self-referred patients complaining of multiple somatic and mental symptoms attributed to dental amalgam fillings were compared with patients with known chronic medical disorders seen in alternative (N = 93) and ordinary (N = 99) medical family practices and patients with dental amalgam fillings (N = 80) seen in an ordinary dental practice. METHOD: The assessments included written self-reports, a 131-item somatic symptom checklist;
Eysenck Personality Questionnaire, the General Health Questionnaire, and Toronto Alexithymia Scale. RESULTS: The dental amalgam sample reported significantly more physical symptoms from all body regions. Self-reports suggested that 62% suffered from a chronic anxiety disorder (generalized anxiety disorder or panic). Forty-seven percent suffered from a major depression compared with 14% in the two clinical-comparison samples and none in the dental control sample. Symptoms suggesting somatization disorder were found in 29% of the dental amalgam sample compared with only one subject in the 272 comparison subjects. One third of the dental amalgam patients reported symptoms of chronic fatigue syndrome compared with none in the dental control sample and only 2 and 6%, respectively, in the two clinical comparison samples. The dental amalgam group reported higher mean neuroticism and lower lie scores than the comparison groups. CONCLUSION: Self-referred patients with health complaints attributed to dental amalgam are a heterogeneous group of patients who suffer multiple symptoms and frequently have mental disorders. There is a striking similarity with the multiple chemical sensitivity syndrome.

(1997) [Allergen decontamination and public sector].

Reduction of allergen exposure is one way to reduce exacerbations in allergic asthma. According to Danish legislation, the local authorities have to support initiatives which can reduce clinically relevant inhouse allergen exposure. A case of grotesque bureaucracy and ignorance of basic allergological facts is presented. Local administration confused allergy to cat dander with allergy to house dust mite and two appeal boards only reviewed legal aspects, not medical. After inquiry by the ombudsman, the case was reviewed by one appeal board and the patient was granted help. After three years the patient had moved to another district and the case was started all over again. It is recommended that direct contact between physicians should be preferred, in order to avoid misinterpretation of specialist statements. Original documents should always be requested to avoid transcription errors. Local public administration should respect legislation and improve the quality of their medical advisors.


Chemical sensitivity appears to be an elusive phenomenon. Studies on individual differences in susceptibility may provide glimpses into the range of sensitivity in a population, which can be used for further study. Preliminary evidence in laboratory animals suggests the range of sensitivity to manufactured chemicals may span orders
of magnitude. Determining the reasons that underlie individual differences in sensitivity is a more difficult enterprise. Conditioning of adverse physiological effects of airborne chemicals may play a vital role in the etiology of chemical sensitivity, and it provides a rigorous laboratory model by which to investigate some aspects of this elusive phenomenon.


Culture of rat pancreatic islets with interleukin-1 (IL-1) results in up-regulation of the inducible isoform of nitric oxide synthase and overproduction of nitric oxide (NO). This is associated with reversible inhibition of both glucose-induced insulin secretion and islet glucose oxidation, and these effects are prevented by the inducible nitric oxide synthase inhibitor NG-monomethylarginine. IL-1 also induces accumulation of nonesterified arachidonic acid in islets by an NO-dependent mechanism, and one potential explanation for that effect would involve an IL-1-induced enhancement of islet glycolytic flux. We have therefore examined effects of IL-1 on islet glycolytic utilization of glucose and find that culture of islets with IL-1 in medium containing 5.5 mM glucose results in suppression of islet glucose utilization subsequently measured at glucose concentrations between 6 and 18 mM. The IL-1-induced suppression of islet glucose utilization is associated with a decline in islet glucokinase mRNA content, as determined by competitive reverse transcriptase-polymerase chain reaction, and in glucokinase protein synthesis, as determined by immunoprecipitation experiments, and all of these effects are prevented by NG-monomethylarginine. These findings suggest that IL-1 can down-regulate islet glucokinase, which is the primary component of the islet glucose-sensor apparatus, by an NO-dependent mechanism. Because reductions in islet glucokinase levels are known to cause a form of type II diabetes mellitus, these observations raise the possibility that factors which increase islet NO levels might contribute to development of glucose intolerance.

OBJECTIVES: The questionnaire 16 (Q16) is commonly used to study prevalences of neurotoxic symptoms among workers exposed to organic solvents. It has also been recommended that exposed workers reporting more than six symptoms should be referred for further examination of possible chronic toxic encephalopathy. It would be useful to know whether symptoms reported in the questionnaire also reflect impairment of similar functions measured with objective or semiobjective methods in a formerly highly exposed group. METHODS: 135 painters and 71 carpenters answered the Q16, were interviewed about symptoms compatible with an organic brain damage, and took a battery of psychometric tests. A subsample of 52 painters and 45 carpenters were interviewed for psychiatric diagnosis according to Diagnostic and Statistical Manual for Mental Disorders, 3rd version (DSM III) and their vibration thresholds in hands and feet were measured. The entire group was followed up in the register of diagnoses at early retirement 1971-93. The lifetime exposure to organic solvents was assessed. Current exposure to organic solvents was found to be low or none. RESULTS: The prevalence of people with more than six symptoms in the Q16 rose with increasing cumulative exposure to solvents. The sensitivity of the questionnaire (more than six symptoms) to detect people who were assessed to exhibit symptoms compatible with an organic brain damage was only 38%. One of seven people who had retired early with a diagnosis compatible with a chronic toxic encephalopathy, and two of five people with a psychiatric diagnosis compatible with this condition, had more than six symptoms in the Q16. The agreement between Q16 replies and psychometric test results, as well as other examinations, was low. CONCLUSIONS: The notable exposure-response relation indicates that the questionnaire is useful for comparison of groups with different exposures to organic solvents. There was low agreement between the number of symptoms on the questionnaire and the assessment of symptoms compatible with organic brain damage, as well as psychiatric, or early retirement diagnoses compatible with chronic toxic encephalopathy. The questionnaire does not seem useful for screening of patients with chronic toxic encephalopathy in groups without ongoing exposure to organic solvents.

(1997) Regulation of GABA(A) receptor subunit mRNA expression by the pesticide dieldrin in embryonic brainstem cultures: a quantitative, competitive reverse transcription-polymerase chain reaction study.

Cyclodiene organochlorine pesticides, such as dieldrin, inhibit gamma-aminobutyric acid (GABA)ergic neurotransmission by blocking the Cl- channel of GABA(A) receptors. This action may make the developing nervous system especially vulnerable to these neurotoxins, which could interfere with the trophic actions of GABA on developing neurons and alter expression of GABA(A) receptors. We have used an in vitro model to determine whether exposure to dieldrin alters developmental expression of GABA(A) receptor subunit mRNA transcripts. Dissociated cell cultures were
prepared from embryonic day 14 (E14) brainstem and cultured in serum-containing medium for 1 day in vitro (DIV), then treated for 2 DIV with 10 microM dieldrin in serum-free medium. This dose was based on preliminary experiments and previous studies (Nagata et al.: Brain Res 645:19-26, 1994; Pomes et al.: J Pharmacol Exp Ther 271:1616-1623, 1994). Absolute amounts of alpha1, beta3, gamma1, gamma2S and gamma2L mRNA transcripts were quantified in these cultures by quantitative, competitive reverse transcription-polymerase chain reaction (RT-PCR) using subunit-selective internal standards. The most abundant GABA(A) subunit transcript was beta3, which was much more highly expressed than gamma2S, gamma1, gamma2L, or alpha1 subunit mRNAs. Dieldrin differentially regulated expression of these transcripts. Levels of beta3 subunit transcripts were significantly increased (by 300%) by dieldrin, whereas expression of gamma2S and gamma2L transcripts were decreased (by 50% and 40%, respectively). However, dieldrin did not alter the ratio of gamma2S to gamma2L transcripts, indicating that it did not affect alternative splicing of gamma2 transcripts. Dieldrin appeared to increase expression of alpha1 subunit transcripts, but this effect was not statistically significant. Dieldrin did not significantly alter expression of gamma1 subunit transcripts. These results support the hypothesis that in utero exposure to cyclodiene pesticides could pose a risk to the developing brain by virtue of their ability to alter gene expression of GABA(A) receptor subunits, which could produce GABA(A) receptors with altered functional properties.


Male subjects with type 2A (n = 12) and 2B (n = 12) solvent-induced toxic encephalopathy and a reference group of healthy men (n = 12) without previous solvent exposure were studied using quantitative EEG and event-related potentials from an odd-ball and a dual-task paradigm. Subjects with toxic encephalopathy of types 2A and 2B showed markedly lower P300 amplitudes than did controls in both paradigms. In the relatively complex dual-task setting, subjects with 2A and 2B showed lower signal detection than did controls.

Lichtenstein, P and Svartengren, M Journal/Allergy. 52: 1079-86.

Various atopic manifestations among adults have been shown to be influenced mainly by genetic factors. With the increase in prevalence of atopic diseases in recent years,
especially among children, a great deal of attention has been given to environmental
causes. In a study of 1480 Swedish twin pairs, 7-9 years old, we examined the
importance of genetic and environmental factors in asthma, hay fever, eczema, and
urticaria. Structural equation model fitting showed 33-76% of the variation in liability to
the diseases to be due to genetic effects. Shared environmental effects were also
important for hay fever and urticaria in both sexes and for eczema among girls. The
clustering of atopic disease in families was almost entirely due to a common set of
genes, but each disease manifestation also seemed to have specific genes of
importance. Investigation of unlike-sex twins showed that boys had a higher cumulative
incidence of asthma and hay fever than girls, whereas girls had a higher incidence of
eczema. Thus, it may be concluded that although genetic factors are of major
importance in atopic manifestation in children, both environmental and sex-related
factors play a role.


Whether multiple chemical sensitivity (MCS) is an organic disease initiated by
environmental exposure or a psychologic disorder is a subject of controversy. The
identification of pathophysiologic or psychophysiologic mechanisms occurring in
patients with MCS after provocative challenges should be illuminating. Fifteen patients
with MCS were challenged with their trigger substances and observed clinically.
Prechallenge and postchallenge pulmonary function tests and PCO2, PO2, and oxygen
saturation were measured. All of the patients whose symptoms were reproduced by the
challenge (11 of 15) showed clinical evidence of acute hyperventilation with a rapid fall
in PCO2 and no change or a rise in oxygen saturation. The symptoms and signs were
consistent with an anxiety reaction with hyperventilation. Pulmonary function was
unchanged; and recovery was rapid, aided in two cases by rebreathing into a paper
bag. The most logical conclusion is that in these patients the MCS disorder is a
manifestation of an anxiety syndrome triggered by their perception of an environmental
insult, with at least some of their symptoms induced by hyperventilation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9111485


Multiple chemical sensitivity (MCS) could be called a phenomenon rather than an
illness. No single widely accepted test of physiological function can be shown to
correlate with the symptoms presented by the patients. In addition to allergy and
Asthma, patient history can include various "illnesses", and the "diagnosis" is often made by the patient, usually alone or with the help of clinical ecologists. This paper reports the experiences from a department of occupational medicine. More than 80% of the patients were women and solvent exposure was the most common cause of chemical intolerance reported by the patients. Many patients also reported psychosocial stressors. The patients also showed mood disorders with irritability, anxiety, sleep disturbances and depression, often with thoughts centered around different organ symptoms. The symptomatology of MCS is still nonspecific and in no way diagnostic of a specific illness or a medically acceptable syndrome. It may indicate many other conditions, both organic disease and psychopathology.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9456070


Biosis copyright: biol abs. rrm meeting report human multiple chemical sensitivity diagnosis toxicology gulf war illness clinical ecology diagnostic method disease-miscellaneous


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9154450


This paper proposes several hypotheses and research strategies for exploring possible psychological factors contributing to multiple chemical sensitivity (MCS). The hypotheses are based on concepts of individual response stereotypy, situational response specificity, classical conditioning of chemical-induced responses, and psychophysiological reactions to active and passive coping orientations. Hypotheses
regarding hypersensitivity to perception and/or aversiveness of chemical stimulation also are presented. Strategies for evaluating these hypotheses are described based on experimental literature on psychophysiology and psychophysics.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167983


This paper examines the symbolic nature of the psychosomatic symptom. It is suggested that the psychosomatic symptom is an informationally rich symbolic derivative of the Self that serves to focus attention on developmental disturbances in the archetypal processes of constructing body image and interpreting dysphoric somatic sensations. Clinical examples are offered to illustrate the changing nature of the psychomatic symptom in society. The therapeutic importance of monitoring affectual transactions in the transference-countertransference field is stressed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9246928


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167973


Natural killer-enhancing factor B (NKEF-B) belongs to a highly conserved family of recently discovered antioxidants. The role of NKEF-B as an antioxidant was demonstrated by its protection of transfected cells to oxidative damage by hydrogen peroxide. To further characterize the antioxidant properties of NKEF-B, we compared the sensitivity of a human endothelial cell line ECV304 and its transfectant, B/1 that hyperexpresses NKEF-B, to various oxidants. In addition, we investigated the changes in the expression of NKEF-B mRNA upon oxidative stress. We found that B/1 was
significantly more resistant than the control cells to the oxidative stresses caused by t-butyl hydroperoxide (t-BHP) and methyl mercury (MeHg). In contrast, there was no difference in the sensitivity of B/1 and the control cells to sulfhydryl reactive agents, diethyl maleate and diamide. B/1 was also as sensitive as the control cells to buthionine sulfoximine. The expression of NKEF-B mRNA was induced when the parental cell line ECV304 was treated with 2 mm HP. The induction reached a maximum level around 2 hr and decreased to the basal level around 4 hr. NKEF-A mRNA was not induced by HP. These results demonstrate antioxidant activities of NKEF-B toward prooxidants such as alkyl hydroperoxide and MeHg. Together with its antioxidant activity, the induction of NKEF-B by HP indicates that NKEF-B is an important oxidative stress protein providing protection against a variety of xenobiotic toxic agents.


(1997) Laboratory testing of the patient with multiple chemical sensitivity.

Multiple diagnostic laboratory tests are frequently used in the clinical evaluation of persons with multiple chemical sensitivity without a clear a priori hypothesis. In addition, many of these tests are performed despite a lack of understanding of the test technical performance characteristics or the clinical significance (test sensitivity and specificity). The result is a plethora of laboratory data that have little clinical relevance and that can be both misleading and misused.


(1997) [Environmental concerns--fear of the environment or concern for the environment?].
Kappos, AD Journal/Z Arztl Fortbild Qualitatssich. 91: 5-10.

Increasing environmental pollution as reported by the media, makes people feel insecure and frightened which contribute to the onset environmental disease. Environmental hazards and risks are perceived differently by lay people and by scientific experts. This is not a matter of irrationality of laymen. The layman's view of
risks includes evaluatory and pragmatic (how to cope with the problem) dimensions. According to Kofler, toxicopy is regarded as a somatic reaction to a suspected threat by environmental pollution usually provoked by respective information by the media. Toxicopy is understood as a survival strategy under uncertain knowledge. Dealing with the fears of patients, the physician has to avoid enhancement of unfounded concern on one side and negating real problems on the other. High priority should be given to establish a trustful and co-operative therapeutic situation, in which the patients feels that his concern is taken seriously.


The brain is able to change the synaptic strength in response to stimuli that leave a memory trace. Long-term potentiation (LTP) and long-term depression (LTD) are forms of activity-dependent synaptic plasticity proposed to underlie memory. The induction of LTP appears mediated by glutamate acting on AMPA and then on NMDA receptors. Cholinergic muscarinic agonists facilitate learning and memory. Acetylcholine depolarizes pyramidal neurons, reduces inhibition, upregulates NMDA channels and activates the phosphoinositide cascade. Postsynaptic Ca2+ rises and stimulates Ca-dependent PK, promoting synaptic changes. Electroencephalographic desynchronization and hippocampal theta rhythm are related to learning and memory, are inducible by cholinergic agonists and elicited by hippocampal cholinergic terminals. Their loss results in memory deficits. Hence, cholinergic pathways may act synergically with glutamatergic transmission, regulating and leading to synaptic plasticity. The stimulation that induces plasticity in vivo has not been established. The patterns for LTP/LTD induction in vitro may be due to the loss of ascending cholinergic inputs. As a rat explores pyramidal cells fire bursts that could be relevant to plasticity.


Overexpression of the trans-membrane drug efflux pump P-glycoprotein is one of the major mechanisms by which cancer cells develop multidrug resistance. We demonstrated previously that noncytotoxic doses of various genotoxic chemicals, particularly DNA cross-linking agents, preferentially altered expression of inducible
genes. These effects occurred principally at the transcriptional level and were closely correlated temporally with DNA damage. Because the mdr1 gene coding for P-glycoprotein has been reported to be highly inducible, we were interested in the effects of genotoxic cancer chemotherapy agents on its expression. We report that the DNA cross-linking agent mitomycin C significantly suppressed mRNA and protein expression of P-glycoprotein and decreased the rate of drug efflux. Mitomycin C pretreatment also significantly increased the sensitivity of cancer cells to subsequent killing by the P-glycoprotein substrate doxorubicin, decreasing the ED50 by 5- to 10-fold. Suppression of P-glycoprotein expression was also observed with subtoxic doses of the DNA cross-linking agents cisplatin, BMS181174, and chromium(VI). These effects occurred in both human and rodent cell lines; in cell lines derived from colon, breast, leukemia, neuroblastoma, and hepatoma tumors; and under both monolayer and "spheroid" culture conditions. These results suggest the basis for novel clinical cancer chemotherapy regimens aimed at drug-resistant tumors, in which a sub-chemotherapeutic dose of a DNA cross-linking agent is used to modulate the multidrug resistance phenotype prior to treatment with a second cytotoxic agent. TAX - RATTUS TAX - HOMO SAPIENS

(1997) [Ecopathology of the kidneys and individual sensitivity to heavy metal salts].
Ignatova, MS, Kharina, EA, Spitsin, VA, Dlin, VV, Iur'eva, EA, Osmanov, IM and Raba, GP

Investigations performed in the region contaminated with heavy metal salts revealed high prevalence of renal diseases in children. The test for blood polymorphic proteins indicated signs of genetic predisposition to renal damage. Greater occurrence in the population with econephropathy of a rare allele of transferrin C3 may be the cause of enhanced oxidative-radical processes in renal cells. Individual sensitivity of children to heavy metal salts assessed by leukocytolysis and high incidence of somatic mutations to determine T-lymphocyte microclones deficient by HGPRT may help in specification of the affections detected in the regions contaminated with heavy metal salts.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9297273

(1997) [The incidence of peculiar IgE in response to inhalant allergens in relation to the age of the patient].
Hofman, T, Madra-Rogacka, D, Skrobisz, W, Buczyłko, K and Brewczynski, P
208 patients between the age of 1 month to 56 years, with symptoms of respiratory tract allergy were investigated. In all cases serum titre of sIgE to birch, thymoty, rye, mugwort pollen, Alternaria Alternata, dog, cat fur, Dermatophagoides pteronyssinus and farinae was determined with the use of Quidel immunoenzymatic method. We have found sIgE to Alternaria Alternata in 8 (38%), birch pollen in 5 (23.8%) dog fur in 5 (23.8%) and thymoty and rye pollen in 3 (14.3%) even among one years-old infants. In the second and third years of life allergy to dog fur, Alternaria Alternata and pollen of birch, thymoty and rye increases while the age of 4 and 5 is less significant, later (6-10 years old patients) increases again. Among teenagers pollinosis gets decreases and adults have development constant level of the disease.

(1997) Enhancement of natural killer cell activity and T and B cell function by buffered vitamin C in patients exposed to toxic chemicals: the role of protein kinase-C.

After exposure to many toxic chemicals, NK function can be decreased significantly. Weeks or months later, natural killer (NK) function can rebound to normal levels in some and can be suppressed for prolonged periods of time in other patients. In view of this, we decided to study the effect of buffered vitamin C on NK, T and B cell function in patients who had been exposed to toxic chemicals. After the first blood draw, 55 patients immediately ingested granulated buffered vitamin C in water at a dosage of 60 mg/Kg body weight. Exactly 24 hours later, blood was again drawn for a follow-up study of NK, T and B cell function. Vitamin C in high oral dose was capable of enhancing NK activity up to ten-fold in 78% of patients. Lymphocyte blastogenic responses to T and B cell mitogens were restored to the normal level after vitamin C usage. Signal transduction enzyme protein kinase C (PKC) appeared to be involved in the mechanism of induction of NK activity by vitamin C. We conclude that immune functional abnormalities can be restored after toxic chemical exposure by oral usage of vitamin C.

(1997) [Multiple chemical sensitivity (MCS)-syndrome].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9333378

--------------------------------------------------------------------------------------------------
(1997) **The role of excitatory amino acids in airway reflex responses in anesthetized dogs.**


In these studies we examined the role of excitatory amino acids (EAAs) neurotransmission in communicating sensory inputs to the airway-related vagal preganglionic neurons, by examining the effects of either NMDA or AMPA/kainate receptor blockade on reflex and chemical responses of tracheal smooth muscle. Experiments were performed in chloralose anesthetized, paralyzed and mechanically ventilated beagle dogs (n = 18), under hyperoxic, normocapnic, and normohydric conditions. Topical application or microinjection of NMDA receptor blockers, into the region of the ventrolateral medulla where airway-related vagal preganglionic neurons are located, insignificantly decreased the reflex changes in tracheal tone. However, topical application or microinjection of AMPA/kainate subtype of glutamate receptor selective antagonists markedly reduced reflex increase in tracheal tone induced by (1) lung deflation, (2) stimulation of laryngeal cold receptors, and (3) activation of peripheral or central chemoreceptors. These effects were potentiated by prior NMDA receptor blockade. Findings indicate that an increase in central cholinergic outflow to the airways by a variety of excitatory afferent inputs is mediated via activation of EAA receptors, mainly AMPA/kainate subtype of glutamate receptors.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9479671

(1997) **Olfactory loss secondary to toxic exposure.**


Biosis copyright: biol abs. rrm book chapter human mouse rat hamster patient animal model otolaryngology toxicology olfactory dysfunction toxic chemicals concentration threshold limit value permissible exposure limit osha occupational health toxic metals heavy metals irritant gases gases solvents multiple chemical sensitivity etiology toxicity immune system disease

(1997) **A quarter of preventable diseases are environmentally caused.**

Hamilton, J Journal/Bmj. 315: 78.

OBJECTIVE: To search for syndromes in Persian Gulf War veterans. PARTICIPANTS: Two hundred forty-nine (41%) of the 606 Gulf War veterans of the Twenty-fourth Reserve Naval Mobile Construction Battalion living in 5 southeastern states participated; 145 (58%) had retired from service, and the rest were still serving in the battalion. DESIGN: Participants completed a standardized survey booklet measuring the anatomical distributions or characteristics of each symptom, a booklet measuring wartime exposures, and a standard psychological personality assessment inventory. Two-stage factor analysis was used to disentangle ambiguous symptoms and identify syndromes. MAIN OUTCOME MEASURES: Factor analysis-derived syndromes. RESULTS: Of 249 participants, 175 (70%) reported having had serious health problems that most attributed to the war, and 74 (30%) reported no serious health problems. Principal factor analysis yielded 6 syndrome factors, explaining 71% of the variance. Dichotomized syndrome indicators identified the syndromes in 63 veterans (25%). Syndromes 1 ("impaired cognition," characterized by problems with attention, memory, and reasoning, as well as insomnia, depression, daytime sleepiness, and headaches), 2 ("confusion-ataxia," characterized by problems with thinking, disorientation, balance disturbances, vertigo, and impotence), and 3 ("arthro-myo-neuropathy," characterized by joint and muscle pains, muscle fatigue, difficulty lifting, and extremity paresthesias) represented strongly clustered symptoms; whereas, syndromes 4 ("phobia-apraxia"), 5 ("fever-adenopathy"), and 6 ("weakness-incontinence") involved weaker clustering and mostly overlapped syndromes 2 and 3. Veterans with syndrome 2 were 12.5 times (95% confidence interval, 3.5-44.8) more likely to be unemployed than those with no health problems. A psychological profile, found in 48.4% of those with the syndromes, differed from posttraumatic stress disorder, depression, somatoform disorder, and malingering. CONCLUSION: These findings support the hypothesis that clusters of symptoms of many Gulf War veterans represent discrete factor analysis-derived syndromes that appear to reflect a spectrum of neurologic injury involving the central, peripheral, and autonomic nervous systems.


OBJECTIVE: To identify risk factors of factor analysis-derived Gulf War-related syndromes. DESIGN: A cross-sectional survey. PARTICIPANTS: A total of 249 Gulf War veterans from the Twenty-fourth Reserve Naval Mobile Construction Battalion. DATA COLLECTION: Participants completed standardized booklets measuring
self-reported wartime exposures and present symptoms. MAIN OUTCOME MEASURES: Associations of factor analysis-derived syndromes with risk factors for chemical interactions that inhibit butyrylcholinesterase and neuropathy target esterase. RESULTS: Risk of syndrome 1 ("impaired cognition") was greater in veterans who reported wearing flea collars during the war (5 of 20, 25%) than in those who never wore them (7 of 229, 3%; relative risk [RR], 8.7; 95% confidence interval [CI], 3.0-24.7; P<.001). Risk of syndrome 2 ("confusion-ataxia") increased with a scale of advanced adverse effects from pyridostigmine bromide (chi² for trend, P<.001), was greater among veterans who believed they had been involved in chemical weapons exposure (18 of 108, 17%) than in those who did not (3 of 141, 2%; RR, 4.3; 95% CI, 1.9-10.0; P=.004). Effects of perceived chemical weapons exposure and advanced adverse effects from pyridostigmine were synergistic (Rothman S, 5.3; 95% CI, 1.04-26.7). Risk of syndrome 3 ("arthro-myo-neuropathy") increased with an index of frequency and amount of government-issued insect repellent containing 75% DEET (N,N-diethyl-m-toluamide) in ethanol applied during the war (chi² for trend, P<.001) and with advanced adverse effects from pyridostigmine (chi² for trend, P<.001). CONCLUSION: Some Gulf War veterans may have delayed, chronic neurotoxic syndromes from wartime exposure to combinations of chemicals that inhibit butyrylcholinesterase and neuropathy target esterase.


OBJECTIVE: To determine whether Gulf War-related illnesses are associated with central or peripheral nervous system dysfunction. DESIGN: Nested case-control study. PARTICIPANTS: Twenty-three veterans with factor analysis-derived syndromes (the cases), 10 well veterans deployed to the Gulf War (the deployed controls), and 10 well veterans not deployed to the Gulf War (the nondeployed controls). METHOD: With investigators blinded to group identities, participants underwent objective neurophysiological, audiovestibular, neuroradiological, neuropsychological, and blood tests. MAIN OUTCOME MEASURES: Evidence of neurologic dysfunction. RESULTS: Compared with the 20 controls, the 23 cases had significantly more neuropsychological evidence of brain dysfunction on the Halstead Impairment Index (P=.01), greater interside asymmetry of the wave I to wave III interpeak latency of brain stem auditory evoked potentials (P=.02), greater interocular asymmetry of nystagmic velocity on rotational testing, increased asymmetry of saccadic velocity (P=.04), more prolonged interpeak latency of the lumbar-to-cerebral peaks on posterior tibial somatosensory
evoked potentials (on right side, $P=0.03$, and on the left side, $P=0.005$), and diminished nystagmic velocity after caloric stimulation bilaterally ($P$ values range from 0.02 to 0.04). Cases (n=5) with syndrome 1 ("impaired cognition") were the most impaired on brain stem auditory evoked potentials ($P=0.005$); those (n=13) with syndrome 2 ("confusion-ataxia") were the most impaired on the Halstead Impairment Index ($P=0.006$), rotational testing ($P=0.01$), asymmetry of saccadic velocity ($P=0.03$), and somatosensory evoked potentials ($P<0.01$); and those (n=5) with syndrome 3 ("arthro-myo-neuropathy") were the most impaired on caloric stimulation ($P<0.01$).

CONCLUSIONS: The 3 factor-derived syndromes identified among Gulf War veterans appear to represent variants of a generalized injury to the nervous system.

---


Growing numbers of patients suffering from many symptoms believe that they have a condition called multiple chemical sensitivity syndrome (MCSS). It has been suggested that this syndrome can be triggered by exposure to any of a large and usually incompletely defined number of natural and synthetic chemical substances. Major medical organizations, including the National Research Council and the American Medical Association, have not recognized MCSS as a clinical syndrome because of a lack of valid, well-controlled studies defining it and establishing pathogenesis or origin. Lately, some have proposed that many patients with MCSS suffer from hereditary coproporphyria. However, this purported association is based chiefly on results from a single reference laboratory of a fundamentally flawed assay for erythrocyte coproporphyrinogen oxidase. Although patients with MCSS may, at times, have modest increases in urinary coproporphyrin excretion, this is a common finding found in many asymptomatic subjects or patients with diverse other conditions (eg, diabetes mellitus, heavy alcohol use, liver disease, and many kinds of anemia). Such secondary coproporphyrinuria does not indicate the existence of coproporphyria. To our knowledge, there is no scientifically valid evidence to support an association between MCSS and coproporphyria, nor is there any unifying hypothesis for rationally linking these 2 disorders.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9040294

---

Acrylamide and carbon disulfide produce central-peripheral distal axonopathy in experimental animals and humans. The main feature of this disease is the focal swellings containing neurofilaments in distal axons, followed by nerve degeneration beyond these swellings. We studied the possible role of tubulin assembly kinetics in this disease. The rats were either administered acrylamide (50 mg/kg, ip, saline) or exposed to carbon disulfide (700 ppm, 9 h) via inhalation for 12 and 15 d, respectively. Tubulin, purified from both acrylamide-(10.37 +/- 0.3 vs 11.3 +/- 0.15) and carbon disulfide-treated (9.72 +/- 0.5 vs 11.18 +/- 0.25) rat brains showed increase in Vmax (OD/min x 10(3)) of its polymerization. However, only acrylamide treatment showed a decrease in time to Vmax, when brain supernatant was used for tubulin polymerization. In vitro addition of acrylamide (0.1-1 mM) to bovine brain tubulin also showed a decrease in time to Vmax (16-21%) of its polymerization. Carbon disulfide treatment of rats, on the other hand, showed a decrease in MAP-2 and an increase in a 120-kDa peptide concentration. The latter showed immunoreactivity with anti-MAP-2. The increase in the rate of tubulin polymerization by acrylamide and carbon disulfide treatment may alter the rate of transport of axonal constituents, including neurofilament, and contribute toward their accumulation in the focal swellings observed in this neuropathy.

(1997) Alteration in neurofilament axonal transport in the sciatic nerve of the diisopropyl phosphorofluoridate (DFP)-treated hen.

Diisopropyl phosphorofluoridate (DFP) is an organophosphorus ester that produces organophosphorus ester-induced delayed neurotoxicity (OPIDN) in hens 7-14 days after a single s.c. dose of 1.7 mg/kg. In this study, hens were treated with a single dose of DFP (1.7 mg/kg, s.c.) 24 hr after [35S]methionine injection into the sacrolumbar region of their spinal cord, and killed 3, 7, 14, or 27 days post-DFP treatment. The rates of transport of labeled high (NF-H), medium (NF-M), and low (NF-L) molecular weight neurofilaments, and tubulin were faster in DFP-treated birds than in controls after 3 days. Subsequently, the rate of transport of these proteins started falling, so that the peaks of labeled proteins in control and DFP-treated hens were overlapping after 7 days. At 14 days, the peaks of NF-H, NF-M, and NF-L in treated hens were distinctly behind the corresponding peaks in control hens. This was again followed by an increase in transport of NF-H and NF-L, but not of NF-M, so that the labeled NF-H and NF-L showed the same pattern in control and treated hens after 27 days. The transient decrease in NF-H and NF-L axonal transport rate, and recovery correlated in a temporal manner with the previously reported increase of Ca2+ calmodulin-dependent protein kinase-mediated phosphorylation of neurofilament proteins and inhibition of calpain activity in the sciatic nerve in OPIDN. Proteinase inhibition has been reported recently to result in enhanced phosphorylation of neurofilaments in some cells. The present study suggests that the enhanced
phosphorylation of neurofilaments by DFP-increased Ca2+/calmodulin-dependent protein kinase activity may be contributing toward alteration in NF axonal transport and the development of OPIDN.


Recent reports have pointed to an increased number of patients presenting with multisystem symptoms which they attribute to chemical exposures or to heightened chemical sensitivity. Twenty patients exposed to wood preservative products, who attended a joint toxicology and psychiatric clinic, were reviewed by a retrospective case note analysis. Thirteen patients attributed their symptoms to the wood preservative soon after the exposure, and seven patients developed the attribution only at a later date. Reported symptoms referred to all body systems, but there were few physical signs. Clinical findings suggest that the acute symptoms were consistent with the expected toxic effects, but the chronic symptoms could not be explained physically. Patient's beliefs about chemical poisoning could be understood as arising in the context of an attributional process, representing a sociopsychosomatic syndrome precipitated by wood preservative exposure. Patient management included a discussion of findings from assessments, published information, along with counseling where appropriate. Follow-up information from their general practitioners indicated a possible improvement in 50% of patients.


The present study was intended (1) to find out whether simultaneous administration of nine chemicals at a concentration equal to the "no-observed-adverse-effect level" (NOAEL) for each of them would result in a NOAEL for the combination and (2) to test the usefulness of fractionated factorial models to detect possible interactions between chemicals in the mixture. A 4-week oral/inhalatory study in male Wistar rats was performed in which the toxicity (clinical chemistry, hematology, biochemistry, and pathology) of combinations of the nine compounds was examined. The study comprised 20 groups, 4 groups in the main part (n = 8) and 16 groups in the satellite part (n = 5). In the main study, the rats were simultaneously exposed to mixtures of all
nine chemicals [dichloromethane, formaldehyde, aspirin, di(2-ethylhexyl)phthalate, cadmium chloride, stannous chloride, butyl hydroxyanisol, loperamide, and spermine] at concentrations equal to the "minimum-observed-adverse-effect level" (MOAEL), NOAEL, or 1/3NOAEL. In the satellite study the rats were simultaneously exposed to combinations of maximally five compounds at their MOAEL. These combinations jointly comprise a two-level factorial design with nine factors (=9 chemicals) in 16 experimental groups (1/32 fraction of a complete study). In the main part many effects on hematology and clinical chemistry were encountered at the MOAEL. In addition, rats of the MOAEL group showed hyperplasia of the transitional epithelium and/or squamous metaplasia of the respiratory epithelium in the nose. Only very few adverse effects were encountered in the NOAEL group. For most of the end points chosen, the factorial analysis revealed main effects of the individual compounds and interactions (cases of nonadditivity) between the compounds. Despite all restrictions and pitfalls that are associated with the use of fractionated factorial designs, the present study shows the usefulness of this type of factorial design to study the joint adverse effects of defined chemical mixtures at effect levels. It was concluded that simultaneous exposure to these nine chemicals does not constitute an evidently increased hazard compared to exposure to each of the chemicals separately, provided the exposure level of each chemical in the mixture is at most similar to or lower than its own NOAEL.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9073463

(1997) Waiting list already 7 months long at Toronto's new Environmental Health Clinic.

Following the head set by Nova Scotia, Ontario now has a clinic devoted to the treatment of patients with "environmental illness." It opened in Toronto last year, and patients must be referred by their family physician and complete a 16-page previsit questionnaire. They receive a 3-hour assessment in which their medical history is explored, plus a full physical examination and blood and urine tests. Dr. Frank Foley, who heads the Toronto clinic, says his patients have seen from 8 to 10 health care professionals in the 2 years before their visit and most have been told the problem is "in your head." He says they need to "have their symptoms validated and their distress acknowledged."

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9084399


Treatment of patients who attribute their environmental illness to mercury from amalgam fillings is largely experimental. On the Symptom Check List, overall distress, and somatization, obsessive-compulsive, depression, and anxiety symptom dimensions, were increased in 50 consecutive patients examined, and Eysenck Personality Questionnaire scores suggested less extroversion and increased degree of emotional liability. Succimer (meso-2, 3-dimercaptosuccinic acid) was given at a daily dose of 30 mg/kg for five days in a double-blind, randomized placebo-controlled trial. Urinary excretion of mercury and lead was considerably increased in the patients who received the chelator. Immediately after the treatment and 5 to 6 weeks later, most distress dimensions had improved considerably, but there was no difference between the succimer and placebo groups. These findings suggest that some patients with environmental illness may substantially benefit from placebo.

Goudsmit, EM Journal/Bmj. 315: 948.

(1997) From sanitation to cellphones: participants and principles involved in environmental health protection.

(1997) Sex differences in task performance associated with attention to ambient odor.

The effects of ambient odor (pleasant, unpleasant, none); odor suggestion (present, absent); and sex of subject on mood and performance measures were explored in a 3 x 2 x 2 experimental design. A total of 40 men and 40 women performed a clerical task and a speed and accuracy task (digit deletion), filled out self-evaluations of mood, predicted performance, and rated the odor quality of the test room. Ambient odor conditions significantly affected room smell ratings, but they had no effect on performance or mood. Odor suggestion produced a significant sex-related interaction
effect on the digit deletion task, irrespective of actual ambient odor. The results are discussed with respect to sex differences observed in laboratory studies and in epidemiological investigations of multiple chemical sensitivity and sick building syndrome.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9169629


The history of "nondisease" dates back, at least 4000 years, to early descriptions of hysteria. More recently somatization became a part of the official diagnostic nomenclature by creation of the DSM III category, "somatoform disorders." Somatization can serve as a rationalization for psychosocial problems or as a coping mechanism, and for some illness, becomes a way of life. One variation of somatization can be the "fashionable diagnosis", for example, fibromyalgia, multiple chemical sensitivities, dysautonomia, and, in the past, "reactive hypoglycemia". These disorders are phenomenologically related to environmental or occupational syndromes and mass psychogenic illness. Fashionable illnesses are characterized by (i) vague, subjective multisystem complaints, (ii) a lack of objective laboratory findings, (iii) quasi-scientific explanations, (iv) overlap from one fashionable diagnosis to another, (v) symptoms consistent with depression or anxiety or both, (vi) denial of psychosocial distress or attribution of it to the illness. Fashionable diagnoses represent a heterogeneous collection of physical diseases, somatization, and anxiety or depression. They are final common symptomatic pathways for a variety of influences including environmental factors, intrapersonal distress and solutions to social problems. A fashionable diagnosis allows psychosocial distress to be comfortably hidden from both the patient and the physician, but premature labeling can also mask significant physical disease. Hysteria remains alive and well and one contemporary hiding place is fashionable illness.

(1997) Comparison of single photon emission computed tomography findings in cases of healthy adults and solvent-exposed adults.

Single photon emission computed tomography (SPECT) is a useful tool in measuring dynamic brain functioning. Its potential to reveal the physiological mechanisms of neurotoxicity has not been fully explored. In the present study, the SPECT findings for 25 healthy control subjects were compared to the findings for 25 mixed organic solvent
exposure subjects. Specific physiological abnormalities related to regional cerebral blood flow activity (rCBF) were revealed. In the early phase of uptake, significantly decreased uptake was found in the mixed organic solvent group; in the late phase of uptake, a significant increase in uptake was found in specific regions of interest. The discovery of this abnormality in brain functioning may be a significant step toward the creation of a biological marker of neurotoxicity. Early detection of neurotoxicity is important in occupational medicine to prevent neurotoxic illnesses in working populations.

(1997) Comparison of single photon emission computed tomography findings in cases of healthy adults and solvent-exposed adults: correction of previous results.


This article provides an overview of the scientific literature in which chemically sensitive patients have been directly evaluated. For that purpose, consideration of various case definitions is offered along with summaries of subjects' demographic profiles, exposure characteristics, and symptom profiles across studies. Controlled investigations of chemically sensitive subjects without other organic illnesses are reviewed. To date, psychiatric, personality, cognitive/neurologic, immunologic, and olfactory studies have been conducted comparing subjects with primary chemical sensitivity to various control groups. Thus far, the most consistent finding is that chemically sensitive patients have a higher rate of psychiatric disorders across studies and relative to diverse comparison groups. However, since these studies are cross-sectional, causality cannot be implied. Demonstrating the role of low-level chemical exposure in a controlled environment has yet to be undertaken with this patient group and is crucial to the understanding of this phenomenon.


(1997) Is the white-ivory assay of Drosophila melanogaster a useful tool in genetic toxicology?

The white-ivory assay of Drosophila is based on the detection of reversions to wild-type phenotype of ommatidia with the white-ivory mutation. A tandem quadruplication of this gene is used in order to increase the reversion probability. Although the exact mechanism implicated in reversion is not known, revertant spots are believed to arise as a consequence of intrachromosomal recombination or related phenomena. Since the white-ivory assay has not been broadly used, the number of chemicals tested until now is still limited. In this work, we have assayed 25 chemicals belonging to several chemical groups, i.e., crosslinking agents, DNA-topoisomerase inhibitors, antimetabolites/nucleotide pool inhibitors, cyclic-adduct inducers, halogenated hydrocarbons, bulky-adduct inducers, intercalating agents, oxidative damage inducers, and a multiple damage inducer, to validate this test. Cross-linking agents, halogenated hydrocarbons, and the multiple damage inducer, dounomycin, were positive. On the contrary, the three antimetabolites/nucleotide pool inhibitors tested were negative. The other chemical groups showed disparate results, since some chemicals were positive, whereas others were negative in each group. A comparison with the results obtained in the w/ w+ and mwh/flr3 assays shows that the wi assay detects a more restricted spectrum of damages than those, although, with respect to carcinogenicity, its sensitivity (0.76, with the 62 chemicals tested until now) is similar to that estimated for the mentioned somatic assays. The conclusion of this work, then, is that the wi assay is not recommended as a general screening test, because the background reversion frequencies show a high variability among solvents, the range of lesion-recognition is lower than in the w/ w+ and mwh/flr3 SMARTs, and the mechanism implicated in the white-ivory reversion is poorly understood. TAX - DROSOPHILA MELANOGASTER,C(1)DX,Y,F/DP(1:1:1:1)W(I)Y(2)


Multiple chemical sensitivity is a controversial diagnosis. Rigorous, controlled, laboratory-based research can reduce this controversy and lead to potential clinical confirmatory tests. The literature on human caffeine discrimination provides a rigorous methodology that can address reports that patients who suffer multiple chemical sensitivity (MCS) are sensitive to usually well-tolerated chemical doses; the studies require patients to discriminate caffeine from placebo under double-blind conditions. Several issues relevant to the conduct of caffeine discrimination studies using MCS patients as subjects are addressed; these issues include study design, determination of safe and tolerable training doses, and discrimination training. Such research will benefit patients and clinicians dealing with a diagnosis of MCS.
(1997) [Diagnosis in environmental medicine: basic principles and problems].
Eis, D and Sonntag, HG Journal/Z Arztl Fortbild Qualitatssich. 91: 11-20.

Diagnosis in environmental medicine only differs from the conventional medical diagnosis in a more detailed expositional evaluation on the basis of a respectively expanded anamnesis and a possible local visit, a surrounding examination as well as a so-called biological monitoring. Thus, the essential element of the "diagnosis" in environmental medicine consists in the resolving of a possible internal exposure (and occasionally resulting effects). From this point of view, physicians in environmental medicine could give an advisory contribution to the conventional medicine in selected cases. In contrast to frequently occurring assertions, there are practically no typical environmental diseases due to usual environmental toxicants. At present, a causality between environmental agents and health related disturbances can only be made plausible in less than 10% of out-patients of environmental medicine. These figures are in total contrast to the expansion of the out-patient and clinical environmental medicine. The expansion of the diagnostic offer gives not only to the public but also to the patients and the physicians the impression of a specific competence in diagnostic and therapy of environmental medicine which to this extent does not exist. The consequences are unnecessary and unsuccessful examinations. This is of no help to the patient. Most of the "environmental patients" suffer from civilization caused psychosomatic and psychosocial disturbances like e.g. phobias, and somatoforme or depressive disturbances. In the genesis probable an increasing readiness for fear, unrealistic threatening convictions (arranged by media, homeopathists, physicians and other authorities), growing fear disturbances as a consequence to this as well as the cognitive connection of "normal" inner disturbances with the suspicious agens play a decisive role. For these patients the clinical environmental medicine lead astray. This is significantly more valid for the numerous "clinical ecologists" who apply scientifically doubtful methods. Considering the clinical approach to environmental medicine urgently needs a critical evaluation by independent research groups.

-----------------------------

(1997) Do organic solvents induce changes in the dopaminergic system?
Positron emission tomography studies of occupationally exposed subjects.

OBJECTIVES: The objective of this study was to test the hypothesis that long-term occupational exposure to organic solvents may effect the levels and turnover of dopamine in man. METHODS: A study was performed on 17 patients with
neuropsychiatric symptoms due to occupational solvent exposure, and 11 healthy non-exposed male volunteers (controls). Positron emission tomography (PET) was used to assess striatal dopaminergic function, using L-[11C]DOPA, [11C]nomifensine and [11C]raclopride as tracers. RESULTS: The rate of dopamine synthesis was significantly increased among subjects with occupational exposure to organic solvents compared with non-exposed controls. After controlling for the difference in age between exposed and controls, the effect of solvent exposure became less apparent and was reduced from +32% (P = 0.009) to +25% (P = 0.07). There were no differences with regard to the binding of [11C]nomifensine. Patients with and without the diagnosis of toxic encephalopathy did not differ with regard to their putaminal uptake of L-[11C]DOPA, [11C]nomifensine and [11C]raclopride. CONCLUSION: The data support the hypothesis that long-term exposure to organic solvents may increase the rate of dopamine synthesis in the brain without affecting the number of presynaptic terminals or postsynaptic dopamine receptors.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9380081

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9099665


Hypersensitivity to cold is a relatively frequent sequel of peripheral nerve injuries but its mechanism is not well understood. We suggested that incomplete recovery of diameter of regenerated fibers is one of the factors involved in cold intolerance after nerve damage. Conduction velocity is correlated to fiber diameter, and is slowed down by
cold. In normal subjects, cold does not desynchronize the volleys of sensory impulses sufficiently to change the intelligibility of the peripheral 'messages'. Sensory perceptions remain accurate although they acquire a characteristic numbness. On the other hand, post-traumatic reduction in fiber diameters causes a permanent distortion of the messages. We considered that when the distortion is severe, the resulting messages may be perceived by the centers as containing nociceptive components. We further hypothesized that, even in cases of moderate permanent distortion, cold acts by increasing the post-traumatic abnormalities of impulse synchronization. In winter, decompensation is observed when a threshold of desynchronization is reached. We constructed a model of peripheral nerve messages in an attempt to represent and quantitate the desynchronizations produced by cold and crush damage lesions in peripheral nerve messages. A number of parameters concerning fiber anatomy, exposure to cold, and type of nerve damage were taken into consideration. Four elementary types of desynchronization could be recognized by considering the times of arrival of pairs of impulses at the nervous centers. The difference between a normal and a distorted message could be expressed by eight variables. Thus, although our model was quite simple, a large amount of data was obtained and a preliminary statistical study was necessary in order to orient the final analysis. Then, we used factor analysis in an attempt to obtain a satisfactory interpretation of the data. The results indicated that peripheral desynchronization might explain, at least in part, the painful sensations experienced in winter by many patients after peripheral nerve injury.


Porphyrias are relatively uncommon inherited or acquired disorders in which clinical manifestations are attributable to a disturbance of heme synthesis (porphyrin metabolism), usually in association with endogenous or exogenous stressors. Porphyrias are characterized by elevations of heme precursors in blood, urine, and/or stool. A number of chemicals, particularly metals and halogenated hydrocarbons, induce disturbances of heme synthesis in experimental animals. Certain chemicals have also been linked to porphyria or porphyrinuria in humans, generally involving chronic industrial exposures or environmental exposures much higher than those usually encountered. A noteworthy example is the Turkish epidemic of porphyria cutanea tarda produced by accidental ingestion of wheat treated with the fungicide hexachlorobenzene. Measurements of excreted heme precursors have the potential to serve as biological markers for harmful but preclinical effects of certain chemical exposures; this potential warrants further research and applied field studies. It has been hypothesized that several otherwise unexplained chemical-associated illnesses, such as multiple chemical sensitivity syndrome, may represent mild chronic cases of porphyria or other acquired abnormalities in heme synthesis. This review concludes
that, although it is reasonable to consider such hypotheses, there is currently no convincing evidence that these illnesses are mediated by a disturbance of heme synthesis; it is premature or unfounded to base clinical management on such explanations unless laboratory data are diagnostic for porphyria. This review discusses the limitations of laboratory measures of heme synthesis, and diagnostic guidelines are provided to assist in evaluating the symptomatic individual suspected of having a porphyria.


It was previously believed that the neuronal type of nitric oxide (NO) synthase was constitutive in nature, and that changes in the concentration of intracellular Ca2+ represent the sole input that regulates its activity. Recent reports, however, suggested that this enzyme could also be induced under certain conditions. We report here that prolonged stimulation of M1 muscarinic acetylcholine receptors results in potentiation of maximal receptor-mediated activation of neuronal NO synthase in Chinese hamster ovary cells. This effect was dependent on the concentration of agonist during the treatment and was abolished by a muscarinic receptor antagonist. These findings are important for understanding the sequelae of prolonged administration of muscarinic agonists in vivo.


This paper develops hypotheses regarding the interactions among stress, immunity, and chemical sensitivities and gives an overview of the questions and hypotheses generated by a working group exploring the application of psychoneuroimmunology to chemical sensitivities. Consideration is given to prospective longitudinal studies designed to find cases among at-risk exposed populations. Relevant immune parameters to be measured longitudinally and in challenge studies for patients with MCS are discussed. Immune system changes in response to the chronic stress of having MCS and as primary responses to chemical exposure also are considered.

Interstitial cystitis (IC) is a relatively uncommon and enigmatic disorder characterized by pain in the bladder and pelvic region, typically accompanied by urinary urgency and frequency. Fibromyalgia is a more common disorder, with the prominent symptoms being diffuse musculoskeletal pain and fatigue, and it has been well established that there is substantial clinical overlap between fibromyalgia and chronic fatigue syndrome (CFS). Although genitourinary and musculoskeletal symptoms predominate in IC and fibromyalgia respectively, both disorders share a number of features, including similar demographics, "allied conditions" (e.g. irritable bowel syndrome, headaches, etc.), natural history, aggravating factors, and efficacious therapy. We hypothesized that there was substantial clinical overlap between fibromyalgia and IC, and examined cohorts of individuals with these two disorders in parallel, to compare the spectrum of symptomatology. Sixty fibromyalgia patients, 30 IC patients, and 30 age-matched healthy controls were questioned regarding current symptomatology. A dolorimeter examination was also performed in the three groups to assess peripheral nociception. We found that the frequency of current symptoms was very similar for the fibromyalgia and IC groups. Both the fibromyalgia and IC patients displayed increased pain sensitivity when compared to healthy individuals, at both tender and control points. These data suggest that IC and fibromyalgia have significant overlap in symptomatology, and that IC patients display diffusely increased peripheral nociception, as is seen in fibromyalgia. Although central mechanisms have been suspected to contribute to the pathogenesis of fibromyalgia for some time, we speculate that these same types of mechanisms may be operative in IC, which has traditionally been felt to be a bladder disorder.
produced by noise or styrene alone. Single simultaneous exposure to noise and carbon monoxide (CO), however, showed some evidence of enhancement of ototoxicity beyond that produced by noise or carbon monoxide alone, although only at high atmospheric concentrations of CO. When 1,3-dinitrobenzene was administered parentally at neurotoxic dose levels with continuous noise exposure, there was an increased severity of effects in the brain stem. Combined exposure to noise and lead and/or cadmium resulted in histopathological heart lesions of undefined severity, a finding which was not observed for either of those agents in isolation. Dermal exposure to dimethylformamide and noise or inhalation exposure to xylene and noise resulted in some biochemical changes in cardiac muscle which were of doubtful toxicological significance. In developing mice, there was evidence that combined exposure to cadmium sulphate and noise caused an increased incidence of external and skeletal malformations but only at dose levels of cadmium which would have induced developmental effects. Overall, for each of these chemicals and endpoints observed there is a suggestion of some interaction with noise exposure. From the data that are currently available, however, inferences cannot be drawn on whether or not interactions would have occurred at lower, more occupationally relevant, levels of exposure. A number of studies have investigated human populations exposed to both noise and industrial chemicals. Due to confounding factors, however, it was concluded that these data were inadequate for assessing the combined effects of noise and chemical exposure on hearing.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9284647


Hazardous materials incidents include gas and vapor releases, spills, explosions, and fires. Incidents involving human exposure are challenging for most health care providers because of the vast number of potential chemicals involved, frequently incomplete incident information, and limited experience in exposure assessment. To facilitate improved evaluation and treatment of patients with chemical exposures, the Washington Poison Center established the Hazardous Materials Exposure Information Service in 1994. During the first 33 months of operation, this service has provided information on 70 incidents, involving a total of 1120 exposed individuals, including 501 patients treated in medical facilities. This paper reviews these incidents, the process used to collect information from the incidental scene, and selected techniques for evaluating the extent of individual chemical exposure.
The potential for bias due to attrition in the National Exposure Registry: an examination of reasons for nonresponse, nonrespondent characteristics, and the response rate.

This study examined attrition in the Trichloroethylene (TCE) Subregistry of the National Exposure Registry (NER). The analyses focused on 3915 persons exposed to the chemical TCE through the drinking water in their home. Baseline data were compared for subgroups of the TCE Subregistry members who were eligible to participate in the first TCE Subregistry follow-up. Study members were grouped according to their participation status in the first follow-up: remainers (n = 3494) and losses (n = 421), and three subgroups of losses: refusals, unable to locate, and unable to contact. The comparison of demographic variables of remainers and losses revealed that remainers had a higher percent of females, currently smoked less, were older, and fewer had no education and more had education beyond high school. These differences occurred for the losses subgroups unable to locate and unable to contact, however, not for refusals. The comparison of reporting rates of remainers and losses for 2.3 health outcomes revealed statistically significant decreases by losses for five health conditions but the pattern of statistically significant differences for the losses subgroups was not clear-cut. Altogether, the analyses indicated that the potential for bias due to attrition was minimal.

Chemical quandary.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9034508

MCS (Multiple Chemical Sensitivity): cooperation between toxicology and psychology may facilitate solutions of the problems: commentary.
Bock, KW and Birbaumer, N Journal/Hum Exp Toxicol. 16: 481-4.

This commentary is the result of a discussion between the authors. After outlining the problem of MCS (A), to which the toxicologist was increasingly and painfully exposed, he was surprised to realise that the problem was well recognised in psychology. (B) In the second round of the discussion therapeutic implications are discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9306133

BACKGROUND: Many patients who are first seen with what has been called multiple chemical sensitivity syndrome (MCS) experience symptoms suggestive of panic disorder including chest tightness, shortness of breath, palpitations, paresthesias, light-headedness, and mental confusion. Although such patients are often convinced that these symptoms reflect toxic effects of environmental "chemicals," direct evidence of this is lacking. To the contrary, a previous study has shown that some of these individuals exhibit hyperventilation responses on exposure to non-noxious stimuli, and it has been suggested that the resulting hypocarbia accounts for their symptoms. We postulated that some patients with self-identified MCS had an underlying condition similar to panic disorder and would therefore demonstrate similar responses to provocative challenges, such as sodium lactate infusion. METHODS: Patients referred to an allergy and clinical immunology service for evaluation of "chemical sensitivity" were investigated to rule out underlying medical conditions, including asthma, as a cause of their symptoms and were enrolled for study after giving informed consent. After a standardized psychiatric assessment was performed, patients underwent single-blind intravenous infusions of normal saline solution (placebo) and sodium lactate (which reproduces symptoms in individuals with underlying panic disorder). All patients were referred for independent psychiatric assessment. RESULTS: The standardized psychiatric assessment identified four of five patients as meeting DSM III-R diagnostic criteria for panic disorder along with other depressive and/or anxiety-related disorders. All five patients with self-identified chemical sensitivity exhibited a positive symptomatic response to sodium lactate compared with placebo infusion. Independent psychiatric assessment confirmed the diagnosis of panic disorder on the basis of DSM III-R criteria in each of the five patients. CONCLUSION: These results suggest that MCS may have a neurobiologic basis similar, if not identical, to that of panic disorder. We speculate that treatments with demonstrated efficacy in panic disorder may also be of benefit in MCS, and conversely, treatments that reinforce anticipatory anxiety and avoidance behavior in patients with MCS may be detrimental.


(1997) Systematic considerations in the area of multiple chemical sensitivity.
Many workers who speculate about multiple chemical sensitivity (MCS) have devised a large number of hypothetical constructs designed to explain the phenomena. Too often these are not logically connected to the larger body of scientific thought but instead appeal to ideas not documented in accessible literature and often appearing metaphysical in nature.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167984

(1997) Time-dependent sensitization of heart rate and blood pressure over multiple laboratory sessions in elderly individuals with chemical odor intolerance.
Bell, IR, Schwartz, GE, Bootzin, RR and Wyatt, JK Journal/Arch Environ Health. 52: 6-17.

In this study, we tested the hypothesis that low-level chemical odor intolerance (i.e., "cacosmia") is a manifestation of heightened sensitizability to environmental stimuli. We examined supine heart rate and blood pressure of elderly individuals, who were classified as either having a higher degree of chemical odor intolerance (n = 12) or a lower degree of chemical odor intolerance (n = 13), upon awakening in a sleep research laboratory on 6 different days during an 8-wk protocol. During the 2 initial wk, they consumed a customary baseline diet (including ad lib milk and other dairy products), followed by 3 wk each of nondairy-containing and dairy-containing diets in randomly assigned, counterbalanced order. Measurements were made on 3 pairs of successive days, distributed over a 6-wk period, and on which different diets were consumed. The high-intolerance group had significantly higher mean supine systolic and diastolic blood pressures than did the low-intolerance group. Although subjects consumed milk products during both the initial baseline and subsequent dairy diet periods, the high-intolerance group had significantly higher heart rates and diastolic blood pressures later in the study than at baseline, especially when they were on the dairy diet. In contrast, the cardiovascular measures of the low-intolerance group lowered on average with time. The high-intolerance subjects had an increased mean diastolic blood pressure on the second days versus the first days in the laboratory (averaged across all diets). Collectively, the data suggest that elderly individuals with a high degree of chemical odor intolerance evidence (a) increased sympathetic tone in the cardiovascular system at rest over multiple measurements; and (b) greater sensitizability and/or lesser habituation of heart rate and diastolic blood pressure over time as a function, in part, of repeated environmental stressor exposures (i.e., a novel laboratory contextual setting and/or specific dietary constituents). Consistent with a sensitization model, the findings emphasize the need for two or more identical sessions at least 24 h apart in physiological studies of individuals with a high degree of intolerance for chemical odors versus normal individuals. The results of the blood pressure observations suggest that the possibility of abnormally labile autonomic
function and cognitive sequelae in individuals with a high degree of intolerance for chemical odor increases with age.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9039852

(1997) Elevation of plasma beta-endorphin levels of shy elderly in response to novel laboratory experiences.

Heightened psychophysiological reactivity to the novel or unfamiliar is a leading characteristic of shy or behaviorally inhibited individuals. To assess one aspect of the physiological stress response in shyness, the authors compared the morning plasma beta-endorphin levels of 15 extremely shy, healthy elderly individuals with beta-endorphin levels of 15 extremely outgoing persons on three pairs of 2 successive days. The primary finding was that shy participants exhibited significantly higher levels of beta-endorphin on the 1st days of each pair of days, compared with the 2nd days in the laboratory. No main effect for shyness or interaction between shyness and diet on endorphin levels was found. The findings are consistent with a peripheral opioid hyperreactivity to novelty in shy elderly persons. Shyness may constitute a risk factor for panic disorder in younger adults and for nasal allergies and certain cancers in older adults. Experimental design and interpretation of future studies of shy individuals' stress responses may need to consider novelty versus familiarity of the procedures and setting.


This paper summarizes the clinical phenomenology of multiple chemical sensitivity (MCS), outlines the concepts and evidence for the olfactory-limbic, neural sensitization model for MCS, and discusses experimental design implications of the model for exposure-related research. Neural sensitization is the progressive amplification of responsivity by the passage of time between repeated, intermittent exposures. Initiation of sensitization may require single toxic or multiple subtoxic exposures, but subsequent elicitation of sensitized responses can involve low or nontoxic levels. Thus, neural sensitization could account for the ability of low levels of environmental chemicals to elicit clinically severe, adverse reactions in MCS. Different forms of sensitization include limbic kindling of seizures (compare temporal lobe epilepsy and simple partial
seizures) and time-dependent sensitization of behavioral, neurochemical, immunological, and endocrinological variables. Sensitized dysfunction of the limbic and mesolimbic systems could account in part for many of the cognitive, affective, and somatic symptoms in MCS. Derealization (an alteration in perception making familiar objects or people seem unfamiliar or unreal) is a common MCS symptom and has been linked with limbic dysfunction in clinical neuroscience research. Sensitization is distinct from, but interactive with, other neurobiological learning and memory processes such as conditioning and habituation (compare adaptation or tolerance). In previous studies, hypotheses for MCS involving sensitization, conditioning, and habituation (adaptation) have often been considered in isolation from one another. To design more appropriate chemical exposure studies, it may be important to integrate the various theoretical models and empirical approaches to MCS with the larger scientific literature on individual differences in these potentially interactive phenomena.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167980

(1997) Testing the neural sensitization and kindling hypothesis for illness from low levels of environmental chemicals.

Sensitization in the neuroscience and pharmacology literatures is defined as progressive increase in the size of a response over repeated presentations of a stimulus. Types of sensitization include stimulant drug-induced time-dependent sensitization (TDS), an animal model related to substance abuse, and limbic kindling, an animal model for temporal lobe epilepsy. Neural sensitization (primarily nonconvulsive or subconvulsive) to the adverse properties of substances has been hypothesized to underlie the initiation and subsequent elicitation of heightened sensitivity to low levels of environmental chemicals. A corollary of the sensitization model is that individuals with illness from low-level chemicals are among the more sensitizable members of the population. The Working Group on Sensitization and Kindling identified two primary goals for a research approach to this problem: to perform controlled experiments to determine whether or not sensitization to low-level chemical exposures occurs in multiple chemical sensitivity (MCS) patients; and to use animal preparations for kindling and TDS as nonhomologous models for the initiation and elicitation of MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167993

------------------------------------------------------------------------

There is a substantial body of literature on psychosocial impacts of chemical and nuclear accidents. Less attention, however, has been focused on the program and policy issues that are connected with efforts to provide psychosocial assistance to the victims of such accidents. Because psychosocial assistance efforts are certain to be an essential part of the response to future environmental emergencies, it is vital that relevant program and policy issues be more fully considered. This article discusses the highly complex nature of contamination situations and highlights some of the key policy issues that are associated with the provision of psychosocial services after environmental accidents. One issue concerns the potential for assistance efforts to become objects of conflict. In the context of the intense controversy typically associated with chemical or nuclear accidents, and with debates over the causation of illness usually at the center of environmental accidents, psychosocial assistance services may themselves become contested terrain. Other significant program and policy issues include determining how to interface with citizen self-help and other voluntary groups, addressing the problem of stigma, and deciding how to facilitate stakeholder participation in the shaping of service provision. This article offers a series of policy proposals that may help smooth the way for psychosocial assistance programs in future environmental emergencies.

---------------------------------------------------------------------------------------------------------------------------


BACKGROUND: IgE/allergen-dependent activation of skin mast cells is involved in acute urticaria and leads to their IL-4 release. Previously we have demonstrated in vitro the induction of the low-affinity receptor for IgE (CD23/Fc epsilon RII) in human keratinocytes (HK) upon stimulation with IL-4. In addition, we have observed that ligation of CD23 on keratinocytes induced type II nitric oxide synthase (iNOS), leading to the release of nitric oxide (NO) and proinflammatory cytokines (TNF-alpha, IL-6). According to these in vitro data, we explored whether keratinocytes could also express iNOS, TNF-alpha, IL-6, and CD23 in acute urticaria, an in vivo model in which activation of mast cells by IgE/allergen immune complexes is involved. MATERIALS AND METHODS: INOS, TNF-alpha, IL-6, and CD23 expression by keratinocytes was studied in acute urticaria (n = 11) in biopsies from lesional and autologous normal skin by immunohistochemistry, in situ hybridization, or RT-PCR. Nitrites and TNF-alpha synthesis were assayed in supernatants of cultured lesional keratinocytes. RESULTS: INOS mRNA expression was demonstrated with RT-PCR in 10 biopsies out of 11 sections of acute urticaria lesional skin. Immunohistochemistry showed that this iNOS
positivity originated from keratinocytes located close to the dermoepidermal junction; TNF-alpha and IL-6 mRNA transcription was observed in all but one iNOS+ biopsy. Immunostaining and in situ hybridization with CD23-specific probes were strong in all but one iNOS+ skin biopsy. Noninflamed autologous skin was negative for iNOS (except for a weak positivity in one case), cytokines, and CD23. CONCLUSION: The colocalization of iNOS, proinflammatory cytokines, and CD23 within keratinocytes in acute urticaria demonstrates that these cells play an important role in the initiation and maintenance of the inflammatory reaction during this disease in humans through activation of the iNOS pathway by CD23 ligation with IgE/allergen immune complexes.


(1997) Stimulation of Fc gamma receptors in rat peritoneal macrophages induces the expression of nitric oxide synthase and chemokines by mechanisms showing different sensitivities to antioxidants and nitric oxide donors.

The induction of nitric oxide (NO) production and the expression of cytokine-induced neutrophil chemoattractant (CINC-1) were studied in rat peritoneal adherent cells stimulated with insoluble immune complexes containing rabbit IgG Ab and OVA as the cognate Ag (IC). Incubation with IC at concentrations as low as 10 microg/ml induced NO production and the expression of inducible NO synthase (iNOS) protein. This was accompanied by the expression of CINC-1 mRNA and the activation of nuclear factor-kappaB (NF-kappaB). However, the expression of iNOS and CINC-1 mRNA induced by IC showed a different temporal pattern and a different sensitivity to both the antioxidant agent pyrrolidine dithiocarbamate (PDTC) and modulation by NO itself. Whereas iNOS mRNA and protein expression were blunted by PDTC and NO-generating compounds, CINC-1 mRNA expression was either enhanced or not affected by PDTC and NO donors. The time course of NF-kappaB activation was parallel to that of iNOS induction and was influenced in the same sense as iNOS induction by antioxidants, NO donors, the protease inhibitor N-tosyl phenylalanine chloromethyl ketone, and inhibitors of protein tyrosine phosphorylation reactions. These data indicate the existence in rat macrophages of a signaling mechanism triggered by Fc gammaR occupancy that leads to nuclear signaling, is initiated by protein tyrosine phosphorylation reactions, and shows specific sensitivities to antioxidants and NO. Whereas trans-activation of the iNOS gene can be fully explained by the stimulation of NF-kappaB, induction of CINC-1 mRNA expression seems influenced by additional regulatory elements.


The Working Group on Neurogenic Inflammation proposed 11 testable hypotheses in the three domains of neurogenic inflammation, perceptual and central integration, and nonneurogenic inflammation. The working group selected the term people reporting chemical sensitivity (PRCS) to identify the primary subject group. In the domain of neurogenic inflammation, testable hypotheses included: PRCS have an increased density of c-fiber neurons in symptomatic tissues; PRCS produce greater quantities of neuropeptides and prostanoids than nonsensitive subjects in response to exposure to low-level capsaicin or irritant chemicals; PRCS have an increased and prolonged response to exogenously administered c-fiber activators such as capsaicin; PRCS demonstrate augmentation of central autonomic reflexes following exposure to agents that produce c-fiber stimulation; PRCS have decreased quantities of neutral endopeptidase in their mucosa; exogenous neuropeptide challenge reproduces symptoms of PRCS. In the domain of perceptual and central integration, testable hypotheses included: PRCS have alterations in adaptation, habituation, cortical representation, perception, cognition, and hedonics compared to controls; the qualitative and quantitative interactions between trigeminal and olfactory systems are altered in PRCS; higher integration of sensory inputs is altered in PRCS. In the domain of nonneurogenic inflammation, testable hypotheses included: increased inflammation is present in PRCS in symptomatic tissues and is associated with a heightened neurosensory response; PRCS show an augmented inflammatory response to chemical exposure. The working group recommended that studies be initiated in these areas.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167992

Baldwin, CM, Bell, IR, O’Rourke, MK and Lebowitz, MD Journal/Eur J Epidemiol. 13: 547-52.

This epidemiological study evaluated respiratory histories in those individuals reporting chemical intolerance (CI) in a community population sample. The subsample of 181 completed standard Respiratory Health Questionnaires. CI was determined from self-ratings of feeling 'moderately' to 'severely' ill from exposure to at least three of five common chemicals (paint, pesticides, car exhaust, new carpet, and perfume); the prevalence rate was 22.7%. The comparison group (CN) (31.5% of the sample) were selected from their reports of 'never' feeling ill from the same chemicals. The
prevalence rate of CI in females was over twice that in males (28% vs 12.9%), a significant difference. There were no significant differences in smoking, age, or education between CI and CN. Prevalence rates for symptoms and Relative Risk Ratios (RR) indicated that the CI were significantly more likely to report chronic cough, phlegm, wheeze, chest tightness, exertional dyspnea, acute respiratory illnesses, hay fever, child respiratory trouble, and physician confirmed asthma. Several of these respiratory symptoms were significantly, though differentially, related to 'current' asthma and hay fever reports. Results suggest a potential vulnerability to and greater interference from respiratory illness for the CI, which have implications for women's health and quality of life.

(1997) Intimidation of researchers by special-interest groups.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9380082

(1997) [Disease characteristics of the population on the territory of the city of Kirovo-Chepetsk].

Medical and ecologic evaluation of ecologic situation in Kirovo-Tchepetsk (Kirov region) included study of morbidity in the town and referent territories. Levels and dynamics of morbidity, prevalence, number of pathologic processes in children and other parameters could characterize the town as an ecologically unfavorable territory.


Biosis copyright: biol abs. rrm meeting report standard human occupational health occupational health and safety toxicology environmental factors multiple chemical sensitivities chemical safety workshop

A 53-year-old man with multiple chemical sensitivities (MCS) received the selective serotonin reuptake inhibitor (SSRI) citalopram for treatment of depression. The treatment was successful and, in parallel to the remission of the depressive symptoms, all MCS symptoms vanished. This suggests that a subgroup of MCS patients may have an atypical depression, that they should be psychiatrically evaluated, and that antidepressive pharmacological treatment may be considered in cases of MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9259230


BIOSIS COPYRIGHT: BIOL ABS. Some individuals have experienced adverse reactions when exposed to emissions of certain carpets. Questionnaires were sent to 110 families who had encountered carpets confirmed in our laboratory as emitting toxic chemicals. Of these, 78 individuals described symptoms which developed after exposure to these carpets. An average of 17 symptoms per/person (range 1-32) were reported. Frequently mentioned were severe fatigue, eye, nose or throat irritation, head, trunk or limb pain, difficulty concentrating or short-term memory loss, difficulty breathing and tremors and weakness. Many of these symptoms resemble the signs of toxicity seen in mice exposed to emissions from these carpets. The symptom list did not form a unique syndrome, but overlapped with the numerous symptoms reported in individuals experiencing multiple chemical sensitivity of various etiologies.


OBJECTIVE: To determine the prevalence of concomitant disease in individuals with interstitial cystitis and to compare these results to the general population. METHODS: We used a questionnaire-based study evaluating 12 disease processes and a survey
of interstitial cystitis characteristics. The population was 2,405 individuals with interstitial cystitis who responded to the initial survey and an additional 277 individuals who were randomly selected and individually contacted. RESULTS: Allergies, irritable bowel syndrome, and sensitive skin were the most common diseases in the interstitial cystitis population. In comparison to the general population, individuals with interstitial cystitis are 100 times more likely to have inflammatory bowel disease and 30 times more likely to have systemic lupus erythematosus. In addition, allergies, irritable bowel syndrome, sensitive skin, and fibromyalgia have an increased association with interstitial cystitis. CONCLUSIONS: Interstitial cystitis has, as yet, an unexplained association with certain other chronic disease and pain syndromes.


http://www.sciencedirect.com/science/article/B6T4S-3W0NPY8-2H/2808856ac635599e3453961b4c0ef5958

(1996) [Multiple chemical sensitivity (MCS)--the so-called chemical multiple hypersensitivity]. Wolf, C Journal/Versicherungsmedizin. 48: 175-8.
Multiple chemical sensitivity syndrome (MCS) is believed to be a multiple organ disease caused by low-level exposure to chemical substances. It is characterized by central-nervous, gastrointestinal and irritative mucocutaneous symptoms. This phenomenon is not recognized in traditional medicine, opponents of the theory of a separate disease attributing all symptoms to psychopathological processes. Since this phenomenon is becoming increasingly prevalent in Western countries, appropriate strategies for its study need to be developed.

Weaver, VM Journal/Regul Toxicol Pharmacol. 24: S111-5.

Multiple chemical sensitivity (MCS) is a complex, chronic disorder characterized by multisystemic symptoms occurring in response to a wide variety of chemical odors or low-level exposures. The etiology is unknown but likely multifactorial. Patient evaluation includes a comprehensive history with a review of past medical records and a physical examination with specific attention to the affected organ systems. Laboratory evaluation is dependent on past testing and patient symptoms. It should be individualized and, although standard baseline tests are helpful, exhaustive testing is not. The evaluation is primarily designed to exclude diseases requiring specific medical therapy. Treatment approaches vary considerably depending on the treating physician and patient responsiveness; many have been adapted from those used for similar chronic illness of unknown etiology. Therapies utilized in MCS patients include supportive care, behavioral techniques, including desensitization, psychotherapy, chemical avoidance, and clinical ecology regimens such as provocation-neutralization protocols. The advantages and disadvantages of these approaches are discussed and the use of clinical ecology regimens is discouraged. A multidisciplinary approach similar to those used in chronic pain patients may be beneficial. Regardless of the treatment chosen, the goal should be to decrease patient disability.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921564

(1996) Psychiatric family history in adolescents with severe asthma.

OBJECTIVE: To examine the hypothesis that an association exists between severe asthma and familial affective and anxiety disorders. METHOD: A parent, usually the mother, of 62 adolescents admitted to a tertiary care asthma center was administered the Family History-Research Diagnostic Criteria Interview. Lifetime prevalence rates of psychiatric disorders in first-degree relatives were compared with previously reported
rates. RESULTS: In relatives of asthmatic adolescents, rates for depression, mania (females only), substance abuse (males only), and antisocial personality disorder were significantly higher than the rates in the non-ill comparison sample. Rates for substance abuse (males only) and antisocial personality disorder were higher than the rates for relatives of the depressed comparison sample. Rates for anxiety disorders were not higher than rates in epidemiological samples. Rates of attention-deficit hyperactivity disorder (females only) and posttraumatic stress disorder in relatives were higher than in community samples. CONCLUSIONS: These results support the presence of a link between severe asthma and familial affective disorders, posttraumatic stress disorder, antisocial personality disorder, and substance abuse. Whether these disorders are genetically associated with asthma or represent an association with severe asthma because of environmental effects on the growing child is discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8755801

(1996) [Ecology and child nutrition].

(1996) [Anthropogenic factors of the environment and "Chernivtsy chemical disease"].
Tsvil, VI and Protsenko, VP Journal/Lik Sprava. 54-6.


PURPOSE: To use MR to examine patients with CNS symptoms indicating +chronic intoxication. MATERIAL AND METHODS: Thirty-two subjects exposed to industrial solvents for 5 to 28 years and 40 age-matched, healthy controls were examined. RESULTS: All patients showed decreased signal in the basal ganglia on T2-weighted images. In 11 of the patients the white matter showed diffuse hyperintensity with loss of the grey-white matter discrimination and with distinct periventricular hyperintensities in 5 of the patients. The controls had no pathological changes in the brain. CONCLUSION: Although the relatively small number of patients may obscure the
significance, findings observed on T2-weighted images were patchy periventricular hyperintensities and hypointensities in the basal ganglia. Fast spin-echo is a good technique with fast acquisition of images with true spin-echo contrast features.


**BACKGROUND:** Many recent studies indicate an increasing morbidity and mortality of asthma in the past two decades. This study uses data from the National Disease and Therapeutic Index (NDTI) to document and analyze trends in drug therapy for asthma in the United States from 1965 through 1992. **METHODS:** The NDTI maintains a continuous rotating national sampling of approximately 1% of US physicians in office-based practice proportionately representative of practicing generalists and specialists who report issuance of drugs in treatment by diagnosis for all patient encounters for a period of two days every 3 months. Annual summaries of five demographic categories and 14 drug categories, characterizing the asthma patient-physician encounters as percent of visits for the 28-year period of 1965 through 1992 are analyzed and characterized. **RESULTS:** Physician visits for asthma treatment have shifted somewhat from generalists to specialists in internal medicine and pediatrics. Allergists treat a significant proportion of the asthmatic population. Most patients are seen in the office. There has been no significant change in rates of inpatient visits. Age distribution of the population of patient visits for asthma has been stable, but there is a steady drop in ratio of males to females. Since the mid-1970s, inhaled adrenergic bronchodilator prescriptions have been issued at a markedly increasing rate. Concurrently, issuance of xanthines and oral adrenergic drugs also rose dramatically but then decreased beginning in the mid-1980s. Corticosteroids are used in 15% to 20% of visits, but only recently has the inhaled route of administration shown prominence. Allergen immunotherapy for asthma has decreased more than 10-fold. Cromolyn is prescribed infrequently. **CONCLUSIONS:** Major changes have occurred in drug treatment by physicians for asthma in the US since 1965. Bronchodilating drugs predominate, and they are being prescribed in more effective forms at a generally increasing rate. Corticosteroid use has increased at a slower rate and in smaller proportion of patient-visits, while allergen immunotherapy has dramatically declined. The male-to-female ratio of asthmatic patients who visit doctors for treatment appears to be decreasing.

(1996) **Vicious cycle involving Na+ channels, glutamate release, and NMDA receptors mediates delayed neurodegeneration through nitric oxide formation.**
The mechanisms by which neurons die after cerebral ischemia and related conditions in vivo are unclear, but they are thought to involve voltage-dependent Na+ channels, glutamate receptors, and nitric oxide (NO) formation because selective inhibition of each provides neuroprotection. It is not known precisely what their roles are, nor whether they interact within a single cascade or in parallel pathways. These questions were investigated using an in vitro primary cell culture model in which striatal neurons undergo a gradual and delayed neurodegeneration after a brief (5 min) challenge with the glutamate receptor agonist NMDA. Unexpectedly, NO was generated continuously by the cultures for up to 16 hr after the NMDA exposure. Neuronal death followed the same general time course except that its start was delayed by approximately 4 hr. Application of the NO synthase inhibitor nitroarginine after, but not during, the NMDA exposure inhibited NO formation and protected against delayed neuronal death. Blockade of NMDA receptors or of voltage-sensitive Na+ channels [with tetrodotoxin (TTX)] during the postexposure period also inhibited both NO formation and cell death. The NMDA exposure resulted in a selective accumulation of glutamate in the culture medium during the period preceding cell death. This glutamate release could be inhibited by NMDA antagonism or by TTX, but not by nitroarginine. These data suggest that Na+ channels, glutamate receptors, and NO operate interdependently and sequentially to cause neurodegeneration. At the core of the mechanism is a vicious cycle in which NMDA receptor stimulation causes activation of TTX-sensitive Na+ channels, leading to glutamate release and further NMDA receptor stimulation. The output of the cycle is an enduring production of NO from neuronal sources, and this is responsible for delayed neuronal death. The same neurons, however, could be induced to undergo more rapid NMDA receptor-dependent death that required neither TTX-sensitive Na+ channels nor NO.


1. In a group of 40 patients with orthostatic intolerance due to hypotension and/or tachycardia, we have compared the pathogenetic roles of impaired contractility of the arterioles and the veins by measuring contractile responsiveness of the arterioles, reflected by increases in diastolic blood pressure and of the veins reflected by measurements of reduction in venous diameter during intravenous noradrenaline infusions. 2. Compared with 27 healthy subjects, patients with diffuse autonomic insufficiency showed striking supersensitivity in diastolic blood pressure (six out of eight) and venous constrictive responses (seven out of eight patients) to noradrenaline, consistent with impaired arteriolar and venous innervation. 3. In contrast, the patients with hyperadrenergic orthostatic hypotension (n = 16) and orthostatic tachycardia (n = 16) showed diastolic blood pressure responses to noradrenaline that were almost invariably within the 95% confidence limits of the changes in normal subjects but supersensitive constrictive responses of foot veins in 22 of 32 subjects and subnormal
venous responses in two individuals. The rate of noradrenaline infusion calculated to cause 50% of maximal venous constriction (the ED50) was significantly lower in the patients [mean (SEM) 6.8 (1.9) ng/min] than in the normal subjects [mean (SEM) 23.2 (3.0) ng/min, P < 0.025]. 4. The finding of significantly supersensitive foot vein constrictive responses to noradrenaline infusion in the patients of all three groups and supersensitive blood pressure responses exclusively in the patients with diffuse autonomic insufficiency indicates that venous pooling in the legs was the predominant pathogenetic mechanism of orthostatic intolerance in all three types of patients studied. 5. Correction of the orthostatic hypotension and/or tachycardia by external compression in virtually all patients confirmed this conclusion.


http://www.sciencedirect.com/science/article/B6T4S-3Y0RTNB-3K/2fc228718114c7484d8c48e53b4462711


There are two distinct paths down which patients "diagnosed" with environmental illness/multiple chemical sensitivities (EI/MCS) can travel. Along the first path, beliefs about low-level, multiple chemical sensitivities as the cause of physical and psychological symptoms are instilled and reinforced by a host of factors including toxicogenic speculation, iatrogenic influence mediated by unsubstantiated diagnostic and treatment practices, patient support/advocacy networks, and social contagion. Intrapsychic factors also reinforce this path through the motivational mechanism of factitious malingering, or unconscious primary and secondary gain, mediated through psychological defenses, particularly projection of cause of illness onto the physical environment. The second path involves restructuring distorted beliefs about chemical sensitivities. Explanations of the placebo effect, the physiology of the stress response, and the symptoms of anxiety and panic facilitate the direction of EI/MCS patients onto this path. A decision model is presented to discriminate among toxicogenic and psychogenic explanations of the EI/MCS phenomenon, based on appraisal of reaction and physiologic and cognitive responses during provocation chamber challenges under double-blind, placebo-controlled conditions. These studies have been helpful therapeutically for some patients in selecting the path that leads to wellness. This paper suggests how various therapeutic techniques can be employed with difficult patients. Often, supportive psychotherapy establishes a therapeutic alliance which
facilitates cognitive therapy to restructure distorted beliefs. In the process of finding alternative explanations to chemical sensitivities, the etiology of symptoms is related to stressful life events, including childhood experiences which may have disrupted normal personality development and coping capacity. Furthermore, biological and physiological sequelae stemming from early, chronic trauma have been identified which could explain many of the multisystem complaints. The incidence of childhood abuse reported by EI/MCS patients is strikingly high, and it is recollection of trauma that many EI/MCS patients avoid by displacing the psychologic and physiologic adults sequelae onto the physical environment. The reenactment of these experiences may be necessary in the therapy of some affected individuals. Despite the significant therapeutic effort expanded, some patients who are imprisoned by a closed belief system about the harmful effects of chemical sensitivities are resigned to travel down the path which ultimately leads to despair and depression, social isolation, and even death.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921563


BIOSIS COPYRIGHT: BIOL ABS. There are two distinct paths down which patients "diagnosed" with environmental illness/multiple chemical sensitivities (EI) can travel. Along the first path, beliefs about low-level, multiple chemical sensitivities as the cause of physical and psychological symptoms are instilled and reinforced by a host of factors including toxicogenic speculation, iatrogenic influence mediated by unsubstantiated diagnostic and treatment practices, patient support/advocacy networks, and social contagion. Intrapsychic factors also reinforce this path through the motivational mechanism of factitious malingering, or unconscious primary and secondary gain, mediated through psychological defenses, particularly projection of cause of illness onto the physical environment. The second path involves restructuring distorted beliefs about chemical sensitivities. Explanations of the placebo effect, the physiology of the stress response, and the symptoms of anxiety and panic facilitate the directi


The first case of chronic beryllium disease (CBD) at the Rocky Flats Environmental Technology Site (Rocky Flats) was diagnosed in a machinist in 1984. Rocky Flats, located 16 miles northwest of Denver, Colorado, is part of the United States Department of Energy (DOE) nuclear weapons complex. Research and development
operations using beryllium began at Rocky Flats in 1953, and beryllium production operations began in 1957. Exposures could have occurred during foundry operations, casting, shearing, rolling, cutting, welding, machining, sanding, polishing, assembly, and chemical analysis operations. The Beryllium Health Surveillance Program (BHSP) was established in June 1991 at Rocky Flats to provide health surveillance for beryllium exposed employees using the Lymphocyte Proliferation Test (LPT) to identify sensitized individuals. Of the 29 cases of CBD and 76 cases of beryllium sensitization identified since 1991, several cases appear to have had only minimal opportunistic exposures to beryllium, since they were employed in administrative functions rather than primary beryllium operations. In conjunction with other health surveillance programs, a questionnaire and interview are administered to obtain detailed work and health histories. These histories, along with other data, are utilized to estimate the extent of an individual's exposure. Additional surveillance is in progress to attempt to characterize the possible risks from intermittent or brief exposures to beryllium in the workplace.


A potentially promising line of animal research relevant to multiple chemical sensitivity (MCS) is that of sensitization in the central nervous system (CNS), particularly limbic pathways in the brain. Sensitization is the progressive and enduring enhancement in behavioral and neurochemical responses that occurs after repeated exposure to psychostimulants or environmental stressors. Since the onset and progression of sensitization has many parallels with that of MCS, it has been proposed that MCS may be initiated through a mechanism similar to the sensitization of CNS components occurring in the rodent. To test this hypothesis, female Sprague-Dawley rats were exposed to formalin vapors (FORM, 11 ppm) or water vapor (control) 1 h/day for 7 days. The next day, a saline injection was given followed by a cocaine injection (15 mg kg, i.p.) 24 h later, and locomotor activity was monitored. Animals pretreated with repeated FORM inhalation demonstrated a significantly enhanced locomotor response to cocaine compared to controls, an indicator that specific limbic pathways may have been sensitized. At 4 weeks of withdrawal from FORM exposure, a subset of animals remained sensitized to a cocaine challenge. No differences were found between groups after a saline injection. In a second experiment, animals were screened prior to FORM or water exposure for their response to a novel situation, a measure believed to reflect an animal's general responsiveness to stimuli. Rats were divided into high responders (HR) or low responders (LR), based on their locomotion in a novel cage. Results from three behavioral tests demonstrated that HR and LR were differentially affected by exposure to FORM. In a passive avoidance test, HR and LR appeared to be different in their distribution of responses, while HR and LR responses in the FORM
group were nearly identical. On the elevated plus maze test of anxiety, HR spent more time on the open arms than LR in both treatment groups, with significant differences between HR and LR in the FORM, but not water, treated group. On a hot plate test to measure nociceptive levels, no differences occurred between HR and LR in the control group, whereas nociception of LR tended toward an increase compared to HR in the FORM-exposed group. Results from the second experiment suggest that the effects of FORM exposure may be obscured by examining behavior in a heterogeneous population (HR and LR). This approach using animal models may help define neural substrates that mediate the amplification of responses of a subpopulation of individuals to chemicals in the environment.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8711729


OBJECTIVES: Exposure to organic solvents increases the risk of neuropsychiatric disability or chronic toxic encephalopathy (CTE). Polymorphisms in the biotransformation of xenobiotics and solvents may influence individual susceptibility to develop toxic effects. In this study the problem of whether there could be any association between the glutathione S-transferase M1 (GSTM1) null genotype and the risk for CTE, with regard to solvent exposure, was investigated. METHODS: Sixty patients referred to a clinic because of some degree of psychiatric or neurological symptoms, as well as exposure to solvents, were examined by means of a validated questionnaire and psychometric testing. The degree of exposure to solvents was assessed by a thorough interview. According to clinical findings, the patients were classified into three categories as those with solvent-induced CTE, those with incipient CTE, and those who were non-CTE patients. Afterwards, leukocyte DNA (deoxyribonucleic acid) was isolated and the GSTM1 null genotype was determined by an assay based on polymerase chain reaction, blindly with regard to both exposure and disease status. RESULTS: The relative proportion (RP) of GSTM1 null genotypes was significantly increased for patients with a diagnosed CTE when they were compared with non-CTE patients (RP 2.55, 95% confidence interval 1.0-6.2). Dichotomizing the patients by high and low exposure revealed an increased risk for both GSTM1 gene carriers and the GSTM1 null genotype in the high-exposure group, the relative risks (RR) being 4.5 and 7.9, respectively. The chi-square for the Mantel extension for trend was 6.2 (P = 0.025). CONCLUSIONS: The GSTM1 null genotype acts as a risk modifier for CTE among patients occupationally exposed to solvents. The risk seems to increase in a dose-dependent fashion.

the specialty of Allergy-Immunology has used human challenge testing procedures to
test theories of causal relationships for decades. This includes highly characterized
airborne allergens and chemicals with allergic sensitization potential. The utility of such
testing to establish allergic sensitivity is well accepted. The causal relationship of
chemical exposure and myriad clinical syndromes is a very contentious issue. The
completion of the challenge chamber facility at EPA’s Human Exposure Research
Facility presents a grand opportunity for government investigators to work
harmoniously with other government investigators in an effort to bring the redeeming
spotlight of scientific discipline to the testy considerations of multiple chemical
sensitivity, chronic fatigue, and Gulf War illness phenomena.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921562

(1996) Cardiac vagal afferent stimulation by free radicals during ischaemia and
reperfusion.

1. Myocardial ischaemia and reperfusion can evoke excitation of cardiac vagal afferent
nerve endings and activation of a cardiogenic depressor reflex (Bezold-Jarisch effect).
We postulate that oxygen free radicals, which are well known to be produced during
ischaemia and reperfusion, contribute to this excitation. 2. Activity from vagal afferent
fibres in rats, whose endings were located in the walls of all four chambers of the heart,
was recorded in response to topical application of pro-oxidant chemicals to the surface
of the heart. Activity was also recorded from vagal afferent fibres, whose endings were
located in the left ventricle, in response to occlusion of the left anterior coronary artery
(LAC) for 30 min and subsequent reperfusion. A majority of the recorded fibres were
classified as chemosensitive C-fibre endings due to their irregular discharge under
resting conditions, their activation in response to the topical application of capsaicin
(1-10 micrograms) to the surface of the heart encompassing the receptive field and
their conduction velocities. 3. Topical application of either H2O2 or xanthine/xanthine
oxidase to the heart activated 50% of the chemosensitive endings and did not directly
affect cardiac mechanoreceptors. This effect was reproducible, dose-dependent and
was not due to [H+]. 4. Administration of the superoxide radical scavenging enzyme,
superoxide dismutase (20000 U/kg, i.v.), decreased the response of fibres to xanthine
xanthine oxidase but had no effect on the activation caused by H2O2. The antioxidants
deferoxamine (20 mg/kg, i.v.) or dimethylthiourea (10 mg/kg, i.v.), which scavenge the
hydroxyl radical, abolished the responses to xanthine/xanthine oxidase and H2O2.
Administration of indomethacin (5 mg/kg, i.v.) had no effect on the afferent response to
H2O2. 5. In response to ligation of the left anterior coronary (LAC), the activity of chemosensitive endings within the ischaemic zone increased within the first 2 min of occlusion. Endings outside the ischaemic zone were not affected at the beginning of ischaemia. Reperfusion activated only chemosensitive endings responsive to topical H2O2. These reperfusion-sensitive endings were located both within and outside the ischaemic zone of the left ventricle. 6. Indomethacin (5 mg/kg, i.v.) prevented activation of chemosensitive endings at the beginning of LAC occlusion regardless of their sensitivity to H2O2 but had no effect on the response to reperfusion. Conversely, defereroxamine (20 mg/kg, i.v.) had no effect on the activation of chemosensitive fibres at the onset of ischaemia, whereas it completely prevented activation at reperfusion. 7. We propose that there are two different mechanisms that activate chemosensitive afferent vagal fibres in the rat heart during ischaemia and reperfusion. The first causes excitation of these endings at the onset of ischaemia and is mediated by prostaglandin synthesis within the ischaemic zone. The second mechanism leads to a more widespread activation of chemosensitive afferents in the left ventricle during prolonged ischaemia and at the moment of reperfusion and is mediated by oxygen free radical formation.


Biosis copyright: biol abs. rrm journal article human mercury latex respiratory tract diseases skin disease allergy

(1996) Multiple chemical sensitivity multiorgan dysesthesia, multiple symptom complex, and multiple confusion: problems in diagnosing the patient presenting with unexplained multisystemic symptoms.

Patients are presenting in increasing numbers with multiorgan symptoms allegedly resulting from exposure to environmental chemicals. Among the symptoms expressed by patients with alleged multiple chemical sensitivities (MCS) are profound fatigue, mental confusion, myalgia, depression, anxiety, dizziness, headache, insomnia, loss of appetite, and numbness of the extremities, all in the absence of objective physical signs. Diagnostic criteria to assess the effects of environmental agents on organ
systems are sorely needed because patients with MCS often have no tissue pathology or physiological abnormalities, but often do have diagnosable psychiatric illnesses. In treating patients with MCS, the physician should first perform a complete history and physical examination, including a comprehensive evaluation of chemical exposure. If the findings strongly suggest the presence of disease related to particular organ systems, further diagnostic evaluation should be undertaken. If abnormal findings are absent, psychiatric advice may be useful. The physician should keep an open mind about MCS but must also remember that a cause-effect relationship between exposure to multiple chemicals and symptoms has not been established.


Some believe that an abnormal immunoregulatory response based on environmental damage to T cells is fundamental to the production of symptoms in patients with alleged "multiple chemical sensitivity" and/or "environmental illness." According to this theory stimulation of T cells or T cell phenotypic subsets by environmental chemicals results in release of cytokines that can effect appropriate target cells of multiple organ systems, resulting in a wide range of symptoms. This concept is reinforced by frequent media reporting of pollution incidents and environmental disasters plus continued isolated reports of immunologic abnormalities in patients with various forms of alleged environmental illness, multiple chemical sensitivities, or other related syndromes. These include reports of slight perturbations in quantity and function of immunoglobulins, complement and its components, B cells, natural killer cells, T cells, phenotypic T cell subsets, and helper suppressor T cell ratios. There are also reports of increased or decreased interleukin levels including IL-1 and IL-2 or their receptors (IL-2R) in these patients. Such assays are not infrequently performed even though there is no evidence for their diagnostic efficacy in these alleged conditions. It is reasonable, however, to anticipate that with the wide development of assays for many of the interleukins and their receptors, these assays may become important in the future diagnosis of many autoimmune, allergic, neoplastic, and infectious diseases. At this time, however, the induction of environmental illness or multiple chemical sensitivity by exposure to trace levels of environmental "immunotoxins" is unproven and remains a matter of speculation. The reproducibility of immunologic test abnormalities reported under these conditions has not been documented, and the data have often not been analyzed statistically. Appropriate controls also have not usually been employed, nor have control values been provided in many cases. Without consideration of these factors, a patient might be erroneously diagnosed as having some form of "immune dysregulation," "environmental immune dysfunction," or "immunotoxic" syndrome on the basis of only a single panel of cellular immunologic profiles or related immunologic tests illustrating slight deviations from the norm and in the absence of overt disease on physical examination. Consideration must also be
given to an understanding of biologic variability and diurnal variations in lymphoid cell numbers in interpreting cellular immunologic profiles. For example, the necessity for age and sex-matched controls, test reproducibility, quantitative versus functional assays, and the significance of major versus minor deviations from the norm must be appreciated. In addition, many other conditions can effect immunologic tests, such as medications, psychologic factors, cigarette smoking, and the presence of concurrent disease, including minor viral infections. All of these variables should be appreciated in test interpretation. Certain clinical indications for analysis of cellular components of the immune system, using flow cytometry, have been provided as guidelines although they are by no means accepted by all groups due to their current incomplete evaluation by the clinical immunology community. These suggested indications are discussed. In this article, attempts are made to outline the various quantitative and functional tests used to assess the immune system, with emphasis on "biomarker" tests to detect possible immune system "damage." Dangers involved in attempting to make clinical evaluations based on results of isolated in vitro assessment of quantity or function of immune system cellular and humoral components without considering the results of a good medical history and physical examination, the many pitfalls involved in the tests, and the many confounding variables that affect the tests are emphasized, as well as the need for proper controls...

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921551


BACKGROUND: Emergency medical service providers have a high degree of exposure to latex products. Patients utilizing emergency medical services can be allergic to latex products used during rescue efforts. OBJECTIVE: To determine the prevalence of latex hypersensitivity among emergency medical service providers. METHODS: Study questionnaires were distributed to a group of emergency medical service providers. Skin prick testing was performed using latex, common aeroallergens, and food extracts. Patch testing was done using latex and individual rubber additives. Serum latex-specific IgE was also measured. RESULTS: A total of 93 completed surveys were collected. Average exposure to latex in the work environment was 8.2 years. Eighty-four (90%) used latex gloves routinely at work. Of those, thirteen (14%) gave history of reaction to latex gloves. Sixty-two percent were not aware of the possibility of latex allergy in themselves or their patients. Forty-one (44%) had skin testing. Of those, four (10%) had positive prick tests for at least one of the four latex preparations used. Five had positive skin tests to avocado extract without supporting clinical history. Two had positive skin tests to banana, one with supporting clinical history for banana allergy. No food cross-reactivity with latex was demonstrated. Latex-specific serum correlated with prick skin test results. No positive reactions were
noted with patch testing. CONCLUSIONS: A significant percentage of emergency medical service providers were not aware of the occupational risk of latex allergy or the potential risk in their patients. A positive prick skin test for latex was present in 4 of 41 (10%), representing one-third of those who reported symptoms from latex exposure.

(1996) Sensitization induced by kindling and kindling-related phenomena as a model for multiple chemical sensitivity.
Rossi, J, 3rd Journal/Toxicology. 111: 87-100.

It has been suggested that the neurobehavioral dysfunction observed in persons presenting with symptoms of Multiple Chemical Sensitivity (MCS) syndrome involves sensitization of neural circuits. Two hypotheses for the route of exposure in induction of neural sensitization in MCS are: (a) direct chemical stimulation of olfactory processes, or (b) general systemic response to inhaled chemicals. In either case, the mechanism of action may involve chemical kindling or kindling-related phenomena. A neural sensitization mechanism based on kindling or kindling-related phenomena is attractive and has been previously demonstrated in both in vitro and in vivo animal models. Without a testable animal model for chemically mediated induction of MCS, however, any argument that MCS is mediated by kindling or kindling-related phenomena is reduced to the circular argument "the mechanism of sensitization is sensitization." The present survey provides an overview of the experimental paradigms that result in sensitization, differentiated on the basis of probable neurophysiological and neurochemical mechanisms. Neurophysiological potentiation, electrical kindling, chemical kindling and behavioral sensitization are evaluated and discussed in relationship to MCS.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8711751

Rodgers, KE Journal/Crisp Data Base National Institutes Of Health.
RPROJ The species and tissue specificity and the molecular mechanism of immune modulation by the organophosphate pesticide, malathion, will be examined. Acute oral administration of malathion to mice at low, noncholinergic doses was shown to lead to peritoneal and dermal mast cell degranulation and increased peritoneal leukocyte function. Based upon this, three lines of inquiry will be pursued in this grant proposal. First, studies are proposed to examine the effect of acute exposure to malathion on the degranulation of basophilic cells from other tissues and from different species. The effect of the route of administration on the degranulation of mast cells will also be characterized. In addition, blood histamine levels will be measured to possibly establish a biomarker for studies involving occupational exposure. Second, examination of the
The contribution of mast cell degranulation to the enhancement of immune and leukocyte function that is observed after malathion administration is proposed. Administration of malathion to mast cell-deficient mice with and without reconstitution of the mast cell component and assessment of immune and leukocyte function will be conducted. The mast cell mediators involved in the increase in macrophage and immune function will be assessed through the administration of inhibitors of mediator synthesis or activity. The mast cell products that will be examined include histamine, platelet-activating factor, arachidonic acid metabolites, tumor necrosis factor and serotonin. In addition, studies to determine the binding characteristics of malathion to mast cells and the effect of metabolism on the activity and binding of malathion will also be conducted. Lastly, the effects of subacute and subchronic administration of malathion and acute administration of other organophosphate pesticides, such as parathion and dichlorovos, on mast cell degranulation and leukocyte function will be determined.


The development and improvements made in the computer based DEREK system, used for qualitative toxicity prediction, were discussed. The DEREK system was described as a knowledge based system derived from the LHASA synthesis planning program. DEREK's user interface allowed query of a single compound by entering its structure, or of a multiple compounds through a link to a structural data base. Improvements in the graphical interface included supportability by Ultrex on DEC stations, and the ability to port DEREK to additional Unix platforms. The need for an intermediate format conversion step when retrieving data from the MACCS system was eliminated. The chemical computer languages PATRAN and CHMTRN were expanded to include new atom and bond qualifiers in PATRAN, and facilitate the use of CHMTRN. The knowledge base of DEREK was expanded to include rules for mutagenicity, skin sensitization, carcinogenicity, irritancy, thyroid function, reproductive effects, neurotoxicity and respiratory sensitization. These rules were generated by the DEREK standard set, the Food and Drug Association, and from a developmental consortium of industrial and government sources. When 250 substances of known toxicity were processed for genotoxicity by DEREK, 98% of the Ames positive compounds were classified by DEREK as genotoxic. DEREK correctly classified 70%
of the nonmutagenic compounds, giving a high number of false positives. Further areas of development for DEREK and StAR, a toxicological risk assessment system, were discussed.


In the past few years, our knowledge of mammalian genomes has increased enormously. Our understanding of the molecular basis of the normal cellular processes of DNA replication and repair and cell cycle control, together with how their fidelity malfunctions as part of tumor development, has increased in parallel. This has led to a clearer appreciation that there are subpopulations that have been generically described as being genetically or otherwise susceptible to the induction of cancer or birth defects. The term susceptibility is a default option, since there clearly will be a very broad range of sensitivities among the so-called susceptible populations, dependent upon the specific underlying mechanism. This could lead to the conduct of risk assessments for each specific situation, involving both genotypes of individuals and agents of concern. This would ideally take into account the effects on response of various modifying factors, genetic and other. One advantage to be gained from this approach is the ability to determine if a particular susceptibility places subpopulations at extreme risk as compared to the overall normal distribution of risk in the population, or whether such a susceptible population presents a slight extension of the upper bound of the risk distribution or lies within the normal distribution. In addition, the specific mechanism of the susceptibility as related to exposure scenarios and the magnitude and demographics of the susceptible populations need to be taken into account. Thus, the management of risk has to be linked to the specific risk assessment. For many of the so-called susceptible populations an uncertainty factor of less than 10, even including 1, would be predicted to bring the risk within the normal distribution. It is hoped that as more mechanistic information on susceptibility becomes available and a specific risk can be defined, the practice of risk management will be considerably improved.
(1996) [The environmental project of Conca Ternana. A gender-based reading of some environmental epidemiological data].

---------------------------------------------------------------

Philipson, LL, Hudson, JM and See, AM Journal/Toxicology. 111: 239-49.

A new methodology for estimating the probabilistic risk from acute toxic exposures is planned as a support tool for the Air Force at the Eastern and Western Ranges. Two such methodologies are programs entitled the Launch Area Toxic Analysis program (LATRA) and the Cold Spill Toxic Risk Analysis program (COSTRA). These programs combine probabilistic models of an accident (when applicable), release cloud formation and dispersion (appropriate to the toxic substance and accounting for meteorological conditions), and new exposure-response functions (ERFs) for sensitive and normal exposed populations. These ERFs, anchored on specific exposure standards, estimate the probability of a given severity of health effect in a particular population as a function of the concentration or dose to which it is exposed. The further development and acceptance of these ERFs by the toxicology community, especially for different sensitivities, are key concerns addressed in this paper.

---------------------------------------------------------------


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921560

---------------------------------------------------------------


Sickness and accident-insurance (sick leave) claims at an automotive stamping and assembly complex were analyzed using Poisson regression over a 4-year period to identify occupational health problems. The incidence of lower-respiratory disability (excluding asthma) was higher in painting operations (rate ratio [RR] = 2.9, 95% confidence interval [CI] = 1.2 to 6.8), and final assembly and processing areas (RR =
2.7, 95% CI = 1.0 to 7.4) at the assembly plant, and in metal assembly (welding) areas (RR = 2.8, 95% CI = 1.4 to 5.7) at the stamping plant. Disability rates for upper-extremity musculoskeletal disorders were statistically significantly higher (RR = 3.1 to 3.8) in major assembly plant production areas, as were back disability rates (RR = 1.5). During the first 6 months of new work assignments in painting or final assembly, respiratory problem rates were four times higher than in other areas. Upper-extremity musculoskeletal rate ratios ranged from 4.4 to 5.7 for new assignments in body, hard trim, and chassis areas. Higher rates in new assignments appeared to result from assignment changes precipitated by developing health problems, or from routine assignments to new tasks, some of which conferred high risk and were tolerated for less than 6 months. Musculoskeletal disability was consistent with known ergonomic hazards and paralleled that reported on the Occupational Safety and Health Administration log. Work-related musculoskeletal and other problems can be readily identified from disability insurance claims without dependence on plant medical visits or workers’ compensation records. Disability insurance appears to absorb considerable work-related medical and absence costs.


Overstreet, DH, Miller, CS, Janowsky, DS and Russell, RW Journal/Toxicology. 111: 119-34.

Multiple Chemical Sensitivity (MCS) is a clinical phenomenon in which individuals, after acute or intermittent exposure to one or more chemicals, commonly organophosphate pesticides (OPs), become overly sensitive to a wide variety of chemically-unrelated compounds, which can include ethanol, caffeine and other psychotropic drugs. The Flinders Sensitive Line (FSL) rats were selectively bred to be more sensitive to the OP diisopropylfluorophosphate (DFP) compared to their control counterparts, the Flinders Resistant Line (FRL) rats. The present paper will summarize evidence which indicates that the FSL rats exhibit certain similarities to individuals with MCS. In addition to their greater sensitivity to DFP, the FSL rats are more sensitive to nicotine and the muscarinic agonists arecoline and oxotremorine, suggesting that the number of cholinergic receptors may be increased, a conclusion now supported by biochemical evidence. The FSL rats have also been found to exhibit enhanced responses to a variety of other drugs, including the serotonin agonists m-chlorophenylpiperazine and 8-OH-DPAT, the dopamine antagonist raclopride, the benzodiazepine diazepam, and ethanol. MCS patients report enhanced responses to many of these drugs, indicating some parallels between FSL rats and MCS patients. The FSL rats also exhibit reduced activity and appetite and increased REM sleep relative to their FRL controls. Because these behavioral features and the enhanced cholinergic responses are also observed in human depressives, the FSL rats have been proposed as a genetic animal model of
depression. It has also been reported that MCS patients have a greater incidence of depression, both before and after onset of their chemical sensitivities, so cholinergic supersensitivity may be a state predisposing individuals to depressive disorders and/or MCS. Further exploration of the commonalities and differences between MCS patients, human depressives, and FSL rats will help to elucidate the mechanisms underlying MCS and could lead to diagnostic approaches and treatments beneficial to MCS patients.


(1996) [Only nerves?].
Ostberg, J Journal/Tidsskr Nor Laegeforen. 116: 300.

(1996) [Trends, environment or a mystery?].
Ostberg, J Journal/Tidsskr Nor Laegeforen. 116: 413.

(1996) The levels of cadmium, zinc and copper in the renal cortex and liver of the inhabitants of the copper basin.

Tissues were analysed from 60 subjects deceased at the age of 18-82 (mean 49 years), inhabitants of the southwestern region of Poland (Legnica Copper Basin). Mean cadmium, zinc and copper concentrations determined by flame AAS were for renal cortex 41.8; 47.8 and 2.3 micrograms Me/g tissue, respectively. The respective levels in the liver were 2.3; 51.6 and 4.6 micrograms Me/g tissue (w.w.). A broad range of cadmium levels was found in renal cortex (4.2-129.3.micrograms/g), with the highest values in the 40-60 age group. The effect of tobacco smoking is more evident than in other countries: 26.3 micrograms/g in non-smokers vs. 54.6 micrograms/g in smokers. Similar proportions were found by computing the whole body burden of cadmium. Compared with other regions of Poland the environmental exposure of humans to cadmium is moderate, however, it is higher than in other European countries.
(1996) [Environmental concern of clients of an environmental medicine counseling center].

Environmental apprehensiveness and anxiety are often regarded as being responsible for unspecific health complaints in the context of environmental exposures if toxicological findings cannot explain them. However, there is a lack of empirical data on the influence exercised by environmental anxiety. A German adaptation of the American Environmental Worry Scale [1] was developed. The questionnaire has been used in a study on clients of the Consultation Centre for Environmental Medicine (CCEM). These clients (n = 51) were compared with a control group of clients of a vaccination centre (n = 238). As expected, the clients of the CCEM showed higher values of environmental worry. Moreover, the clients of the CCEM revealed scores of trait-anxiety which were more than one standard deviation above the level of the reference group. Environmental worry was weakly associated with a higher degree of trait-anxiety.

-------------------------------------------------------------------------------------------------------------------------------------------

(1996) Whither multiple chemical sensitivities?
Nethercott, JR Journal/Am J Contact Dermat. 7: 199-201.

query.fcgi?cmd=Retrrieve&db=PubMed&dopt=Citation&list_uids=8955481

-------------------------------------------------------------------------------------------------------------------------------------------

(1996) Neuronal ion channels as the target sites of insecticides.

Certain types of neuronal ions channels have been demonstrated to be the major target sites of insecticides. The insecticide-channel interactions that have been studied most extensively are pyrethroid actions on the voltage-gated sodium channel and cyclodiene/lindane actions on the GABAA receptor chloride channel complex. With the exception of organophosphate and carbamate insecticides which inhibit acetylcholinesterases, most insecticide commercially developed act on the sodium channel and the GABA system. Pyrethroids show the kinetics of both activation and inactivation gates of sodium channels resulting in prolonged openings of individual channels. This causes membrane depolarization, repetitive discharges and synaptic disturbances leading to hyperexcitatory symptoms of poisoning in animals. Only a very small fraction (approximately 1%) of sodium channel population is required to be modified by pyrethroids to produce severe hyperexcitatory symptoms. This toxicity
amplification theory applies to pharmacological and toxicological action of other drugs that go through a threshold phenomenon. Selective toxicity of pyrethroids between invertebrates and mammals can be explained based largely on the responses of sodium channels and partly on metabolic degradation. The pyrethroid-sodium channel interaction is also supported by Na+ uptake and batrachotoxin binding experiments. Cyclodiene and lindane exert a dual action on the GABAA system, the initial transient stimulation being followed by a suppression. The stimulation requires the presence of the gamma 2 subunit. The suppression of the GABA system is also documented by Cl- flux and ligand binding experiments. It appears that the sodium channel and the GABA system merit continuing efforts for development of newer and better insecticides. Nitromethylene heterocycles including imidacloprid act on nicotinic acetylcholine receptors. Insect receptors are more sensitive to these compounds than mammalian receptors. Single-channel analyses of the nicotinic acetylcholine receptor of PC12 cells have shown that imidacloprid increases the activity of subconductance state currents and decreases that of main conductance state currents. This may explain the imidacloprid suppression of acetylcholine responses.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8841090


Indoor bioaerosols (viruses, bacteria, dust mites, molds, etc.) have become the subject of discussion on indoor environments. A number of epidemiologic studies on the health effects of molds and home dampness, the latter being an important determinant of mold growth, have been conducted mainly in Europe and the United States. In this paper, a review of these epidemiologic studies is described. Questionnaires are used as the method of exposure assessment in most of the studies. The necessity for developing objective methods of dampness/mold exposure assessment has been expressed by some researchers. Respiratory symptoms, especially asthmatic attacks and wheezing for children, have been utilized in many investigations as a health effect index. Positive relationship between home dampness/mold and respiratory symptoms have been shown in numerous studies. Dampness and/or molds in dwellings may effect respiratory symptoms, but several problems for determining causal inference still remain: exposure assessment, temporal relationship, etc. While the differences in house structure and lifestyle between Japan and Europe/U.S.A. should be considered, the health effects of home dampness and molds need to also be examined in Japan which is a country with high humidity levels.
(1996) A case of drug eruption due to simultaneous sensitization with three different kinds of drugs.

We reported a case of drug eruption induced by combined treatment with three different kinds of drugs, amoxapine, mexiletine hydrochloride and cefaclor. A 63-year-old Japanese woman suffering from 11 years of standing reflex sympathetic dystrophy developed multiple erythematous papules on her trunk and extremities after taking 14 kinds of drugs. The provocation challenge produced positive reactions to amoxapine, mexiletine hydrochloride, and cefaclor, but was negative to the other drugs. We discussed the mechanism of simultaneous sensitization to three different kinds of drugs in our case.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9037924

(1996) Potent modulation of neuronal nicotinic acetylcholine receptor-channel by ethanol.

Controversies remain over which ion channels are the most sensitive to ethanol. We have found that ethanol potently modulates the neuronal nicotinic acetylcholine receptor-channel at micromolar concentrations with an EC50 of 88.5 microM, which is significantly lower than most values previously reported for other ion channels. Prolonged application of ethanol accelerated the decay phase of acetylcholine-induced currents, caused single-channels to open in bursts, and shortened the mean open time, all of which reflect increased receptor desensitization. However, ethanol slowed the decay phase of the current induced by a brief application of acetylcholine, which may indicate that ethanol manifests its action by causing an increase in the affinity of the receptor for acetylcholine. These results suggest that neuronal nicotinic acetylcholine receptors may be important target sites of ethanol, particularly in the early stages of ethanol intoxication.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8916104

(1996) [Multiple chemical sensitivity (MCS) syndrome].
Several different meanings have been attached to the term "chemical sensitivity" by those who use it. Feeling ill from odors is a symptom reported by approximately one-third of the population. The syndrome of chemical sensitivity, frequently called "Multiple Chemical Sensitivity" or "MCS" has been the subject of three federally-sponsored workshops; at least five different case definitions for research on MCS have been proposed. In contrast, the hypothesis that chemical sensitivity may be a mechanism for disease posits that a broad spectrum of "recognized" chronic illnesses, ranging from asthma and migraine to depression and chronic fatigue, may be the consequence of environmental chemical exposures. According to this theory, a two-step process occurs: (1) an initial salient exposure event(s) (for example, a one-time, intermittent, or continuous exposure to pesticides, solvents, or air contaminants in a sick building) interacts with a susceptible individual, causing loss of tolerance for everyday, low level chemical inhalants (car exhaust, fragrances, cleaning agents), as well as for foods, drugs, alcohol, and caffeine; (2) thereafter, such common, formerly well-tolerated substances trigger symptoms, thus perpetuating illness. "Masking" (acclimatization, apposition, and addiction) may hide these exposure-symptom relationships, thus obfuscating the environmental etiology of the illness. Accumulating clinical observations lend credence to a view of chemical sensitivity as an emerging theory of disease causation and underscore the need for its testing in a rational, scientific manner. While chemical sensitivity may be the consequence of chemical exposure, the term "toxicant-induced loss of tolerance" more fully describes the two-step process under scrutiny.

BACKGROUND: Reactive airways dysfunction syndrome is a chronic asthma-like condition developing after an acute irritant exposure, and chronic inflammation has been seen on endobronchial biopsy. Reactive upper-airways dysfunction syndrome is chronic rhinitis developing in temporal association with a toxic inhalation exposure, but the pathophysiology is unknown. OBJECTIVES: To study biopsies of the nasal mucosa
in patients with reactive upper-airways dysfunction syndrome and in some cases reactive airways dysfunction syndrome developing in temporal association with a chlorine dioxide exposure, to see if a histologic basis for the persistent rhinitis and sensitivity to chemical irritants could be determined. METHODS: Specimens were stained with hematoxylin-eosin and immunoperoxidase stains for substance P, vasointestinal peptide, and S-100 (nerve fibers), and fixed in glutaraldehyde for electron microscopy. Biopsies of three nonexposed subjects were performed for comparison. A pathologist blinded to clinical data interpreted the specimens. RESULTS: Inflammation ratings of exposed individuals were higher than for the nonexposed individuals. The number of nerve fibers stained was greater for patients vs controls. Substance P and vasointestinal peptide staining was nonspecific. Electron microscopy showed desquamation of the epithelium and permeability of epithelial cell junctions. CONCLUSION: This study suggests a mechanism by which ongoing low level exposures perpetuate airway inflammation after an inducing toxic inhalation. A possible overlap between reactive airways dysfunction syndrome, reactive upper-airway dysfunction syndrome and the multiple chemical sensitivity syndrome is suggested.

Meggs, WJ, Dunn, KA, Bloch, RM, Goodman, PE and Davidoff, AL Journal/Arch Environ Health. 51: 275-82.

The objectives of this study were (a) to determine the self-reported prevalence of allergy and chemical sensitivity in a rural population of eastern North Carolina, (b) to determine the type and frequency of symptoms for each condition, and (c) to determine the demographic groups affected. A random general telephone survey was conducted during the period May 14, 1993, to September 10, 1993, and questions about allergy and chemical sensitivity were asked. Of the 1,446 households contacted, 1,027 (71%) individuals agreed to participate. Allergies were reported by 365 (35%) individuals. Thirty percent of allergic individuals reported that symptoms occurred once or more each week, whereas 61% reported that symptoms occurred, at most, once each month. Allergic symptoms that occurred daily were reported by 5.3% of the total population. Chemical sensitivity was reported by 336 (33%) individuals. Thirty-five percent of chemically sensitive individuals reported symptoms at least once each week, whereas 53% reported that symptoms occurred once (or less) each month. Symptoms of chemical sensitivity that occurred daily were reported by 3.9% of the total population. Both allergy and chemical sensitivity were distributed widely across age, income, race, and educational groups. Simultaneous allergy and chemical sensitivity were reported by 16.9% of the population, allergy without chemical sensitivity by 16.0%, chemical sensitivity without allergy by 18.2%, and neither condition by 48.9%. If the prevalence of sensitivity to chemical irritants is, in fact, equivalent to that of allergy, as was found in this study, then support for the scientific investigation of chemical sensitivity is justified.
(1996) Research initiatives at the University of Toronto Environmental Hypersensitivity Research Unit.

The Environmental Hypersensitivity Research Unit at the University of Toronto is following a research strategy to develop and evaluate diagnostic methods for environmental hypersensitivity. These methods will be used to identify cases for inclusion in studies of disease etiology and therapy. The Research Unit has actively sought consultation and collaboration with researchers at the University of Toronto, clinicians from a variety of specialties, and patients. It is hoped that such a multidisciplinary approach will lead to the generation and testing of innovative hypothesis with rigorous methodology and, ultimately, to increased understanding of the complex conditions known as environmental hypersensitivity.

McFadden, SA Journal/Toxicology. 111: 43-65.

Proper bodily response to environmental toxicants presumably requires proper function of the xenobiotic (foreign chemical) detoxification pathways. Links between phenotypic variations in xenobiotic metabolism and adverse environmental response have long been sought. Metabolism of the drug S-carboxymethyl-L-cysteine (SCMC) is polymorphous in the population, having a bimodal distribution of metabolites, 2.5% of the general population are thought to be nonmetabolizers. The researchers developing this data feel this implies a polymorphism in sulfoxidation of the amino acid cysteine to sulfate. While this interpretation is somewhat controversial, these metabolic differences reflected may have significant effects. Additionally, a significant number of individuals with environmental intolerance or chronic disease have impaired sulfation of phenolic xenobiots. This impairment is demonstrated with the probe drug acetaminophen and is presumably due to starvation of the sulfotransferases for sulfate substrate. Reduced metabolism of SCMC has been found with increased frequency in individuals with several degenerative neurological and immunological conditions and drug intolerances, including Alzheimer's disease, Parkinson's disease, motor neuron disease, rheumatoid arthritis, and delayed food sensitivity. Impaired sulfation has been found in many of these conditions, and preliminary data suggests that it may be important in multiple chemical sensitivities and diet responsive autism. In addition, impaired sulfation may
be relevant to intolerance of phenol, tyramine, and phenyllic food constituents, and it may be a factor in the success of the Feingold diet. These studies indicate the need for the development of genetic and functional tests of xenobiotic metabolism as tools for further research in epidemiology and risk assessment.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8711748

(1996)  Topical Bibliography of Published Works Regarding the Health of Veterans of the Persian Gulf War, Revision 1.
This updated bibliography on the health of veterans of the Persian Gulf War and related topics for the use of researchers contained 2,158 references. The references were divided into the following 21 categories: anthrax, cancer, chemical warfare, chronic fatigue syndrome, fibromyalgia, gastrointestinal disease, insecticides, leishmaniasis, multiple chemical sensitivity, other infectious disease, other psychiatric disease, other toxins and their treatment, posttraumatic stress disorder, pyridostigmine, Q-fever, reproductive disease, respiratory disease, smoke effects, war and disease, magazine articles, and newspaper articles.


Psychological and toxic effects of air pollution can lead to psychiatric symptoms, including anxiety and changes in mood, cognition, and behavior. Increased levels of some air pollutants are accompanied by an increase in psychiatric admissions and emergency calls and, in some studies, by changes in behavior and a reduction in psychological well-being. Numerous toxic pollutants interfere with the development and adult functioning of the nervous system. Manifestations are often insidious or delayed, but they can provide a more sensitive indicator of toxic effects than cancer rates or mortality data. Other medical effects of air pollution, such as asthma, can indirectly affect psychological health. The sick building syndrome and multiple chemical sensitivity are conditions with toxicologic and psychiatric aspects. Psychosocial stress can cause symptoms similar to those of organic mental disorders. Reactions to stress depend on cultural, individual, and situational variables. We must understand these factors to be able to alleviate and prevent the consequences of environmental trauma. Expanded research is recommended in three main areas: (1) how people perceive and cope with environmental health risks, (2) the effects of air pollution on behavior and neuropsychological functioning, and (3) neurotoxicologic evaluation of air pollutants with both behavioral and in vitro studies.

http://www.sciencedirect.com/science/article/B6T4S-3Y0RTNB-5G/2f33741983dc9c9038b8c1896268e2397

(1996) [Multiple chemical sensitivity disorder in patients with neurotoxic illnesses].

The data of 466 subjects suffering from neurologic disorders which are suggested to be caused by neurotoxic agents in their environment retrospectively was evaluated and documented. Among these cases there were 151 subjects with symptoms of Multiple Chemical Sensitivity Disorder (MCSD). The relationship between the neurological health impairments and neurotoxic agents in the environment of these patients was characterised using five different categories (probable = A, possible = B, uncertain = C, unclarified = D, not probable = E). From the 466 patients 320 subjects (69%) could be assigned to the categories A and B, respectively. Within these 320 cases with chronic neurotoxic health impairments 136 subjects (79 females and 57 males) showed signs of MCSD. Age and gender of cases as well as duration and character of exposure to neurotoxic substances retrospectively were assessed from the explicit files of the patients, which had been made anonymous for this purpose. Frequency of characteristic symptoms of neurotoxicity were analysed. Results are given for patients with neurotoxic health impairments with MCSD (n = 136) and without MCSD (n = 184). Neurotoxic substances which were used as indoor wood preservatives (mainly Pentachlorophenol and/or Lindane) were found to be the causative agents in 63% of the cases with neurotoxic health impairments and MCSD. Other important neurotoxic substances to which the patients were mainly exposed were organic solvents (25%), formaldehyde (15%), dental materials (15%), pyrethroides (13%), and other biocides (19%) (multiple exposures were possible). The time of exposure was calculated as being > or = 10 years for 55% of the patients with MCSD and for 50% of the group with neurotoxic health impairments but without MCSD. Out of the 184 cases with neurotoxic health impairments but without MCSD there were 22%, and out of the 136 cases with MCSD there were 39% who showed all symptoms of chronic fatigue syndrome. 53% of the cases with MCSD had an allergic disposition compared to only 20% of the cases without MCSD. This work is not a controlled epidemiological study but a retrospective documentation and evaluation of data related to environmental medicine. With the
present documentation in this purely descriptive manner the proof of a causal relationship was not possible or intended. But because corresponding epidemiological studies are lacking, this documentation can give important information on characteristic features of Multiple Chemical Sensitivity Disorder and chronic neurotoxic health impairments. Such information is essential for planning and carrying out epidemiological studies urgently needed in this field.


(1996) Sulfate concentrations as an indicator of ambient particulate matter air pollution for health risk evaluations.

Retrospective population studies that have compared regression coefficients for mortality and morbidity for sulfate (SO4\(^{2-}\)), fine particles (PM2.5; aerodynamic diameter < 2.5 microns), thoracic particles (PM10; aerodynamic diameter < 10 microns), and total suspended particulates (TSP; undefined and variable upper cut-size) generally have found SO4\(^{2-}\) concentrations to be correlated with effects as well as or better than PM2.5. In addition, both SO4\(^{2-}\) and PM2.5 have yielded somewhat stronger associations with adverse health effects than PM10, and much stronger associations than TSP. Sulfate has advantages over PM2.5 for retrospective epidemiology, at least in the United States, because considerably more data on sulfate have been collected in recent decades, and there is a broader epidemiological database in the literature for comparison to other studies. While SO4\(^{2-}\), per se, is an unlikely causal factor for mortality or morbidity, it often is correlated closely with variations in the strong acid component of ambient particulate matter (H\(^+\)) and PM2.5 concentrations (especially in summer), which are more likely causal factors. A detailed analysis of the SO4\(^{2-}\) epidemiological database is presented in this paper. In addition, drawing on our substantial archives of SO4\(^{2-}\) and H\(^+\) data, we show that SO4\(^{2-}\) and H\(^+\) correlate, both spatially and over time, in the eastern United States. We demonstrate the utility of SO4\(^{2-}\) as a useful surrogate for ambient PM2.5 and H\(^+\) in epidemiological studies and as an index of PM exposure in ambient air quality guidelines and standards.

(1996) [A study and treatment of a group of patients with electro-hypersensitivity. More than half of the patients were able to return to work].

(1996) Stress - restress: an animal model of HPA abnormalities in PTSD.
http://www.sciencedirect.com/science/article/B6T4S-3Y0RTNB-23/2
41e4678738f42055ff8166c31cf842e5


Multidrug resistance (MDR) to chemically unrelated therapeutic anticancer agents in mammalian cells is mediated by the overexpression of an ATP-dependent 150- to 180-kD membrane glycoprotein P-glycoprotein (P-gp). Although the complete physiological role of P-gp is unknown, it is proposed to function in cellular detoxification of xenobiotics. In this study, we investigated whether the organophosphorus insecticide chlorpyrifos (O,O-diethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate) or its metabolites interact with P-gp. Immunohistochemical analysis of tissues from male Fischer 344 rats administered chlorpyrifos (7.6 mg/kg gavage) showed increased P-gp expression in the kidney, adrenal, liver, jejunum, and stomach (tissues associated with elimination of xenobiotics), compared to control tissues. The most prominent increase was detected in the large bile ducts of the liver and the proximal tubule region of the kidney. P-gp expression was increased throughout the adrenal medulla and cortex, while a moderate increase was detected in the epithelial layers of the stomach and jejunum. To examine further the interaction between chlorpyrifos and P-gp, we evaluated whether chlorpyrifos or its active metabolite, chlorpyrifos oxon, could inhibit [3H]azidopine labeling of P-gp in MDR1 baculovirus-infected insect Sf9 cells. A concentration-dependent inhibition of [3H]azidopine labeling of P-gp was detected with chlorpyrifos oxon, while significant inhibition was not detected with chlorpyrifos. To correlate the binding of chlorpyrifos oxon to P-gp with a biochemical effect, we examined its ability to stimulate P-gp-mediated ATPase activity in these Sf9 cells. Chlorpyrifos oxon stimulated P-gp ATPase activity 1.75 times that of the positive control (10 microM verapamil). Taken together, these results suggest that chlorpyrifos
oxon interacts with P-gp, and support the hypothesis that P-gp may play a role in the cellular detoxification of insecticides in mammalian tissues. To our knowledge this is the first report of an organophosphorus insecticide interacting with and increasing the expression of P-gp.

Lanning, CL, Fine, RL, Corcoran, JJ, Ayad, HM, Rose, RL and Abou-Donia, MB

Since pesticides have been shown to interact with P-glycoprotein (P-gp), the purpose of this study was to examine the possible role of P-gp in pesticide resistance in the tobacco budworm (Heliothis virescens). Using three P-gp antibodies, P-gp expression in various resistant populations of tobacco budworms was found to be 2-6-times that of the susceptible larvae. Tobacco budworm P-gp was glycosylated and localized primarily in the cuticle and fat body with little expression in the mid gut. To determine the role of P-gp in pesticide resistance, resistant tobacco budworm larvae were treated with a P-gp inhibitor, quinidine, and challenged with various doses of thiodicarb. Inhibition of P-gp decreased the LD50 for thiodicarb by a factor of 12.5. Quinidine treatment did not result in a significant inhibition of the P-450 system nor did it alter the feeding of the larvae, suggesting the potential involvement of P-gp in pesticide resistance. An age-dependent increase in P-gp expression was detected in resistant larvae as compared to control, susceptible larvae. This correlates with the reported age-dependent increase in resistance and is further evidence supporting the role of P-gp in the development of pesticide resistance.

Lanning, CL, Ayad, HM and Abou-Donia, MB

Pesticides have been shown to interact with the multidrug resistance protein associated with cancer chemotherapy, P-glycoprotein (P-gp). P-gp, therefore, has also been implicated in the development of pesticide resistance. The purpose of this study was to characterize the effect P-gp has on the accumulation of the carbamate pesticide, thiodicarb. For these studies, resistant tobacco budworm larvae, expressing four times the P-gp as susceptible larvae, were pretreated with the P-gp inhibitor, quinidine, and challenged topically with thiodicarb. Quinidine enhanced thiodicarb toxicity in a dose-dependent manner, with mortality in the presence of P-gp inhibition increased up to 33%. Quinidine treatment increased [14C]thiodicarb accumulation 2- to 3-fold as compared to thiodicarb treatment alone. This study suggests that P-gp
contributes to quinidine synergism of thiodicarb toxicity and suggests that P-gp may be involved in cuticular resistance to pesticides.

Health hazards associated with exposure to indoor air pollution were reviewed. An introduction to the ubiquitous problem of indoor air pollution was provided. A definition for total personal exposure was presented. Adverse effects of exposure to indoor air pollution have included the induction of clinically evident disease such as carbon-monoxide (630080) poisoning, hypersensitivity pneumonitis, and Legionella pneumonia, exacerbation of established diseases such as asthma and cystic fibrosis, an increased risk for disease, physiological impairment, and a decreased perception of well being. Specific health effects associated with exposures to carbon-monoxide, nitrogen-dioxide (10102440), environmental tobacco smoke, wood smoke, organic compounds, radon (10043922), asbestos (1332214) and man made fibers, and biological agents including acarids, insects, domestic animals, rodents, fungi, pollens, and bacteria were described and discussed. In addition, the clinical implications of indoor air pollution exposure, particularly syndromes such as sick building syndrome and multiple chemical sensitivity, were explored. General considerations with regard to control strategies and regulations were discussed.

(1996) [Microflora of the in furniture factors as a potential occupational hazard: concentration and composition of microflora and immunologic reactivity of workers to microbial aeroallergens].
Microbiological studies of the air were performed in two furniture factories. The concentration of microorganisms in the air was low, being of the order 10(3) cfu/m3. The most common organisms were corynebacteria (Arthrobacter, Corynebacterium, Brevibacterium, Microbacterium) and fungi (Aspergillus fumigatus, Rhodotorula rubra). Some of the species found in this environment possess known allergenic properties. Allergologoble examinations of the workers with environmental aeroallergens have been performed in three departments of one factory. The highest frequency of positive skin reactions were observed among the workers of the varnishing department which may be due to synergistic effects of chemical pollutants. The incidence of precipitin reactions was low among all workers.

TD3: The Environmental Health Investigations Branch (EHIB) of the California Department of Health Services (CDHS) convened an advisory group that would assist the Department to (1) design questionnaire instruments which would identify people with perceived chemical sensitivities, (2) develop a battery of physical exams and laboratory tests that might correlate with descriptions of this condition and (3) recommend epidemiologic study designs for applying these instruments. Final rept. Sponsored by Agency for Toxic Substances and Disease Registry, Atlanta, GA. Div. of Health Studies.


Both clinical and epidemiological studies of the effects of exposure to toluene have shown that long-term exposure may result in chronic toxic encephalopathy, where one of the major symptoms is memory deficits. We have attempted to identify the structural basis of the toxic effects of toluene in the hippocampus, a region of the brain known to be involved in learning and memory processes and well suited for stereological analysis. Rats were exposed to 1500 ppm of toluene, six hours per day, five days per week for six months. This was followed by a four-month-period without exposure prior to sacrifice. The total number of neurons in each of the five subdivisions of hippocampus of six exposed and six control rats was estimated with the optical fractionator. A statistically significant neuron loss of 16% was found in regio inferior (CA3 and CA2) of the exposed rats.


Two train conductors had chest tightness, painful breathing, muscle cramps, and nausea after fighting a fire in a battery box under a passenger coach. Shortly thereafter, they became anosmic and had excessive fatigue, persistent headaches, sleep disturbances, irritability, unstable moods, and hypertension. Urinary cadmium and nickel levels were elevated. Neurobehavioral testing showed, in comparison to referents, prolonged reaction times, abnormal balance, prolonged blink reflex latency, severely constricted visual fields, and decreased vibration sense. Test scores showed that immediate verbal and visual recall were normal but delayed recall was reduced. Scores on overlearned information were normal. Tests measuring dexterity, coordination, decision making, and peripheral sensation and discrimination revealed abnormalities. Repeat testing 6 and 12 months after exposure showed persistent abnormalities. Cadmium and vinyl chloride are the most plausible causes of the neurotoxicity, but fumes from the fire may have contained other neurotoxic chemicals.


Although case-control studies are suitable for assessing gene-environment interactions, choosing appropriate control subjects is a valid concern in these studies. The authors review three nontraditional study designs that do not include a control group: 1) the case-only study, 2) the case-parental control study, and 3) the affected relative-pair method. In case-only studies, one can examine the association between an exposure and a genotype among case subjects only. Odds ratios are interpreted as a synergy index on a multiplicative scale, with independence assumed between the exposure and the genotype. In case-parental control studies, one can compare the genotypic distribution of case subjects with the expected distribution based on parental genotypes when there is no association between genotype and disease; the effect of a genotype can be stratified according to case subjects' exposure status. In affected relative-pair studies, the distribution of alleles identical by descent between pairs of
affected relatives is compared with the expected distribution based on the absence of genetic linkage between the locus and the disease; the analysis can be stratified according to exposure status. Some or all of these methods have certain limitations, including linkage disequilibrium, confounding, assumptions of Mendelian transmission, an inability to measure exposure effects directly, and the use of a multiplicative scale to test for interaction. Nevertheless, they provide important tools to assess gene-environment interaction in disease etiology.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8757225

(1996) Increased exhaled nitric oxide in asthma is mainly derived from the lower respiratory tract.
Kharitonov, SA, Chung, KF, Evans, D, O'Connor, BJ and Barnes, PJ Journal/Am J Respir Crit Care Med. 153: 1773-80.

Nitric oxide (NO) is detectable in the exhaled air of human subjects, and its concentration is increased in patients with asthma. We have investigated the origin of the increase in exhaled NO in asthmatic patients by using different expiratory maneuvers and by direct sampling from the upper and lower respiratory tracts. Exhaled NO was measured by a chemiluminescence analyzer. Concentrations of NO measured during expiration against the resistance of the analyzer with exhaled flow of 1 L/min, were 78 +/- 3 ppb in normal subjects (n = 46) and significantly elevated in patients with asthma (301 +/- 26 ppb, n = 30, p < 0.001). Values of exhaled NO were lower when measured during unobstructed expiration with a flow of 5 L/min with sampling from a side-arm (7 +/- 1 ppb), but again were elevated in patients with asthma (46 +/- 6 ppb, p < 0.001). Breath-holding for 20 s resulted in an initial peak of NO, but end-expiration values similar to the unobstructed expiration. The concentration of NO in the nose was considerably greater than in expired air (996 +/- 39 ppb) and was elevated in patients with asthma (1,390 +/- 71 ppb, p < 0.002). Direct sampling from trachea and right middle lobe bronchus via a fiberoptic bronchoscope gave similar values in five normal and 15 asthmatic subjects to the values recorded during unobstructed expiration, and there was a good correlation between values in expired air and direct sampling (trachea r = 0.91, right middle lobe r = 0.87, p < 0.001). We conclude that exhaled NO measured in an unobstructed breath reflects concentrations in the lower respiratory tract, but that breath-holding or expiration against resistance is contaminated by
residual NO derived from the upper respiratory tract. We also provide evidence that the elevated levels of exhaled NO in asthmatic patients are derived predominantly from the lower respiratory tract.

(1996) **Women, health and the environment.**

This paper develops a conceptual framework for gender-sensitive research and policy analysis that centres on women's interaction with the biophysical environment, and the implications of that interaction for their environmental health. The paper reviews the lack of data on women's non-reproductive health, and argues that there is a need for increased research and policy formulation dealing with women's environmental health in both the developing and the developed countries. One important dilemma for most researchers interested in women's environmental health is the lack of an appropriate conceptual model. The paper argues that attention to women's interaction with the biophysical environment within their own life spaces' reveals that women are exposed to the hazards of environmental illness in a manner that is clearly gender-differentiated. The paper reviews the impact of poverty, illiteracy and gender bias on women's life spaces, and argues that the failure to recognize and protect women's life spaces in economic policy and planning commonly leads to "disease environments" for women and their children. Evidence of the impact of such disease environments on women's environmental health is drawn from the urban setting and from women's experience of desertification in Africa and Asia. The paper reviews the policy issues that emerge from this analysis, and makes a series of suggestions for national and international policy and action in support of improvements in women's environmental health.

(1996) **Clinical ecologists.**

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8676329

(1996) **Habitual and genetic factors that affect urinary background levels of biomarkers for organic solvent exposure.**
Kawamoto, T, Koga, M, Oyama, T and Kodama, Y Journal/Arch Environ Contam Toxicol. 30: 114-20.
Urinary hippuric acid, phenol, and o-cresol, which are biomarkers for toluene, benzene, and phenol exposures, are usually present in a significant amount in urine collected from subjects who have not been occupationally exposed to the organic solvents. With the improvement of working environments, the urinary concentrations of the biomarkers have become lower and closer to the levels of urine from unexposed subjects. It is very useful to clarify the background levels of these biomarkers and the factors which effect the background levels of the biomarkers in order to make effective use of biological monitoring under low level exposure. In the present study, the effects of life habits and the genetic polymorphisms of the metabolizing enzymes on the background levels of urinary hippuric acid, phenol and o- and p-cresol were clarified, using 351 males (means age: 38.6, range: 19-71) who were not occupationally exposed to hazardous chemical materials. Their life habits, smoking, alcohol consumption, and dietary habits were examined by means of a questionnaire. The genotypes of five metabolizing enzymes, that is, low Km aldehyde dehydrogenase (ALDH2), polymorphic N-acetyl transferase (NAT2), cytochrome P-4501A1 (CYP1A1), cytochrome P-4502E1 (CYP2E1), and glutathione-S-transferase mu (GSTM1) were determined from peripheral blood samples. The urinary hippuric acid and creatinine were analyzed by HPLC and urinary phenol, o-, p- and m-cresol were determined by GC/MS. Recoveries and the coefficients of variance of phenol, o-cresol, and p-cresol ranged from 92.7 to 107.8% and 1.3% to 6.7%, respectively. Linear relationships between the concentrations of phenol, o- and p-cresol, and their peak area ratios were observed.(ABSTRACT TRUNCATED AT 250 WORDS)

(1996) Fibromyalgia or multi-organ dysesthesia? 

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8546733


(1996) [The ratio of hereditary and environmental factors in the origination of
noninfectious human diseases]. 
Ivanov, VI Journal/Tsitol Genet. 30: 36-42.
Recent investigations in clinical genetics have shown, that manifestations of common nontransmissive diseases in humans are determined by the interactions of hereditary, internal and environmental factors in the same way as it was earlier demonstrated for hereditary diseases and studied on animals and plants for many quantitative and qualitative traits.


Multiple chemical sensitivities (MCS) has become an increasingly frequent diagnosis assigned to patients with symptoms associated with exposures to environmental chemicals. Since the characteristic symptoms of MCS are triggered by very low concentrations of chemicals, in the range of olfactory thresholds, it is widely believed that the intranasal chemoreceptive senses are involved in the pathophysiology of MCS. Thus, the present study addressed both the olfactory and trigeminal systems: using a double-blind approach we investigated whether MCS patients show differences in responses after exposure to either room air or low concentrations of a widely used chemical agent (2-propanol). A total of 23 patients participated in the experiments (mean age 47 years; 13 female, 10 male). MCS was diagnosed according to Cullen's criteria. Performance of the nasal chemical senses was established by means of chemosensory event-related potentials (CSERP) and subjective measures of olfactory function (odor discrimination, phenylethyl alcohol odor thresholds). CSERP were recorded in response to olfactory (H2S), and trigeminal (CO2) stimuli. The study provided three major results: (1) Approximately 20% of patients diagnosed with MCS presented symptoms regardless of the type of challenge, suggesting the susceptibility of MCS patients to unspecific experimental manipulations. (2) Changes in CSERP latencies indicated a change in the processing of both olfactory and trigeminal stimuli. (3) While odor threshold remained unchanged, the patients' ability to discriminate odors decreased after exposure to room air. In contrast, this decrease was less pronounced after exposure to 2-prop. Summarily, MCS patients respond to challenge with 2-prop with changes of chemosensory perception which might increase their susceptibility to environmentally volatile chemicals. Changes in the pattern of event-related potentials are interpreted as the possible change of the orientation of cortical generators, i.e., neuronal populations that were involved in the processing of chemosensory information. However, investigations in healthy controls are needed in order to draw further conclusions.

Intricate regulation of nitric oxide synthesis in neurons.

There is little doubt that nitric oxide (NO) is one of the most important second messengers yet to be discovered, particularly in relation to its diverse roles in the regulation of neuronal function. As expected, synthesis of such a multifunctional molecule has to be under very tight control. For example, there is evidence that the rate of production of NO in neurons is regulated by several second messengers and their related protein kinases. NO by itself is also able to elicit negative feedback on the activity NO synthase (NOS) to attenuate its own rate of synthesis. Furthermore, NO modulates the release of neurotransmitters and alters the sensitivity of receptors that are coupled to stimulation of its synthesis. In healthy neurons, all of these intricate mechanisms are expected to cross-talk in harmony to result in the generation of optimal amounts of NO.

Primary allergic sensitization to environmental antigens: perinatal T cell priming as a determinant of responder phenotype in adulthood.

Measures of tuning and suppression in single-fiber and whole-nerve responses in young and quiet-aged gerbils.

Tuning and suppression were examined in the auditory nerves of young-control and quiet-aged gerbils. Tuning curves obtained from single-fiber responses were compared to those obtained with the compound action potential (CAP) using masking procedures. Tuning was measured in terms of the high-frequency slope of the tuning curve and Q values obtained 10 dB and 40 dB (Q10 dB and Q40 dB, respectively) above the threshold at its best frequency. The study had two objectives: first, how CAP measures of tuning and suppression correspond to single-fiber measures in presbyacusic cochleas; and second, how the above measures of tuning change with age without the confounding effects of noise exposure. It was found that measures derived from the CAP responses in aged gerbils remained similar to the trends of the single-fiber data, despite the many morphological changes that are known to occur in the presbyacusic ear. Thus, CAP procedures remain an appropriate alternative to single-fiber recording in aged animals where the stability of the preparation can be tenuous. With regard to tuning and suppression, our results show that single-fiber and CAP tuning curves in quiet-aged animals are similar to those of young controls except
for higher thresholds near the best frequency. The tail response remained largely stable with age, and no instances of tail hypersensitivity were found. The slopes of the high-frequency legs of the curves were similar in young and aged animals, and were associated with the presence of two-tone suppression on the high-frequency side. In a few instances high-side suppression was absent in the aged gerbils and was associated with tuning curves with shallow high-frequency slopes and characteristic frequency (CF) threshold shifts of 30 dB or greater. Mean high-frequency slopes and Q values increased with best frequency in young controls, but were fairly constant with best frequency in quiet-aged animals. Thus, in comparison to controls, the frequency selectivity of quiet-aged gerbils tends to decrease somewhat at frequencies above 4 kHz. Many of these changes with age may be ascribed to a chronic decline of the endocochlear potential (EP) acting on an intact hair-cell system in quiet-aged gerbils. With this assumption, CF thresholds are most sensitive to the EP decline, whereas boundaries of tuning and two-tone suppression taken at more intense levels are least affected.

(1996) Significance of indoor environment for the development of allergic symptoms in children followed up to 18 months of age.

The development of symptoms possibly related to allergy or other forms of hypersensitivity was studied in a group of 638 children on two occasions: when the children were 3 and 18 months of age. Standardized questions were used to collect basic information about the child, technical characteristics of the home, and the mother's perception of the indoor climate. All reported exposure factors were analyzed in relation to the child's symptoms at 18 months of age, by logistic regression techniques. A family history of atopy was associated with a high incidence of most of the investigated symptoms. Attendance at a day nursery before 18 months of age increased the risk of recurrent colds and the need for several courses of treatment with antibiotics. If the mother smoked, the children more often suffered from protracted coughing episodes. If the child has a sibling, the risk of developing a wheeze, repeated colds, and the need for antibiotic treatment increased. No building factors, such as size of the home, heating and ventilation system, type of foundation, dampness, or presence of wall-to-wall carpets, showed a significant correlation to symptoms reported in the children. However, if the mothers reported symptoms that are often connected with "sick buildings", the children more often had eczema, dry skin, or reactions to food. The mothers' complaints about indoor air quality and climate and mucous membrane symptoms were significantly related to the type of building and presence of condensation on the windows in winter, a finding which may indicate that indoor climate factors also have some effect on the health of the children. This study reports the prevalences of symptoms until the age of 18 months. At this age, the allergic manifestations are usually nonspecific, and follow-up examinations to 4-5 years of age
are needed before any definite conclusions can be drawn about the development of atopic diseases due to indoor climate factors.

(1996) Alterations in the neutral proteinase activities of central and peripheral nervous systems of acrylamide-, carbon disulfide-, or 2,5-hexanedione-treated rats.

Proteinases are widespread in neuronal or nonneuronal eukaryotic cells. They are suggested to play an important role in the turnover of proteins in neuronal perikaryon and axon, and digestion of the transported cytoskeletal proteins in synaptic terminals. We examined the effect of acrylamide (50 mg/kg, ip), carbon disulfide (700 ppm, 9 h, 7 d a week), and 2,5-hexanedione (2,5-HD) (1% in drinking water) treatment of rats on mCANP (2 mM Ca2+), microCANP (0.1 mM Ca2+), and CINP (Ca(2+)-independent) activity in telencephalon + diencephalon (FB), rhombencephalon + mesencephalon (LB), spinal cord (SC), and sciatic nerve (SN). The proteinase activity was determined in the 30,000g supernatant fraction of tissues using 14C-methylated casein as the substrate. mCANP activity in FB, LB, and SC was inhibited only by acrylamide. Acrylamide or 2,5-HD treatment had no effect on microCANP and CINP activities of SN, whereas carbon disulfide enhanced microCANP after 15 d and CINP activity after 10 d. It is suggested that alteration in in vitro calpain activity shown by these chemicals may not be directly related to their neurotoxic effect. However, calpain may still be playing a role in this polyneuropathy by alteration in activity through inflow of Ca2+, release of Ca2+ from intracellular organelles, or other factors. Modification of cytoskeletal proteins making them more susceptible to proteases and the role of some other proteinase is also possible.


Nonsteroidal agent tamoxifen (Tam), a therapeutic/chemopreventive agent for breast cancer, inhibits protein kinase C (PKC), which is considered to be one of its extra-estrogen receptor sites of action. This drug is required at higher (>100 microM) concentrations to inhibit PKC in the test tube, whereas it is required at lower (1-10 microM) concentrations to induce inhibition of cell growth in estrogen receptor-negative cell types. To identify additional mechanisms of action of Tam on PKC and cell growth, studies with MDA-MB-231, an estrogen receptor-negative breast carcinoma cell type, have been carried out. Upon treatment with 5-20 microM Tam, a cytosol to membrane translocation of PKC occurred within 30 min, which was then followed by a
down-regulation of the enzyme within 2 h. A transient generation of Ca2+
lipid-independent activated form of PKC was observed during this period. Rapidly
growing cells require nearly 2-3-fold lower concentrations (2-5 microM) of Tam than do
confluent cells to induce changes in PKC. Furthermore, phorbol ester binding observed
with intact cells also decreased in Tam-treated cells only under the conditions PKC
was inactivated. Unlike phorbol esters, Tam did not directly support the membrane
association of PKC. The release of arachidonic acid correlated with the PKC
membrane translocation. Studies carried out with [3H]Tam revealed that Tam
partitioned into the membrane, and there was no appreciable covalent association of
[3H]Tam with cellular proteins within this limited time period (2 h). Various antioxidants
(vitamin E, vitamin C, beta-carotene, catalase, and superoxide dismutase) inhibited all
these cellular effects of Tam. Moreover, vitamin E strikingly blocked Tam-induced
growth inhibition. To determine whether oxymetabolites of Tam can affect PKC
permanently, OH-Tam was tested with purified PKC. In contrast to Tam, which
reversibly inhibited PKC, OH-Tam permanently inactivated the enzyme by modifying
the catalytic domain at lower concentrations. The vicinal thiols present within this
domain were found to be required to induce this inactivation. This effect was partially
blocked by various antioxidants. This is the first report showing the role of oxidative
stress in mediating the actions of Tam. Taken together these results suggest that Tam,
by initially partitioning into the membranes, induces a generation of transmembrane
signals and an oxidative stress to elicit the membrane association of PKC, followed by
an irreversible activation, and subsequent down-regulation of this enzyme, which, in
part, may lead to cell growth inhibition.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8662863

Griffiths, BB, Rea, WJ, Johnson, AR and Ross, GH Journal/Microbios. 86: 127-34.

Mycotoxins have compromising effects on varied biological systems, even when
ingested at levels which do not evoke manifestations of clinical mycotoxicoses. No data
have been previously found as to the therapeutic and mitogenic effects of mycotoxins.
This was the objective of the present work. Human peripheral T4 lymphocytes were
obtained by venipuncture, propagated in RPMI 1640 medium and challenged with
varied concentrations of aflatoxins, B1, B2, G1, and G2. The cells were stained with
propidium iodide and fluorescent isothiocyanate (FITC) and examined
microfluorometrically. All the mycotoxins were significantly mitogenic on the basis of
dose response. No adverse effects were observed when doses of 10, 50 and 100
micrograms were administered on a modest clinical basis to volunteers.
(1996) Obtaining information about susceptibility from the epidemiological literature.
Grassman, JA Journal/Toxicology. 111: 253-70.

Whether people become ill after encountering environmental pollutants depends on the magnitude of their exposure and their capacity to respond. Exposure and intrinsic response capabilities vary within the population. Those that become ill when the general population remains largely unaffected are considered to be highly susceptible. The U.S. Environmental Protection Agency (USEPA), responsible for protecting the public from environmental pollutants, has developed risk assessment procedures to assist in evaluating the likelihood of health effects. However, the Agency's ability to evaluate the risk faced by highly susceptible populations is often hindered by the paucity of adequate health effects data. Response variability can be assessed with animal models and human epidemiological studies. Although animal models are useful when evaluating the effect of gender and developmental stage on susceptibility, inbred rodent strains underestimate the genetic and lifestyle-induced variability in susceptibility found in human populations. Epidemiological approaches are the preferred source of information on variability. This paper reviews the epidemiological literature from the perspective of a risk assessor seeking data suitable for estimating the risk to highly susceptible populations. Epidemiological approaches do not measure the full range of population response variability. Rather, "susceptibility factors" are evaluated either as risk factors or by focusing on the susceptible population, e.g. children. Susceptibility factors due to genetics, developmental stage, gender, ethnicity, disease state and lifestyle are most frequently encountered. Often, the information describing the health impact of the susceptibility factor is incomplete due to, (1) a failure to consider factors modifying susceptibility; (2) inadequate exposure data; (3) a failure to evaluate the health impact of the susceptibility factor. In addition, for a given exposure agent, several susceptibility factors may be relevant. While incomplete data describing susceptibility factors limits the opportunity for quantitative estimations of risk, available information can supplement qualitative evaluations and risk management.


Some individuals are highly susceptible to disease caused by chemical exposures and this hypersusceptibility can be genetically determined. Because biomarker technology for the determination of genetic predisposition is at the disposal of researchers, the capability therefore exists to include genetic screening in epidemiologic studies. The application of this technological advance in population-based research is, however, fraught with ethical tensions heretofore unknown. Moral duties alone are of limited use in resolving these problems. Scientific documentation is almost always insufficient to
clarify the exact nature of the ethical implications, and ways to deal with uncertainties arising as a result of information generated from genetic screening studies must be considered. The most important tensions relate to autonomy and the right to privacy, fairness and equality, while balancing potential public interest in paternalistic measures. Because no moral framework has been accepted for dealing with this technological advance, an ethical discourse in an open forum is required with all affected parties. Scientists alone, or any other group in isolation, should not expect to resolve these questions, but they should participate in and facilitate the process.

(1996) Multiple chemical sensitivities: distinguishing between psychogenic and toxicodynamic.

The fundamental issue in the multiple chemical sensitivity (MCS) debate is whether this phenomenon is primarily a psychogenic or toxicodynamic disorder, that is, whether symptoms are due to an emotional response to perceived chemical toxicity or to a pathological interaction between chemical agents and organ systems. The distinction between psychogenic or toxicodynamic is essential to the medical management of an MCS patient. A behavioral origin leads to a behavioral therapy, whereas a toxicodynamic etiology may necessitate avoidance and exposure control methodologies. Regulatory, legislative, judicial, and occupational control responses are also dependent upon the critical distinction between psychogenic and organic etiologies. If people are being poisoned by low levels of chemicals, one set of responses follows. If, on the other hand, MCS sufferers are symptomatic for emotional reasons, the response is different. Everything that is known about MCS to date strongly suggests behavioral and psychogenic explanations for symptoms. The premature use of the term multiple chemical sensitivities has hampered effective exploration of and response to this phenomenon, because it suggests, to the lay person, a physiological explanation. It is time that this disorder be properly characterized so that sufferers receive the care they need and so that new "victims" are not recruited.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921550

(1996) [Persons with amalgam problems should be examined from different aspects].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921549

(1996) Sensitive skin and stratum corneum reactivity to household cleaning products.
Goffin, V, Pierard-Franchimont, C and Pierard, GE Journal/Contact Dermatitis. 34: 81-5.

Products intended for individuals with sensitive skin are being increasingly developed by formulators of household cleaning products. However, there is currently no consensus about the definition and recognition of the biological basis of sensitive skin. We sought to determine the relation between the nature of environmental threat perceived as aggressive by panelists, and the stratum corneum reactivity to household cleaning products as measured by the corneosurfametry test. Results indicate substantial differences in irritancy potential between proprietary products. Corneosurfametry data show significant differences in stratum corneum reactivity between, on the one hand, individuals with either non-sensitive skin or skin sensitive to climate/fabrics, and, on the other hand, individuals with detergent-sensitive skin. It is concluded that sensitive skin is not one single condition. Sound information in rating detergent-sensitive skin may be gained by corneosurfametry.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8681562

(1996) Concentration of putrescine in plasma, frontal cortex and hippocampus of rats after systemic administration of the convulsants N-methyl-D-aspartate, pentylentetrazol, picrotoxinine, lindane and 4-aminopyridine.

The motor responses (such as stereotypic behavior or convulsions induced in rats by N-methyl-D-aspartate (NMDA) administered systemically were followed by a rapid, moderate increase in the putrescine concentration in plasma which preceded an increase in this amine in the brain. This effect was not observed following the convulsions evoked by pentylentetrazol, picrotoxinine, lindane or 4-aminopyridine. However, all the convulsants assayed induced a mild increase in the concentration of
putrescine in the frontal cortex and hippocampus. A differential activation of the ornithine decarboxylase (ODC)/polyamine system in both cerebral and peripheral tissues could account for these results.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9035825


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8551916


Fischer, AB and Eikmann, T Journal/Toxicol Lett. 88: 359-64.

In a German kindergarten cockroaches were destroyed by a commercial firm. A preparation containing pyrethrum and its synergist piperonyl butoxide and the organic phosphorus pesticide chlorpyriphos was sprayed. While cleaning the rooms, the staff complained of health effects. Thereupon the kindergarten was closed until further notice, samples were taken by the health authorities for chemical analysis, and an environmental medical evaluation was initiated. The analytical results are presented. The toxicological significance of the employed insecticides, their environmental persistence, and the problems associated with pest control in such institutions are discussed and recommendations given.

BIOSIS COPYRIGHT: BIOL ABS. The purpose of the New Jersey Center for Environmental Hazards Research is to define the illness referred to as Persian Gulf Syndrome (PGS). Our preliminary data indicated that more than half of the Persian Gulf Registry (PGR) veterans reported illness characterized by severe fatigue and symptoms consistent with chemical sensitivities. Therefore, our research approach focuses on investigations of veterans with chronic fatigue syndrome (CFS) and multiple chemical sensitivities (MCS). Project 1 is an epidemiological study of 2800 PGR veterans. Symptoms, indices of Chronic Fatigue (CF) and Chemical Sensitivity (CS), and risk factors will be surveyed with mailed questionnaires. Risk factors include demographics, past medical history, psychosocial variables, Gulf War experiences such as prophylactic medication use, occupational and environmental exposures, and pesticide exposures. Symptoms will be clustered to define Gulf War Syndromes. Significant associations between risk


The present study had two objectives: 1) to determine the characteristics that differentiated subjects with multiple chemical sensitivities (MCS), chemical sensitivities (CS), and chronic fatigue syndrome (CFS); and 2) to evaluate the psychiatric and neuropsychological complaints of these groups relative to normal controls. A cross-sectional comparison was made of the following groups matched for age, sex, and education: 1) patients whose sensitivities to multiple low level chemical exposures began with a defined exposure (MCS; N = 23); 2) patients with sensitivities to multiple chemicals without a clear date of onset (CS; N = 13); 3) patients meeting CDC criteria for Chronic Fatigue Syndrome (CFS; N = 18); and 4) normal controls (N = 18). Subjects with sensitivities to chemicals (MCS and CS) reported significantly more lifestyle changes due to chemical sensitivities and significantly more chemical substances that made them ill compared with chronic fatigue and normal controls. MCS, CS, and CFS patients had significantly higher rates of current psychiatric disorders than normal controls and reported significantly more physical symptoms with no medical explanation. Seventy-four percent of MCS and 61% of CFS did not qualify for any current Axis I psychiatric diagnosis. Chemically sensitive subjects without a defined date of onset (CS) had the highest rate of Axis I psychiatric disorders (69%).
On the MMPI-2, 44% of MCS, 42% of CS, 53% of CFS, and none of the controls achieved clinically significant elevations on scales associated with somatoform disorders. With the exception of one complex test of visual memory, no significant differences were noted among the groups on tests of neuropsychological function. Standardized measures of psychiatric and neuropsychological function did not differentiate subjects with sensitivities to chemicals from those with chronic fatigue. Subjects with sensitivities to chemicals and no clear date of onset had the highest rate of psychiatric morbidity. Standardized neuropsychological tests did not substantiate the cognitive impairment reported symptomatically. Cognitive deficits may become apparent under controlled exposure conditions.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8677287


The purpose of the New Jersey Center for Environmental Hazards Research is to define the illness referred to as Persian Gulf Syndrome (PGS). Our preliminary data indicated that more than half of the Persian Gulf Registry (PGR) veterans reported illness characterized by severe fatigue and symptoms consistent with chemical sensitivities. Therefore, our research approach focuses on investigations of veterans with chronic fatigue syndrome (CFS) and multiple chemical sensitivities (MCS). Project 1 is an epidemiological study of 2800 PGR veterans. Symptoms, indices of Chronic Fatigue (CF) and Chemical Sensitivity (CS), and risk factors will be surveyed with mailed questionnaires. Risk factors include demographics, past medical history, psychosocial variables, Gulf War experiences such as prophylactic medication use, occupational and environmental exposures, and pesticide exposures. Symptoms will be clustered to define Gulf War Syndromes. Significant associations between risk factors and these symptom clusters will also be investigated. Subjects identified as CF, CS, or both will be recruited into Projects 2 and 3. In Project 2, healthy veterans will be compared to veterans with CF, CS, and CF concurrent with CS. Veterans will undergo four studies: (1) viral-immunological, (2) psychiatric, psychological, behavioral, and neuropsychological, (3) autonomic dysregulation, and (4) marker of P4501A2 induction resulting from exposure to combusting material. The purpose of Project 3 is to test the autonomic, immunologic, neuropsychologic, and psychologic responses of veterans with CS or CF to two stressors: controlled chemical exposure and exercise. CS subjects will undergo chemical exposures in our Controlled Environment Facility (CEF) to assess their biologic and psychologic response to low-level exposure. CF subjects will undergo a maximal treadmill exercise test. Circadian patterns of catecholamines and axillary temperature, viral burden, and cardiovascular and endocrine reactivity will be measured in response to this physical stressor. Project 4 is an animal study.
evaluating the interaction between stress and pathology/physiology when rats are predisposed to disease by exposure to Soman or to Dioxin. Two strains of rats that differ in stress reactivity will be used to determine the interaction of hereditary factors and chemical exposure.


Neuropsychological methods for the detection and assessment of toxicity resulting from exposure to neurotoxicants were discussed. Approaches currently utilized in the assessment of neurotoxicity were reviewed. Individual factors which may increase sensitivity to neurotoxicants and sensitivity in symptom detection in low level exposure scenarios were described. These included overall verbal and spatial relations abilities, concentration and attention, motor skills, visuomotor skills, memory, sensation, and affect and personality. Suggestions for improving the reliability and sensitivity for neuropsychological tests were given. Other issues related to the detection of symptoms for multiple chemical sensitivities (MCS) were discussed, such as individual susceptibility and test parameters. The author concludes that improved testing methods are needed for the reliable detection of neurotoxicity among exposed individuals, especially those afflicted with MCS.


BACKGROUND--Although nitric oxide (NO) has been found to have a role in gut inflammation and to modulate immunoglobulin production, little is known about its part in food hypersensitivities. AIM--This study aimed to evaluate the role of NO through the inhibition of constitutive and inducible NO synthase (cNOS and iNOS respectively) on the sensitisation process (antibody titres) and on intestinal anaphylactic responses (colonic hypersecretion upon antigen challenge). ANIMALS AND METHODS--Guinea pigs sensitised to cow's milk proteins were treated either during the sensitisation period or before antigen challenge by N-nitro-L-arginine methyl ester (L-NAME) (inhibiting both cNOS and iNOS) or amino-guanidine (selective iNOS inhibitor).
RESULTS--Chronic treatment by L-NAME or aminoguanidine reduced antibody titres and the secretory response to antigen challenge. In contrast, only L-NAME
administered before challenge was able to antagonise the hypersecretion induced by the challenge. CONCLUSIONS--NO generated by iNOS has a role in the sensitisation process: iNOS inhibition results in lower rates of antibodies leading to a reduced secretory response upon challenge. In contrast, blockade of colonic hypersecretion by L-NAME but not by aminoguanidine suggests that NO via cNOS is a key mediator in intestinal anaphylactic reactions.


(1996) What can research contribute to regulatory decisions about the health risks of multiple chemical sensitivity?

Multiple Chemical Sensitivity (MCS), which may not be caused by chemicals at all, is a serious medical problem of unknown origin and uncertain etiology that raises many fundamental science and policy questions. Regulators, for example, are confronted with a dilemma: what, if anything, should be done to protect people from the scientifically uncertain health risks of exposures to extremely low levels of environmental chemicals. Regulatory agencies, such as the Environmental Protection Agency, do not have the luxury of waiting until conclusive scientific evidence is available before making a decision; however, our present lack of scientific understanding about MCS is so acute that it is not possible to ascertain whether the cause of MCS-related symptoms is chemical, biological, physical, psychosocial, or some combination thereof. Nevertheless, many MCS sufferers and advocates for the chemically induced hypothesis are clamoring for regulatory action to reduce putative health risks from very-low-level exposures to chemicals in the environment. Unless steps are taken to improve the quantity and quality of the existing scientific data base, we cannot, with any acceptable degree of certainty, evaluate the extent to which regulatory decisions about MCS are either protective of public health or cost-effective. This article examines how research can strengthen the scientific basis for risk-related decisions about MCS, and proposes a framework for establishing research directions and priorities. It is argued that high-priority research on MCS is distinguishable by four attributes: (1) results are valuable for risk-related decisions; (2) findings significantly advance scientific knowledge and understanding; and the hypothesis being tested is both (3) biologically plausible and (4) readily testable.


(1996) Bioaccumulated chlorinated hydrocarbons and red/white blood cell parameters.

The potential relationships between chlorinated hydrocarbon contamination in human serum and red/white blood cell profiles were investigated by multivariate techniques to assess the cellular response patterns to high and low organochlorine levels in the serum. Twenty-three healthy control subjects and fourteen patients with unexplained and persistent fatigue were divided on the basis of (a) high or low total organochlorine content, (b) high or low DDE (1,1-dichloro-2,2-bis(p-chlorophenyl) ethene) content, and (c) high or low HCB (hexachlorobenzene) content. Discriminant function analysis revealed that the groups with high organochlorine content had significantly different red white blood cell profiles compared with the low organochlorine groups ((a) P < 0.017, (b) P < 0.015, and (c) P < 0.0002). As a variable, the percentage of neutrophils was the most important discriminant parameter for differentiating between the high and low total organochlorine groups. Thirteen of the fourteen fatigued patients were characterized as "high total organochlorine content" (P < 0.04). The red cell distribution width was elevated in the high DDE group (P < 0.04) and was the most important discriminant parameter for differentiating between the high and low DDE groups. The percentage of eosinophils and the hemoglobin content were both reduced in the high HCB group (P < 0.009, P < 0.003, respectively) and the percentage of eosinophils was the most important discriminant parameter for differentiating between the high and low HCB groups. Those patients with unexplained and persistent fatigue had significantly higher levels of DDE compared with the controls and had different specific blood cell responses to organochlorines compared with control subjects.

---------------------------------------------------------------


---------------------------------------------------------------


Toxicology has two goals. The first is to identify and characterize the adverse effects that can be produced in biological systems by exposure to chemicals and the second is to use this information to predict the type and severity of responses in other species and exposure situations. The tools that the toxicologist uses to detect and describe the adverse effects of chemical exposure include the traditional acute, subchronic, and chronic studies in animals plus a variety of special studies designed to demonstrate specific organ damage, reproductive and teratogenic effects, neurotoxicity,
immunotoxicity, genotoxicity, and other responses. These are often supplemented with studies of the kinetics and the mechanism of action and more recently with studies designed to elucidate the molecular basis for cancer and other effects. Theses studies together with the information on exposure provide the basis for subsequent toxicologic predictions. Although general effects such as weight loss and mortality are included in toxicity protocols, most of the toxicology tests are related to specific end-organ toxicity or to mechanism or behavioral studies. We do not have animal protocols to study individually the subjective symptoms described for multiple chemical sensitivity, such as depression, fatigue, headache, and memory loss, and our tests lack sufficient specificity to evaluate a syndrome which is composed primarily of such symptoms. Since all chemicals can produce adverse effects under some conditions of exposure, toxicologic predictions are most useful when they specify both the type of adverse effect anticipated and the dose required to produce the effect. Multiple chemical sensitivity does not appear to consistently involve specific chemicals or specific adverse effects and the effects observed are reported to lack evidence of a threshold and to occur at extremely low levels. It is difficult to include these parameters in any reasonable toxicologic prediction relating cause and response in multiple chemical sensitivity or similar conditions.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921557

(1996) How to marshal the power of the Americans with Disabilities Act to minimize your company’s exposure to liability to individuals seeking accommodations for "multiple chemical sensitivity disabilities."

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921572


This review article considers evidence regarding the toxicological impact of new carpet emissions on indoor air quality and human health. It compares emissions data from several studies and describes the dominant compounds found in those emissions. The toxicity of each these compounds is assessed for animal and human data, with a focus on inhalation exposure. Data for acute and chronic exposures are presented, and synergistic effects are considered. Differences and similarities between health responses caused by toxicity and/or by immunological reactions are discussed.
Possible neurogenic pathways and associations between these and immune changes are considered as they might relate to inflammatory-based human reactions. Additionally, factors affecting human odor responses are described. The roles that a variety of psychological factors may also play in the etiology of potentially related phenomena, such as the sick building syndrome, pathogenic illness, and multiple chemical sensitivity, are considered. Gaps in the literature are identified within the article and suggestions for future research are offered. In particular, it is noted that few, if any, prior studies have evaluated both neurogenic and immune-mediated inflammation status within the same study. Based on the present information available, it is concluded that under normal environmental circumstances, VOC emissions from new carpets are sufficiently low such that they should not adversely affect indoor air quality or pose significant health risk to people.

(1996) Induction of nitric oxide synthase by chlorinated pesticides (p,p'-DDT, chlordane, endosulfan) in rat liver.

The aim of this study is to investigate the effect of certain polychlorinated pesticides on the induction of rat liver Ca(2+)-independent nitric oxide synthase (NOS) and compare it with the effect of bacterial lipopolysaccharide. Our results show that endosulfan and p, p'-DDT treatment significantly increases the NOS activity while no significant induction by any route of administration was observed in the case of chlordane. Our results show therefore that a wide variety of chlorinated pesticides, which are considered as hepatic tumor promoters, can stimulate the expression of NO synthase in vivo.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9167060

(1996) Substance P and capsaicin-induced mechanical hyperalgesia in the rat knee joint; the involvement of bradykinin B1 and B2 receptors.

1. Substance P (SP) and capsaicin induced a mechanical hyperalgesia when injected into rat knee joints. 2. The NK1 receptor antagonists CP 99994 (10-100 nmol) and RP 67580 (0.1-1 nmol) blocked the development of, and also reversed, SP-induced hyperalgesia. Capsaicin (10 nmol)-induced hyperalgesia was blocked by capsaizepine (0.5-5 nmol). 3. Capsaicin-induced hyperalgesia was prevented and reversed by the NK1 receptor antagonists CP 99994 (100 nmol) and RP 67580 (1 nmol). 4. The bradykinin B2 receptor antagonist icatibant (5 pmol) blocked the development of both SP and capsaicin-induced hyperalgesia. Icatibant (100 pmol kg-1, i.v.) also reversed
an established SP and capsaicin-induced hyperalgesia. 5. Both low dose SP (1 nmol) and capsaicin (1 nmol)-induced hyperalgesia were potentiated by the kininase II inhibitor captopril (100 micrograms). 6. The B1 receptor antagonists desArg9Leu8-bradykinin (BK) (0.5-5 nmol) and desArg10[Hoe 140] (5-50 pmol) only blocked the development of SP-induced hyperalgesia for 30 min after administration. desArg9Leu8-BK (10 nmol kg-1 i.v.) did not reverse an established SP-induced hyperalgesia. 7. Capsaicin-induced hyperalgesia was blocked by desArg9Leu8-BK (0.5 nmol) and this antagonist also reversed an established capsaicin-induced hyperalgesia. 8. Interleukin-1 receptor antagonist (IL-1ra 0.1 microgram) reduced the development of SP-induced hyperalgesia up to 4 h after administration, but did not reverse an established hyperalgesia. IL-1ra (0.1 microgram) also blocked the development of and reversed an established capsaicin-induced hyperalgesia. 9. Indomethacin pretreatment (1 mg kg-1, s.c.) did not reduce the development of either SP- or capsaicin-induced hyperalgesia but following indomethacin-pretreatment desArg9Leu8-BK (10 nmol kg-1, i.v.) failed to reverse a capsaicin-induced hyperalgesia. 10. In conclusion, both SP and capsaicin can induce behavioural hyperalgesia when injected into the knee joint of rats. In addition, blockade of NK1, bradykinin B1, B2 and IL-1 beta receptors can substantially modulate this hyperalgesia.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8864563


Self-reported information about health and mental health status and history on (a) three diverse samples of individuals who reported multiple chemical sensitivities syndrome (n = 60) and (b) one sample of the general population (n = 60) was collected by telephone interview. Subjects from the general population were selected randomly from the telephone directory and were matched for age, gender, and socioeconomic status with index subjects. Data on an additional 10 subjects with multiple chemical sensitivities syndrome were also available for comparison on many of the variables of interest. The four diverse groups of patients with multiple chemical sensitivities syndrome had very similar general and specific indices of illness and sensitivity to chemicals. Members of the general population reported mild sensitivity to chemicals, and even those with more sensitivity differed from the multiple chemical sensitivities syndrome groups with respect to number and types of symptoms reported, duration and frequency of response, and associated features. Multiple chemical sensitivities syndrome was associated consistently with only one psychiatric variable, elevated negative affect scores, which were correlated significantly with the presence of illness. Patients with multiple chemical sensitivities syndrome from the diverse samples had
very similar characteristic features, despite whether they had or had not received treatment by clinical ecologists.


(1996) **Multiple chemical sensitivity syndrome: the wavering influence of the courts on public policy.**


(1996) **Environmental illness and multiple chemical sensitivity.**


(1996) **Beyond Dobris: a continent commits to change.**

(1996) **Exposure and sensitization to environmental allergen of predominantly Hispanic children with asthma in San Diego's inner city.**

BACKGROUND: Environmental living conditions co-sorting with economic status may influence the disease morbidity rate of childhood asthma in ethnic minority urban poor populations. OBJECTIVES: This study was carried out to assess exposure and sensitization to environmental allergens in southeast San Diego children with current asthma-related symptoms and to determine the utility of environmental control measures. METHODS: Children, 9 to 12 years old, with current asthma-related symptoms were identified and enrolled at four school sites. Skin prick testing with
aeroallergens was performed, and allergen in collected dust (from mattresses, pillows, and bedroom carpets) was quantified by enzyme immunoassay. Environmental control instruction and products were provided. RESULTS: Of 41 subjects who underwent skin testing, 51.2% were reactive to environmental allergens (39% to mite, 22% to cockroach, and 9.8% to cat). Mean allergen levels for sensitized subjects were: Der p 1 (11 subjects), 18,722 ng/gm dust; Der f 1 (8 subjects), 5345 ng/gm dust; Fel d 1 (3 subjects), 214 ng/gm dust; Bla 1 (8 subjects), 7.15 U/gm dust; and Bla 2 (8 subjects) 7.13 U/gm dust. Environmental allergen exposure levels were not significantly different between sensitized and nonsensitized subjects. Environmental control measures for mite exposure were completed in six homes of sensitized subjects. One month after treatment, allergen levels fell 91.2% for Der p 1, 98.9% for Der f 1, and 88.2% for Fel d 1. One year after treatment, mite and cat allergen levels remained low. Environmental control had no consistent impact on cockroach allergen levels. CONCLUSION: Environmental allergen sensitization and exposure may be cofactors contributing to increased disease severity in urban poor populations.

(1996) Increased response to antigen and histamine release in smaller sensitized canine bronchi.
Chitano, P, Sigurdssohn, SB, Stephens, AM, Becker, AB, Kepron, W and Stephens, NL
Journal/Respir Physiol. 103: 253-61.

We studied the Schultz-Dale response in vitro in large and small size branches from 3rd to 6th generation bronchi from ragweed-sensitized dogs. The response to electric field stimulation (EFS) increased after antigen from 65.56 +/- 8.11 to 78.6 +/- 9.0 mN mm2 of smooth muscle (P < 0.01), but no topographical difference was observed. The response to ragweed (% of the response to EFS) was 158.3 +/- 12 and 67.1 +/- 11.7 in strips from small and large branches respectively (P < 0.01), while no difference was observed between generations; when clustering bronchi according to dimension, it was 129.9 +/- 13.4 in small and 71.9 +/- 19.8 in large bronchi (P < 0.01). Histamine released from small and large branches was 2.90 +/- 1.01 and 0.76 +/- 0.20 (ng/mg of tissue) respectively (P < 0.05); no difference was found between generations. In conclusion, in sensitized dogs a greater response to antigen, which involves a higher histamine release, occurs in small compared to large bronchi. We suggest that control of distribution of ventilation occurs mainly at small bronchi level, which becomes the elective tissue to study the Schultz-Dale response. Finally, the classification of bronchi into generations is inadequate to study allergic bronchospasm.


This paper provides an historical assessment of the development of the concepts of pharmaco- and ecogenetics, including their relationship to major developments in the areas of pharmacology, industrial hygiene, and cancer research in animal models as well as the assessment of inborn metabolic disorders. How this information may be used to evaluate the range of human genetic diversity and its relationship to differential responses to environmental toxins is also considered. The paper concludes by providing a brief summary of several specific conditions in which human genetics traits affect susceptibility to toxic substances.

(1996) [Unconventional concepts in environmental medicine].
Burkhard, B Journal/Versicherungsmedizin. 48: 179-84.

More and more people are convinced to be afflicted with diseases caused by ill-defined environmental factors. Until now it has also not been possible to delineate unambiguously common features to describe a syndrome-like pattern which is the essential requirement for rational prophylactic and therapeutic intervention. Despite of this scientific status a wide variety of supposedly diagnostic and therapeutic methods of unproven efficacy is currently advertised and often applied in a polypragmatic manner. Besides providing a description of the different techniques their clinical relevance is critically evaluated.

Brod, BA Journal/Am J Contact Dermat. 7: 202-11.

Multiple chemical sensitivities (MCS) syndrome is a controversial diagnosis that has arisen in the latter half of the 20th century. Clinical ecologists strongly believe that multiple common environmental chemicals assault the immune system in certain individuals, producing multisystem disease. Mainstream medicine, however, largely believes that the symptoms of MCS syndrome can be attributed to a conditioned response to the environment and psychiatric disease. This review examines the
controversy surrounding MCS syndrome in regard to the etiology, diagnosis, and management.


Braun, M Journal/Hear Res. 97: 1-10.

The mechanical function of the basilar membrane (BM) in the mammalian cochlea has been newly debated after the discovery of frequency selectivity of single hair cells. Decisive information on this matter can be expected from hydropic ears, since hydrops presumably alters cochlear mechanics by (1) impeding BM motion and (2) uncoupling outer hair cell (OHC) stereocilia from the tectorial membrane (TM). Therefore hearing in Meniere's disease (MD) was examined analysing data on epidemiology of MD types and audiogram types, 2f thresholds, over-recruitment, loudness intolerance, and otoacoustic emissions. Further, hearing in experimental hydrops (XH) was examined analysing data on: morphological changes on TM and OHCs in relation to hydrops duration; morphological and electrophysiological changes upon acoustic overstimulation. The results were unequivocal on two points: (1) co-occurrence of hydrops and normal hearing thresholds can appear both in MD and XH, (2) co-occurrence of non-hearing-loss hydrops and loudness hypersensitivity is typical both in MD and XH. The conclusion is that BM motion apparently is no necessary element in the chain of cochlear sound transmission but obviously is an auxiliary element for overload protection through resonant absorption. The results are further indicative of audiometric methods for an early detection of incipient MD.


The results of a symptom checklist of three matched-pair studies (N = 460) of the following exposed groups are presented: Study 1, a primarily white community (N = 220) environmentally exposed to the pesticide metam sodium; Study 2, a Hispanic group (N = 180) who worked in a microelectronics plant and had extensive past exposure (M = 6.7 yrs) to multiple organic hydrocarbon solvents; and Study 3, an African-American group (N = 168) environmentally exposed to sulfuric acid. Each exposed group was compared to a matched (race, age +/- 3 years, gender, education +/- 2 years and number of children) unexposed reference group, resulting in 90 pairs...
for the white metam sodium group, 62 pairs for the Hispanic organic solvent group, and 78 pairs for the African-American sulfuric acid group. Symptom prevalence rates and relative risk ratios show very strong associations: in Study 1, the relative risk for all 33 symptoms ranged from 1.5 to 37; in Study 2, the relative risk for 31 of the symptoms ranged from 1.5 to 11.1; and in Study 3, the relative risk for 16 of the symptoms ranged from 1.5 to 6. Mann Whitney U results of each symptom indicate significantly greater symptomatology in the exposed vs. the reference groups in all three studies: in Study 1, at p < .01 for all 33 symptoms; in Study 2, at p < .01 for 31 symptoms, and p < .05 for one additional symptom; and in Study 3, at p < .01 for 24 symptoms and p < .05 for another three symptoms. These results suggest a robust symptom complex following chemical exposure regardless of specific chemical.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9086503


Individuals with Multiple Chemical Sensitivities (MCS) frequently report difficulties in attention/concentration, memory and accuracy and speed of problem solving. We evaluated neurobehavioral functioning in 35 chemically exposed patients referred to our Occupational and Environmental Neurology Clinic. Of these 35 patients, 17 presented with symptoms of MCS and 16 patients reported no symptoms of MCS. In addition, we used a group of 126 healthy controls for comparison. The performance of the MCS group was not significantly different from that of the control group on tests of verbal learning and memory, executive functioning, and psychomotor functioning. The MCS group performed below the control group on a test of visual learning and memory, but this performance was similar to the group with chemical exposure and no MCS. Therefore, performance on objective neurobehavioral tests did not confirm the most frequently reported subjective complaints of patients with MCS. These results suggests that patients with symptoms of MCS do not have compromised central nervous system functioning.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921556


Individuals with multiple chemical sensitivity (MCS) report decreased attention concentration, memory loss, disorientation, confusion, fatigue, depression, irritability,
decreased libido, sleep disturbances, headaches, and weakness. These neurobehavioral symptoms represent possible alterations in the central nervous system (CNS). The evaluation of neurobehavioral functioning using neuropsychological techniques provides an indirect method for determining the integrity of the CNS. However, caution must be used in interpreting neuropsychological test results, since this technique is extremely sensitive but is not specific. Clinically significant aberrant test performance may be noted after chemical exposure as well as with other diseases of the CNS. In addition, neuropsychiatric conditions such as anxiety and depression are often manifested as cognitive difficulties that are similar in pattern to the cognitive dysfunction caused by toxic chemicals. Herein, limitations and cautions in the interpretations of neuropsychological test results are discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921555

---------------------------------------------------------------------


---------------------------------------------------------------------

(1996) Psychiatric perspective of persons with "environmental illness".

---------------------------------------------------------------------

(1996) Iatrogenic (physician-induced) hypochondriasis. Four patient examples of "chemical sensitivity".

---------------------------------------------------------------------

(1996) Effect of c-kit ligand, stem cell factor, on mediator release by human intestinal mast cells isolated from patients with inflammatory bowel disease and controls.
The regulation of mediator release in human intestinal mast cells is largely unknown. Apart from IgE receptor crosslinking no secretagogues have been described so far. This study examined the effect of two cytokines (c-kit ligand and interleukin 3) and other agonists on human intestinal mast cell function. Cells were isolated from surgery specimens of 47 patients undergoing intestinal resection because of tumours or inflammatory bowel disease. Cell suspensions contained 3.6% mast cells (mean of 50 experiments). After preincubation without or with c-kit ligand or interleukin 3, cells were stimulated by IgE receptor crosslinking, C5a or formyl-methionyl-leucyl-phenylalanine (fMLP). Histamine and sulphidoleukotriene release was measured in supernatants. The sequential stimulation of the cells with c-kit ligand and IgE receptor crosslinking induced the release of high amounts of histamine and leukotrienes, whereas each agonist by itself induced only marginal mediator release. Interleukin 3 induced no release by itself, but enhanced the IgE receptor dependent release, possibly by an indirect mechanism. No significant mediator release was seen in response to C5a and fMLP, even if the cells were pretreated with c-kit ligand. The mediator release, particularly that of leukotrienes, was higher in cells isolated from actively inflamed tissue from patients with inflammatory bowel disease compared with controls. In conclusion, it was found that, apart from IgE receptor crosslinking, c-kit ligand and interleukin 3 regulate mediator release in human intestinal mast cells. The enhancement of mediator release by cytokines may be of particular relevance in the pathogenesis of inflammatory bowel diseases and food intolerance reactions.

(1996) Multiple chemical sensitivity: state of the art symposium. The role of chemical allergens.  

Multiple chemical sensitivity (MCS) has been defined as "an acquired disorder of recurrent symptoms, referable to multiple organ systems, occurring in response to chemically unrelated compounds at doses far below those established in the general population to cause harmful effects" [Cullen, State Art Rev. Occup. Med. 2, 655 (1987)]. The pathophysiologic basis for the MCS syndrome has not been clearly defined. However, allergic reactions to specific chemicals encountered in the environment are much better understood.


(1996) Slowed reaction time performance on a divided attention task in elderly with environmental chemical odor intolerance.  
Previous research has suggested an association between the subjective report of illness from environmental chemical odors and poorer cognitive task performance in persons with industrial levels of xenobiotic exposures. The present study investigated baseline morning performance on a computerized divided attention task in active retired adults without occupational exposures or clinical disorders who nonetheless rated themselves currently high versus low in episodic illness from the odor of certain environmental chemicals. The chemically intolerant group showed slower reaction times in registering both centrally and peripherally placed stimuli, but no difference in making target tracking errors. Measures of negative affect did not account for these findings. Taken together with evidence for heightened neurobehavioral sensitization in this population, the data suggest disturbances in allocation of attention and related cognitive functions.

---------------------------------------------------------------


This paper summarizes the key features of the olfactory-limbic, neural sensitization model for multiple chemical sensitivity (MCS) and presents relevant data on chemically intolerant human subjects from laboratory studies using quantitative electroencephalography, polysomnography, neuropsychological tests, cardiovascular measurements, and blood markers. MCS is a poorly understood chronic, polysymptomatic condition in which some prior controlled research studies have failed to find evidence to differentiate active from placebo tests. Closer examination of past MCS research, however, reveals that studies have failed to incorporate the design and methodological approaches necessary to test for nonimmunological sensitization. Time-dependent sensitization (TDS) is a well-documented phenomenon in the pharmacology literature involving the progressive increase in a given response by the passage of time between the initial and subsequent exposures to a substance or a stressor. As in MCS, multiple, chemically unrelated agents can trigger TDS. Females time-sensitize more readily than do males. Pharmacological and nonpharmacological (stress) stimuli can cross-sensitize. Dopaminergic pathways in the brain and the hypothalamic-pituitary-adrenal axis are likely involved in TDS. Data on the symptomatology of MCS point to central nervous system involvement, including limbic regions that receive input from both olfactory (odor) and trigeminal (irritant) pathways. Limbic and mesolimbic brain regions are among the most sensitizable to repeated, intermittent environmental stimuli. Sensitizable individuals can show no difference or lesser responses to a test substance on initial exposure, but later exhibit much greater increases in responsivity on the next exposure after a period of days. For future research, it is essential to distinguish chemical intolerance symptoms such as derealization, sudden mood changes, musculoskeletal pain, menstrual dysfunction, and uncontrollable sleepiness from chemical phobia and avoidance behaviors. This
model permits hypothesis-driven research on MCS and has major implications for interpretation of apparently positive and negative tests for "true" as opposed to "perceived" sensitivity to low levels of environmental chemicals.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8921554

---------------------------------------------------------------


The psychological, neuropsychiatric, and somatic characteristics of young adults who have different degrees of cacosmia (i.e., feeling "ill" from the odor of xenobiotic chemicals) and who have self-described "chemical sensitivity" were examined. A total of 800 college students completed the following: a self-rating scale for frequency of odor intolerance for 10 common substances, Simon Environmental Illness Symptom Survey, the SCL-90-R, Barsky Amplification Scale, Pearlin-Schooler Mastery Scale, Cheek-Buss and Kagan Shyness scales, Marlowe-Crowne Social Desirability Scale, and a health-symptom and physician-diagnosed checklist. Two pairs of groups were compared: (1) subjects in the top 16% (i.e., cacosmics) and bottom 15% (noncacosmics) of the sample with respect to odor intolerance scale scores; and (2) subjects from the entire sample who did (28%) or did not (72%) consider themselves to be "especially sensitive to certain chemicals." Cacosmics and the chemically sensitive subjects scored significantly higher on measures of psychological distress and amplification of somatic symptoms, but there was little evidence of lifestyle change, as assessed by the Simon Survey. Compared with their respective comparison groups, cacosmic and chemically sensitive groups had significantly higher incidences of illnesses associated with chemicals, alcohol intake, opiate drug use, and caffeine use, even after controlling for the psychological measures and histories of atopic allergy. Subjects with and without neuropsychiatric symptoms were differentiated with respect to chemical odor intolerance, but subjects with and without atopic allergies and possible autoimmune diseases were differentiated with respect to chemical sensitivity. Females were more cacosmic than males. Cacosmia is defined by a population subset, with or without occupational xenobiotic exposures or disability, that has distress and symptom amplification and neuropsychiatric and somatic symptoms, none of which are explained fully by psychological measures. Prospective clinical studies are possible with such individuals. The data are also consistent with a time-dependent sensitization model for illness from low-level chemical exposures.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8629870
Bell, IR, Bootzin, RR, Ritenbaugh, C, Wyatt, JK, DeGiovanni, G, Kulinovich, T, Anthony, JL, Kuo, TF, Rider, SP, Peterson, JM, Schwartz, GE and Johnson, KA

Subjective sleep complaints and food intolerances, especially to milk products, are frequent symptoms of individuals who also report intolerance for low-level odors of various environmental chemicals. The purpose of the present study was to evaluate the objective nature of nocturnal sleep patterns during different diets, using polysomnography in community older adults with self-reported illness from chemical odors. Those high in chemical odor intolerance (n = 15) exhibited significantly lower sleep efficiency (p = .005) and lower rapid-eye-movement (REM) sleep percent (p = .04), with a trend toward longer latency to REM sleep (p = .07), than did those low in chemical intolerance (n = 15), especially on dairy-containing as compared with nondairy (soy) diets. The arousal pattern of the chemical odor intolerant group differed from the polysomnographic features of major depression, classical organophosphate toxicity, and subjective insomnia without objective findings. The findings suggest that community elderly with moderate chemical odor intolerance and minimal sleep complaints exhibit objectively poorer sleep than do their normal peers. Individual differences in underlying brain function may help generate these observations. The data support the need for similar studies in clinical populations with chemical odor intolerance, such as multiple chemical sensitivity patients and perhaps certain veterans with "Persian Gulf Syndrome."

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8793044

Bell, IR, Bootzin, RR, Davis, TP, Hau, V, Ritenbaugh, C, Johnson, KA and Schwartz, GE

This study examined plasma beta-endorphin as a marker of the physiological stress response in community elderly who were either high (n = 15) or low (n = 15) in self-rated frequency of illness from environmental chemical odors. Individuals who report nonatopic multiple sensitivities to or intolerances for low levels of environmental chemicals also claim high rates of comorbid food sensitivities or intolerances. Subjects gave 9 AM blood samples for plasma beta-endorphin 90 min after ingesting either 1% fat cow's milk or a soy-based nondairy drink, on six different mornings in the laboratory after all-night sleep recordings. The six sessions were divided into three sets of two successive days each, with each set involving baseline (ad lib milk), nondairy...
(soy-based), and dairy diets] separated from the next by 3 weeks. In the chemically tolerant subjects, stably lower beta-endorphin levels suggested that milk may have been a physiologically less stressful beverage than was the soy drink. In contrast, the chemical odor intolerant group exhibited a) increased levels of plasma beta-endorphin averaged over the 6 days ($p = .02$); and b) marked fluctuations in endorphin from one laboratory day to the next (Group x Diet x Day interaction, $p = .005$). The findings were consistent with time-dependent, context-dependent sensitization of beta-endorphin in the chemical odor intolerant individuals.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8793045

---------------------------------------------------------------

**1996**  Clinically relevant EEG studies and psychophysiological findings: possible neural mechanisms for multiple chemical sensitivity.
Bell, IR Journal/Toxicology. 111: 101-17.

This paper addresses the evidence for the face, construct, and criterion-related validity of the olfactory-limbic/neural sensitization model for multiple chemical sensitivity (MCS). MCS is a poorly-understood, controversial condition in which low levels of environmental chemicals are reported to trigger disabling levels of illness in certain individuals. Neural sensitization processes could generate an endogenous amplification of responsivity to exogenous substances, thereby providing a plausible explanation for the apparent lack of a classical toxicological dose-response relationship in MCS. Convergent data from both survey and psychophysiological studies of MCS patients and of persons from the community without MCS, but who report elevated frequency of illness from chemical odors (cacosmics), support the involvement of the limbic system and the sensitizability of cacosmics, as predicted by the model. Recent studies show that cacosmics do sensitize their heart rate, blood pressure, and plasma beta-endorphin responses to repeated exposures to a novel laboratory procedure involving dietary manipulations over time. Cacosmia may represent a pathological form of neural plasticity. Taken together, the model and the available evidence suggest the need for more intensive investigation of MCS from the standpoint of possible neurobiological mechanisms affecting cognitive, emotional, and somatic functions.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8711727

---------------------------------------------------------------

**1996**  [Environmental diseases, diseases of the 21st century? Multiple chemical hypersensitivity].

Human variability can be addressed during each stage in the risk assessment of chemicals causing noncancer toxicities. Noncancer toxicities arising from oral exposure to trichloroethylene (TCE) are used in this paper as a case study for exploring strategies for identifying and incorporating information about human variability in the chemical specific hazard identification and dose-response assessment steps. Toxicity testing in laboratory rodents is the most commonly used method for hazard identification. By using animal models for sensitive populations, such as developing fetuses, testing can identify some potentially sensitive populations. A large variety of reproductive and developmental studies with TCE were reviewed. The results were mostly negative and the limited positive findings generally occurred at doses similar to those causing liver and kidney toxicity. Physiologically based pharmacokinetic modeling using Monte Carlo simulation is one method for evaluating human variability in the dose-response assessment. Three strategies for obtaining data describing this variability for TCE are discussed: (1) using in vivo human pharmacokinetic data for TCE and its metabolites, (2) studying metabolism in vitro, and (3) identifying the responsible enzymes and their variability. A review of important steps in the metabolic pathways for TCE describes known metabolic variabilities including genetic polymorphisms, enzyme induction, and disease states. A significant problem for incorporating data on pharmacokinetic variability is a lack of information on how it relates to alterations in toxicity. Response modeling is still largely limited to empirical methods due to the lack of knowledge about toxicodynamic processes. Empirical methods, such as reduction of the No-Observed-Adverse-Effect-Level or a Benchmark Dose by uncertainty factors, incorporate human variability only qualitatively by use of an uncertainty factor. As improved data and methods for biologically based dose-response assessment become available, use of quantitative information about variability will increase in the risk assessment of chemicals.

Ashford, NA and Miller, CS Journal/Int Arch Occup Environ Health. 68: 367-76.


In the current review, a biopsychosocial perspective is applied to current changes in the health of populations. It is proposed that the psychosocial environments either promote health or precipitate disease. Changes in the types of stress that people experience as well as its prevalence over time are discussed. In addition, possible biological mechanisms linking the psychosocial environments to health are presented. "Food for thought" is the possible interaction between the physical/chemical and the psychosocial environments and changes in health of individuals. Clearly, our traditional view of disease mechanisms is not sufficient to understand recent phenomena, such as environmental illness and chronic fatigue syndrome. Issues worthy of further discussions are the role of the "just-in-time" society, where individuals increasingly have to change jobs, cope with reorganizations and increased production pressure, and its impact on health and well-being. Further, in what way can we develop better models to truly assess the impact of an increasingly complex interaction between individual and environmental factors on health? A major obstacle to enhancing our understanding of causes of change in the health of populations is the use of inappropriate or outdated statistical analytical models. Finally, it is suggested that prospectively controlled studies of the impact on health of changes in the health and welfare systems are carried out. This would further add to our understanding of factors contributing to changes in the health of population.


Many recreational and elite runners participate in distance races each year. When these events are conducted in hot or cold conditions, the risk of environmental illness increases. However, exertional hyperthermia, hypothermia, dehydration, and other
related problems may be minimized with pre-event education and preparation. This position stand provides recommendations for the medical director and other race officials in the following areas: scheduling; organizing personnel, facilities, supplies, equipment, and communication; providing competitor education; measuring environmental stress; providing fluids; and avoiding potential legal liabilities. This document also describes the predisposing conditions, recognition, and treatment of the four most common environmental illnesses: heat exhaustion, heatstroke, hypothermia, and frostbite. The objectives of this position stand are: 1) To educate distance running event officials and participants about the most common forms of environmental illness including predisposing conditions, warning signs, susceptibility, and incidence reduction. 2) To advise race officials of their legal responsibilities and potential liability with regard to event safety and injury prevention. 3) To recommend that race officials consult local weather archives and plan events at times likely to be of low environmental stress to minimize detrimental effects on participants. 4) To encourage race officials to warn participants about environmental stress on race day and its implications for heat and cold illness. 5) To inform race officials of preventive actions that may reduce debilitation and environmental illness. 6) To describe the personnel, equipment, and supplies necessary to reduce and treat cases of collapse and environmental illness.


Patients with odor-triggered symptoms, meeting the case definition of multiple chemical sensitivities (MCS), continue to be seen in our institution and other health science centers [Amundsen, Mayo Clinic Dept. Intern. Med. Newslett. 9(1) (1986)]. The term MCS, unfortunately, feeds the thesis that symptoms are allergic-immune system in origin, a theory that has not withstood scientific scrutiny [American College of Physicians, Ann. Intern. Med. 111, 168-178 (1989); Terr, Ann. Intern. Med. 119, 163-164 (1993)]. It has been proposed that some of these cases may be examples of classical (Pavlovian) conditioning: many MCS patients meet diagnostic criteria for psychiatric illnesses, especially mood, anxiety, and somatoform disorders. Attention is turning to the complex relationship between olfactory stimulation, memory, and mood (psyche) in an attempt to understand why some individuals develop odor aversion symptoms and how to best manage these, frequently, severely disabled patients. Two subjects with typical odor-triggered symptoms have been treated, using behavioral medicine techniques, with marked improvement in both cases. The term "odor aversion" is proposed rather than MCS to describe patients with these symptoms.

(1996) Neurological investigations in 23 cases of pyrethroid intoxication reported to the German Federal Health Office.

In 1993, 64 cases of chronic pyrethroid intoxication were reported to the Federal Health Office in Germany. Shortly afterwards the media spoke of thousands of cases of pyrethroid intoxication in homes. 23 of the persons reported were examined in a neurological department on an inpatient basis using clinical neurological, neuroradiological and laboratory investigations, including the examination of pyrethroid values in blood and urine. The pyrethroid exposure involved carpets, moth killers, pesticide sprays and wood preservatives. Nine of the cases presented with severe somatic or psychiatric disorders with completely different clinical diagnoses, such as pituitary tumor, radiogenic lumbosacral plexus paralysis, Guillain- Barre syndrome, spinal muscular atrophy, with no plausible relationship to exposure. Eight cases presented with multiple chemical sensitivity syndrome (MCS) and normal somatic findings. In six of the cases, a causal link between acute complaints and pyrethroid exposure could be established or not ruled out. There was, however, not a single case in which evidence for irreversible PNS or CNS lesions could be found.


Of the three-quarters of a million service personnel involved in the Persian Gulf War, approximately 30,000 have complained of neurological symptoms of unknown etiology. One contributing factor to the emergence of such symptoms may be the simultaneous exposure to multiple agents used to protect the health of service personnel, in particular, the anti-nerve agent pyridostigmine bromide (PB; 3-dimethylaminocarbonyloxy-N-methylpyridinium bromide), the insect repellent DEET (N,N-diethyl-m-toluamide), and the insecticide permethrin (3-(2,2-dichloro-ethenyl)-2,2-dimethylcyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester). This study investigated neurotoxicity produced in hens by individual or simultaneous exposure to these agents (5 d/wk for 2 months to 5 mg kg/d PB in water, po; 500 mg/kg/d DEET, neat, sc; and 500 mg/kg/d permethrin in corn oil, sc). At these dosages, exposure to single compounds resulted in minimal toxicity. Combinations of two agents produced greater neurotoxicity than that caused by individual agents. Neurotoxicity was further enhanced following concurrent administration of all three agents. We hypothesize that competition for liver and plasma
esterases by these compounds leads to their decreased breakdown and increased transport of the parent compound to nervous tissues. Thus, carbamylation of peripheral esterases by PB reduces the hydrolysis of DEET and permethrin and increases their availability to the nervous system. In effect, PB "pumps" more DEET and permethrin into the central nervous system. Consistent with this hypothesis, hens exposed to the combination of the three agents exhibited neuropathological lesions with several characteristics similar to those previously reported in studies of near-lethal doses of DEET and permethrin. If this hypothesis is correct, then blood and liver esterases play an important "buffering" role in protecting against neurotoxicity in the population at large. It also suggests that individuals with low plasma esterase activity may be predisposed to neurologic deficits produced by exposure to certain chemical mixtures.

(1996) Increased neurotoxicity following concurrent exposure to pyridostigmine bromide, DEET, and chlorpyrifos.

The operating environment of the service personnel during the Persian Gulf War involved psychological, biological, and chemical elements including exposure to pesticides such as the insect repellent DEET (N,N-diethyl-m-toluamide) and the insecticide chlorpyrifos (O,O-diethyl O-3,5,6-trichloropyridinyl phosphorothioate) and to pyridostigmine bromide (PB,3-dimethylaminocarbonyloxy-N-methylpyridinium bromide) that was administered as a prophylactic agent against possible nerve gas attack. The present study was designed to determine the toxicity produced by individual or coexposure of hens 5 days/week for 2 months to 5 mg PB/kg/day in water, by gavage; 500 mg DEET/kg/day, neat, sc; and 10 mg chlorpyrifos kg/day in corn oil, sc. Coexposure to various binary treatments produced greater neurotoxicity than that caused by individual exposures and was characterized by severe neurologic deficit and neuropathological alterations. Also, neurotoxicity was further enhanced following concurrent administration of the three chemicals. Severe inhibition of plasma butyrylcholinesterase (BuChE) activity was produced in hens treated with PB (activity 17% of control) compared to those treated with chlorpyrifos (activity 51% of control) or DEET (activity 83% of control). BuChE inhibition was further increased in binary and tertiary treatment groups compared to individual treatment groups. In contrast, a significant inhibition of brain acetylcholinesterase (AChE) was produced in hens administered chlorpyrifos alone (activity 67% of control), while those given chlorpyrifos in combination with other compounds exhibited a significant inhibition of brain AChE activity ranging from 43 to 76%. Brain neurotoxicity target esterase (NTE) was not inhibited in any of the individual treatment groups or PB/DEET, but was significantly inhibited and had activity expressed as a percentage of control in groups administered combined chlorpyrifos with PB of 73% or DEET of 74% and in the tertiary treatment group of 71%. We hypothesize that test compounds may compete for xenobiotic metabolizing enzymes in the liver and blood and may also compromise the integrity of
the blood-brain barrier, leading to an increase in their "effective concentrations" in the nervous system to levels equivalent to the toxic doses of individual compounds. This is consistent with the present observation of increases in (1) the inhibition of brain AChE and NTE, (2) the extent of neurologic dysfunction, and (3) the severity and frequency of neuropathologic lesions in the combined treatment groups compared to those administered individual compounds.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9082485


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7490998

Mediating processes can be inferred from self-report data only if it can be assumed that the patient has a valid capacity for introspection. That assumption is invalid when beliefs can be shown to influence sensory perception and symptom reports. Another serious limitation of self-reporting is that the individual has only a limited awareness of his or her psychological state. Also, we cannot ignore the observations that come from the psychodynamic tradition, that unconscious or subconscious ideas also can affect and distort self-reporting. The lack of validity of self-reports is summarized by Brewin: "[T]he value of self-reports would appear to be more in their relation to intentional future actions than in any insight they might provide into complex feeling states or into the contingencies governing past behavior." A more objective procedure for obtaining information about EI/MCS patients' beliefs is clearly needed before their symptom reports can be taken at face value.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7670917


After describing two patients seen by the author, we define multiple chemical sensitivities and discuss the scope of the problem and the epidemiology. Although the incidence of multiple chemical sensitivities is not known, the demographics are similar to that of agoraphobia. The classical conditioning model is proposed as a useful description of multiple chemical sensitivities. The desensitization approach to the diagnosis and treatment is proposed. Results with three patients were encouraging and the approach seems worthy of further evaluation and refinement.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7897764


The relationship between hematological variables and the ability to perform behaviorally in two learning tests was evaluated in male F344 rats aged 22-24 months. Rats were screened for ability to meet criterion for learning one-way active avoidance in a straight runway task. Rats failing to meet criterion were given no further testing and were assigned to Group 1 (G1). Rats meeting criterion were tested in a 14-unit T-maze (2 days, 10 trials/day). Failure to negotiate the T-maze within 600 s on any three trials resulted in assignment to Group 2 (G2) with no further testing. Rats successfully completing both tasks constituted Group 3 (G3). Trunk blood was collected following behavioral testing and was assayed to determine red blood cell count (RBC), hematocrit (HCT), hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC), bands (BND), polymorphs (POLY), lymphocytes (LYM), monocytes (MON), and eosinophils (EOS). The combined G1/G2 group had significantly lower RBC, HCT, HGB, and EOS but significantly higher MCV and MCH than G3 rats. Correlation analysis revealed a positive relationship of group membership (i.e., learning test completion) to RBC, HCT, HGB, and EOS, but a negative correlation of group membership to MCH. No significant correlation emerged between any hematological characteristic and performance in either behavioral task. These results suggest that a simple blood test to determine HCT may be a useful screen for removal of moribund rats from aging studies attempting to control for effects of health on behavioral performance in rodent models.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7713339


Taste and smell are chemical senses that play a crucial role in food selection. Damage to taste and smell receptors can impair food intake, nutritional status, and survival. The purpose of this study was to determine the effects of 11 environmental pollutants (nine insecticides and two herbicides) on electrophysiological taste responses in the gerbil. Integrated chorda tympani (CT) recordings were obtained from gerbils to a range of tastants before and after a 4-min application of 1 of 11 environmental pollutants. The taste stimuli were: sodium chloride (100 mM), calcium chloride (300 mM), magnesium chloride (100 mM), HCl (10 mM), potassium chloride (500 mM), monosodium glutamate (MSG) (50 mM), sucrose (100 mM), fructose (300 mM), sodium saccharin (10 mM), quinine HCl (30 mM), and urea (2 M). The nine insecticides included organophosphorous, carbamate, and pyrethroid insecticides. The seven organophosphorous insecticides tested were: acephate, carbofuran, chlorpyrifos, chlorpyrifos oxon, demeton, malathion, and methamidophos. The carbamate insecticide carbaryl and the pyrethroid insecticide fenvalerate were also tested. Two herbicides, paraquat and glyphosate, were tested, and dose-response curves for each of these two herbicides were also determined. All of the 11 insecticides and herbicides had an effect on some of the taste stimuli tested. Application of 10 mM methamidophos exhibited the greatest amount of suppression on the 11 taste solutions. Each taste stimulus was significantly suppressed with the exception of 2 M urea. Herbicides paraquat and glyphosate also reduced responses to several tastants. These data indicate that environmental pollutants can modify taste responses in the gerbil.


A 44 year old woman is described who appears to have idiopathic anaphylaxis triggered by chemical odors. Her case and a general discussion of anaphylaxis are...
presented. The known causes of anaphylaxis and a discourse on idiopathic anaphylaxis are given. The treatment of idiopathic anaphylaxis is discussed.


(1995) The environment was right for Nova Scotia's new environmental health clinic.

With a $1-million contribution from the Nova Scotia government, Dalhousie University medical school is establishing an environmental health clinic that will research and treat the controversial condition known as multiple-chemical sensitivity. Already several hundred Nova Scotians, including about 100 former employees of Halifax's Camp Hill Hospital, have been referred to a part-time clinic that addresses environmental illness and other unexplained conditions. Some physicians contend that the sensitivity is largely psychosomatic and treatments provide little more than a placebo effect, but proponents believe research will support environmental health's goal of becoming a new, recognized speciality.


(1995) In vitro calcium and calmodulin-dependent kinase-mediated phosphorylation of rat brain and spinal cord neurofilament proteins is increased by glycidamide administration.

This study was carried out to determine the action of glycidamide (2,3-epoxy-1-propanamide), a neurotoxic metabolite of acrylamide, on Ca2+ calmodulin (CaM)-dependent protein kinase phosphorylation of cytoskeletal proteins. Acrylamide has been shown to increase Ca2+/CaM-dependent phosphorylation of neurofilament (NF) triplet proteins and autophosphorylation of Ca2+/CaM-dependent protein kinase II (CaM kinase II; EC 2.7.1.37). A daily intraperitoneal dose of 0.7 mmol kg b.wt. of glycidamide or deionized water was administered to male Sprague-Dawley rats. Animals were sacrificed when signs of severe neurotoxicity became apparent at 13-16 days of treatment. Axonal floatation was used to isolate neurofilaments (NFs) and endogenous kinases from brains and spinal cords of treated and control animals. Samples isolated from brain and spinal cord of glycidamide-treated animals showed increased in vitro Ca2+/CaM-dependent phosphorylation of endogenous and exogenous NF proteins and increased autophosphorylation of CaM kinase II when
compared with controls. CaM binding to the alpha, beta, and beta’ subunits of CaM kinase II and antibody binding to the alpha-subunit of CaM kinase II in brain supernatant isolates was increased as a result of glycidamide treatment. These results suggest that increased Ca2+/CaM-dependent phosphorylation of cytoskeletal proteins may be involved in the pathogenesis of glycidamide-induced neurotoxicity.

(1995) Practical application of air-quality research incorporated in CMHC’s research house.

The Canada Mortgage and Housing Corporation has been looking at ways to improve indoor air quality since 1984 and now hopes to interest house designers and manufacturers in the results of its research. Its flagship project has been the construction of a proto-type research house for environmentally hypersensitive people.


Every doctor in clinical practice is familiar with the patient who presents with multiple 'soft' symptoms. Where organic pathology cannot be demonstrated, there is a tendency to apply psychiatric labels. Indeed, it has been suggested that the risk of psychiatric disorder increases linearly with the number of presented symptoms. In psychiatric practice, the mere absence of an organic cause of disease is often regarded as adequate reason to invoke a psychological mechanism. However, this action precludes the possibility of any other diagnosis, and thus constricts therapeutic management to the psychiatric realm. Such psychologization of illness is commonplace, overworked and infrequently challenged. This highlights the longstanding controversy over multiple allergy and the role of psychiatric disorder.


The involvement of bradykinin (BK) B1 and B2 receptors in cytokine-induced hyperalgesia has been studied in the rat. Intraplantar injections of interleukin (IL) 1
beta and tumor necrosis factor alpha (TNF alpha) induced thermal hyperalgesia, with in the the case of IL-1 beta, contralateral hyperalgesia also present. Subsequent to administration of IL-1 beta, but not after TNF alpha, des-Arg9-BK reduced the withdrawal latency in both ipsi- and contra-lateral paws. Mechanical hyperalgesia was also induced by IL-1 beta, IL-2, and IL-8 when injected into rat knee joints, whereas IL-6 and TNF alpha were without effect. Co-administration of des-Arg9,Leu8-BK prevented the development of the cytokine-induced hyperalgesia for the duration of the experiment (6 h), but HOE-140 only reversed the hyperalgesia for the 1st h. At 3.5 h after IL-1 beta, IL-2, or IL-8, administration of des-Arg9,Leu8-BK or HOE-140 (iv) completely reversed the hyperalgesia. Twenty-four hours after pretreatment with IL-1 beta, injection of des-Arg9-BK into the joint produced opposite effects, depending on the dose: at 50 pmol the hyperalgesia was reversed, but at 0.5 nmol there was further hyperalgesia. Both responses were blocked by B1 but not B2 receptor antagonists. These data suggest that both B1 and B2 receptors are involved in the induction and maintenance of cytokine-induced hyperalgesia. B1 receptors appear to play a more important role than B2 receptors in the development of mechanical hyperalgesia.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8846417


OBJECTIVE: To compare the neuromuscular-blocking and hemodynamic effects of doxacurium vs. pancuronium administered by intermittent bolus to intensive care unit (ICU) patients who required neuromuscular block to facilitate mechanical ventilation for > or = 24 hrs. DESIGN: A multicenter, prospective, double-blind, randomized study comparing doxacurium, a new benzylisoquinolone neuromuscular-blocking agent, with pancuronium. SETTING: ICUs of three tertiary care hospitals. PATIENTS: Forty critically ill patients (29 male, 11 female) with an average age of 52.5 yrs (range 19 to 80). INTERVENTIONS: With approval of our Institutional Review Boards and after obtaining informed consent, 40 critically ill patients were entered into the study. Histories and the results of physical examinations were recorded, laboratory data were collected, and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated during the 8 hrs before the start of the study medication. Patients received either doxacurium (initial dose of 0.04 mg/kg) or pancuronium (initial dose of 0.07 mg/kg) by bolus injection with continuous measurement of vital signs every minute for 15 mins. We measured the degree of neuromuscular blockade using a peripheral-nerve stimulator to measure the Train-of-Four count. Patients were rebolused (doxacurium dose of 0.025 mg/kg, pancuronium dose of 0.05 mg/kg) based on clinical criteria, which were substantiated by measurement of the Train-of-Four
count. The neuromuscular-blocking drugs were stopped when the patient no longer required paralysis or after 5 days of therapy, whichever came first. Group comparisons were made using repeated measures analysis of variance, Fisher's exact test, and two sample t-tests, when appropriate. Spearman's rank-correction coefficients were calculated to assess the relationship of onset time and recovery time with all baseline laboratory values and the APACHE II scores. A p < .05 was used to establish statistical significance. MEASUREMENTS AND MAIN RESULTS: There were no differences between the two groups with respect to age, gender, or APACHE II scores. There were no differences between groups in terms of adverse experiences, nor with respect to time of onset of block, number of doses, or the duration of neuromuscular blockade (2.6 vs. 2.2 days for doxacurium vs. pancuronium, respectively). There was a statistically significant increase in heart rate after the initial dose of pancuronium (120 +/- 23 vs. 109 +/- 22 beats/min postinjection vs. preinjection, respectively; p < .05) without any differences noted after doxacurium (107 +/- 21 vs. 109 +/- 21 beats/min, respectively). Furthermore, once neuromuscular block was discontinued, the pancuronium group had a more prolonged and variable recovery time (279 +/- 229 mins) compared with the doxacurium group (138 +/- 46 mins, p < .05). CONCLUSIONS: In critically ill patients requiring neuromuscular block for > 24 hrs, doxacurium was well tolerated without evidence of tachycardia and with a relatively prompt recovery profile.

(1995) Actual questions and strategies of environmental protection and environmental medicine--aspects for Lebanon?


OBJECTIVES. Preexisting data sets were used to investigate the association between hospital admissions for congestive heart failure and air pollutants. METHODS. Medicare hospital admissions data, ambient air pollution monitoring data, and meteorological data were used to create daily values of hospital admissions for congestive heart failure, maximum hourly temperature, and maximum hourly levels of carbon monoxide, nitrogen dioxide, sulfur dioxide, and ozone. Data were compiled for each of seven cities (Chicago, Detroit, Houston, Los Angeles, Milwaukee, New York, and Philadelphia) for 1986 through 1989. Single-pollutant and multipollutant models with adjustments for temperature, seasonal effects, and weekly cycles were used in
conducting negative binomial regression analyses. RESULTS. Ambient carbon monoxide levels were positively associated with hospital admissions for congestive heart failure in the single-pollutant and multipollutant models for each of the seven cities. The relative risk of hospital admission for congestive heart failure associated with an increase of 10 ppm in carbon monoxide ranged from 1.10 in New York to 1.37 in Los Angeles. CONCLUSIONS. Hospital admissions for congestive heart failure exhibited a consistent association with daily variations in ambient carbon monoxide. This association was independent of season, temperature, and other major gaseous pollutants.


One hundred twelve individuals who reported onset of multiple chemical sensitivity following well-documented exposure to either (1) a cholinesterase-inhibiting organophosphate or carbamate pesticide or (2) remodeling of a building completed mail-out/mail-back questionnaires concerning their exposure, symptoms, sensitivity to ingestants and inhalants, utilization of health-care resources, and impact of their illness on lifestyle. It was hypothesized that if multiple chemical sensitivity resulted from neurotoxic exposure, then organophosphate-exposed respondents should report greater severity of illness resulting from the relatively greater neurotoxicity of this class of chemicals. Pesticide-exposed and remodeling-exposed multiple chemical sensitivity groups reported similar patterns of symptoms and identified similar inhalants and ingestants as triggers for their symptoms; these results suggested a common mechanism (biological and/or psychological) for their conditions. The pesticide-exposed group, however, reported significantly greater symptom severity than did the remodeling-exposed group, especially for neuromuscular, affective, airway, gastrointestinal, and cardiac symptoms. These findings provide evidence for (1) a possible biological basis for multiple chemical sensitivity and (2) a distinct pathophysiology or final common pathway for the condition that, while as yet undefined, appears to be shared by these two groups. Although subjective multisystem health complaints characterize both multiple chemical sensitivity and somatoform disorder, features of this multiple chemical sensitivity sample were inconsistent with somatoform disorder, i.e., onset after 30 y of age in 83%, the predominance of severe cognitive symptoms, and attributions of environmental causation. No group differences were found with respect to lifestyle impact. Eighty-one percent of respondents said they had been working full-time at the time they were exposed, yet at the time of the survey (on average, 7.7 y post exposure) only 12.5% were working full-time. The majority said they had quit their jobs, changed jobs, or changed careers because of their illness. Approximately 40% reported that they had consulted 10 or more medical practitioners. The persistent, disabling neuropsychological symptoms reported by these multiple chemical sensitivity groups are strikingly similar to those reported among individuals exposed occupationally to pesticides and solvents. These parallel findings
suggest that the types and levels of exposures associated with extermination and remodeling may not be inconsequential, at least for a subset of the population. Further studies from a variety of perspectives, including human challenge studies and the development of animal models, are needed to define the pathophysiological and psychological mechanisms underlying this costly condition.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7786048

---------------------------------------------------------------


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8749737

---------------------------------------------------------------

(1995) Multiple chemical sensitivities--chemical sensitivity as a symptom of airway inflammation.

The term multiple chemical sensitivity confuses etiology with diagnosis. Chemical sensitivity is a symptom expressed by patients. The symptoms complex is also expressed by the majority of patients with asthma reactive airway dysfunction syndrome or rhinitis following a single acute exposure, called reactive upper airway dysfunction syndrome. The chemically sensitivity patient merits evaluation for upper airway and bronchial reactivity that may cause extra-airway symptomatology.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7897747

---------------------------------------------------------------

(1995) Multiple chemical sensitivities--chemical sensitivity as a symptom of airway inflammation [editorial].

The term multiple chemical sensitivity confuses etiology with diagnosis. Chemical sensitivity is a symptom expressed by patients. The symptoms complex is also expressed by the majority of patients with asthma reactive airway dysfunction syndrome or rhinitis following a single acute exposure, called reactive upper airway dysfunction syndrome. The chemically sensitivity patient merits evaluation for upper airway and bronchial reactivity that may cause extra-airway symptomatology.
Meggs, WJ Journal/Environ Health Perspect. 103: 54-6.

Neurogenic switching is proposed as a hypothesis for a mechanism by which a stimulus at one site can lead to inflammation at a distant site. Neurogenic inflammation occurs when substance and other neuropeptides released from sensory neurons cause an inflammatory response, whereas s from the binding of antigen-antibody or leukocyte receptor inflammation. Neurogenic switching is proposed to explain for systemic anaphylaxis, in which injection of the skin or gut with an antigen produces systemic symptoms and circulatory systems, and an experimental model with this hypothesis. Food-allergy-inducing asthma, urticaria, arthritis fibromyalgia are other possible examples of neurogenic switching provides a mechanism possibly emotional stress can exacerbate conditions, asthma, and arthritis. A role in the sick building syndrome and the multiple switching would explain the respiratory irritants lead to symptoms at other.


We performed serological testing for a large number of infectious agents in 26 patients from Atlanta who had chronic fatigue syndrome (CFS) and in 50 controls matched by age, race, and sex. We did not find any agent associated with CFS. In addition, we did not find elevated levels of antibody to any of a wide range of agents examined. In particular, we did not find elevated titers of antibody to any herpesvirus, nor did we find evidence of enteroviral exposure in this group of patients.


Nitric oxide (NO) is known to be present in measurable quantities in the exhaled air of normal subjects and at higher concentrations in asthmatic subjects not treated with glucocorticoids. We confirmed these findings by analyzing the mean mixed expired NO
concentrations of 43 stable asthmatics and 90 normal subjects; NO levels were higher in the asthmatic population (13.9 parts per billion [ppb] versus 6.2 ppb, p < 0.001). Although the effects of glucocorticoids on the NO content of mixed expired air are known, it is not known if beginning systemic glucocorticoid therapy reduces exhaled NO levels in a given individual. To examine this question, seven patients needing emergency therapy for asthma underwent repeated measurements of mixed expired NO levels during their course of treatment with glucocorticoids. All patients had a reduction in mixed expired NO concentration (p = 0.002) and an accompanying improvement in airway obstruction. The decrease in exhaled NO was evident as early as 48 h after the initiation of therapy (p = 0.05). These data suggest mixed expired NO concentrations may prove useful as an index of asthma severity and treatment efficacy for an individual patient.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7633745


This case study describes an indoor environment investigation initiated in response to numerous health and comfort complaints suspected of being associated with a two-story office building. Conventional indoor environment investigation techniques were applied in an attempt to identify one or several contributing factors, such as inadequate outdoor air ventilation and the presence of a respiratory irritant. The air quality satisfaction percentage in the building was well above 80%; however, at least one individual was experiencing a fairly severe reaction only upon entering the subject building. Evaluating the building indoor conditions as acceptable without attempting to address all possible building-related causes and communicating findings to interested occupants would likely have resulted in more occupant complaints and increased the potential for hysteria conditions. This investigation necessarily addressed a sensitive individual and involved an occupational physician as a constructive participant in the investigation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7502995

This study examined the effects of Hurricane Andrew on physical symptoms and functional impairments in a sample of chronic fatigue syndrome (CFS) patients residing in South Florida. In the months after Hurricane Andrew (September 15-December 31, 1992), 49 CFS patients were assessed for psychosocial and physical functioning with questionnaires, interviews, and physical examinations. This sample was made up of 25 CFS patients living in Dade county, a high impact area, and 24 patients in Broward and Palm Beach counties, areas less affected by the hurricane. Based on our model for stress-related effects on CFS, we tested the hypothesis that the patients who had the greatest exposure to this natural disaster would show the greatest exacerbation in CFS symptoms and related impairments in activities of daily living (illness burden). In support of this hypothesis, we found that the Dade county patients showed significant increases in physician-rated clinical relapses and exacerbations in frequency of several categories of self-reported CFS physical symptoms as compared to the Broward/Palm Beach county patients. Illness burden, as measured on the Sickness Impact Profile, also showed a significant increase in the Dade county patients. Although extent of disruption due to the storm was a significant factor in predicting relapse, the patient’s posthurricane distress response was the single strongest predictor of the likelihood and severity of relapse and functional impairment. Additionally, optimism and social support were significantly associated with lower illness burden after the hurricane, above and beyond storm-related disruption and distress responses. These findings provide information on the impact of environmental stressors and psychosocial factors in the exacerbation of CFS symptoms.


BACKGROUND: Atracurium consists of a mixture of ten stereoisomers. One of these isomers, 51W89, is a potent intermediate-acting nondepolarizing neuromuscular blocking agent. Its ED95 is 0.05 mg.kg-1 in patients receiving nitrous oxide/opioid anesthesia. In preclinical trials, 51W89 did not show evidence of histamine release in cats at doses up to 80 times the human ED95. This study was undertaken to determine the cardiovascular effects and histamine-releasing properties of 51W89 in patients undergoing elective surgical procedures. METHODS: Sixty patients, ASA physical status 1 or 2, anesthetized with nitrous oxide/fentanyl/thiopental were studied. Patients received either 2 times the ED95 of atracurium or 51W89 or 4 or 8 times the ED95 of 51W89 as a rapid intravenous bolus under stable anesthesia, before surgical stimulation. Blood pressure and heart rate were measured by oscillometry and the electrocardiogram in patients receiving 2 times the ED95 of 51W89 or atracurium and by an intraarterial catheter and a tachograph triggered by the arterial pulse waveform in patients receiving 4 or 8 times the ED95 of 51W89. Maximal blood pressure and heart rate changes during the 5 min after administration of the muscle relaxant were recorded. Venous blood samples were obtained before the administration of relaxant and at 2 and 5 min after the administration of relaxant for determination of plasma histamine concentrations by radioenzymatic assay. RESULTS: Maximal blood pressure and heart rate changes in all groups of patients receiving 51W89 were small and similar to those observed in patients receiving 2 times the ED95 of atracurium. The mean maximum percent changes (+/- SE) in heart rate and mean arterial pressure were -0.6 +/- 1.5 and 0.4 +/- 2.5, respectively, in the group receiving 2 times the ED95 atracurium; -1.3 +/- 3.3 and 2.3 +/- 4.4, respectively, in the group receiving 2 times the ED95 51W89; -2.6 +/- 1.0 and 2.6 +/- 1.5, respectively, in the group receiving 4 times the ED95 51W89; and -2.4 +/- 1.5 and -1.0 +/- 1.3, respectively, in the group receiving 8 times the ED95 51W89. No patient developed a decrease in blood pressure > or = 20% or an increase in heart rate > or = 20% that was attributable to muscle relaxant administration. There was no dose-related change in plasma histamine concentration associated with the administration of 51W89. One patient in the study developed transient facial flushing after the administration of atracurium. CONCLUSIONS: 51W89 is a benzylisoquinolinium-type, nondepolarizing muscle relaxant that does not affect plasma histamine concentrations. No cutaneous flushing or clinically important cardiovascular effects were noted after rapid injection of doses up to and including 8 times its ED95 (0.4 mg.kg-1) in healthy patients undergoing elective surgical procedures.


Triphenyl phosphite (TPP) is a weak acetylcholinesterase inhibitor and a type II organophosphorus compound-induced delayed neurotoxic agent. The current study examined the cognitive effects of a single 250 mg/kg ip dose of TPP administered to
either 3-mo- or 1-yr-old male Sprague-Dawley rats. Starting 4 d after TPP
administration, the rats began training on a T-maze spatial alternation task for food
reinforcement. Over five sessions of acquisition training, the TPP-treated rats showed
significantly lower alternation scores than controls. There was no difference in spatial
alternation performance in the first session, when both groups were performing at
near-chance levels. In sessions 2-5, the controls improved dramatically to an average
of 85.3 +/- 3.2% correct, while the TPP-treated rats did not significantly change, with
69.7 +/- 3.1 percent correct. During sessions 2 and 3 there was a significant TPP
treatment-related deficit. This TPP-induced choice accuracy deficit was persistent in
that it was seen well after the acute exposure. With continued training the
TPP-exposed rats were able to learn the task as well as controls. There were no
significant TPP effects on response latency. These data show that acute TPP
administration has persistent effects of impairing T-maze learning that do not appear to
result from effects on motor function.

(1995) Psychosocial correlates of immune responsiveness and illness episodes
in US Air Force Academy cadets undergoing basic cadet training.
Lee, DJ, Meehan, RT, Robinson, C, Smith, ML and Mabry, TR Journ/J Psychosom

This study examined psychosocial correlates of immune function and illness in 89 male
first-year US Air Force Academy cadets. A psychosocial questionnaire was
administered to cadets prior to their arrival at the academy and was readministered
during cadet orientation and during the stressful environment of Basic Cadet Training
(BCT). Immune responsiveness was analyzed by PHA-, PMA-, or anti-CD3-stimulated
thymidine uptake in mononuclear leucocytes. Illness episodes were assessed via
medical chart review and self-reported symptoms. There were significant increases in
distress levels as cadets entered BCT. No psychosocial measure assessed prior to
arrival at the academy predicted level of PHA-, PMA-, and anti-CD3-stimulated
thymidine uptake or risk of illness. However, hostility levels reported during BCT
predicted risk of illness in the four weeks following psychosocial assessment (odds
ratio = 7.1; 95% confidence interval: 1.4-36.1). Elevated response to environmental
stressors and lower well-being levels also predicted impending illness, but only in the
cohort of cadets who had not contracted food poisoning prior to assessment during
BCT (OR = 9.3, CI = 1.9-46.7; OR = 0.09, CI = 0.02-0.53). These results suggest that
self-report measures of hostility, response to environmental stressors and well-being
may be useful predictors of impending illness episodes in males encountering high
stress environments.

Thirty-five people with work-related Multiple Chemical Sensitivities were studied to learn about the onset and progression of illness. The subjects were selected from patients at an occupational health clinic. Individuals were identified as subjects if they fulfilled a seven-point case definition for Multiple Chemical Sensitivities and if onset of symptoms was related to workplace exposures. Three occupational exposures to solvents, poor indoor-air quality, and remodeling were associated with onset of Multiple Chemical Sensitivities in 63% of the subjects. Symptoms indicative of a nervous-system disorder topped the list of the most frequently reported symptoms. Commonalities in exposures and symptoms suggest that Multiple Chemical Sensitivities represents a distinct diagnostic category. Even with an incomplete understanding of etiology, it may be possible to limit the onset of work-related Multiple Chemical Sensitivities.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8572720

---------------------------------------------------------------


The history of and nomenclature of the multiple chemical sensitivities are reviewed. The author's definition of multiple chemical sensitivity is a symptom complex 1) triggered by odor or a perceived exposure; 2) occurring at exposure levels below those of allergic sensitivity or irritation; 3) analogous to the symptoms of panic disorder as defined by DSM-IV-R; 4) lacking objective clinic pathologic criteria; and 5) responsive to panic disorder management.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7897746

---------------------------------------------------------------


Cisatracurium (Nimbex) is an intermediate-acting benzylosoquinolinium neuromuscular blocker that is one of the stereoisomers of atracurium. It causes no clinically significant cardiovascular side effects or histamine release in doses up to 8 x ED95 in healthy
patients. Seventy patients undergoing elective myocardial revascularization consented to participate in an Institutional Review Board approved pilot study (10 patients) and an open-label, randomized, controlled trial comparing the hemodynamic effects of cisatracurium with vecuronium (60 patients) at two centers. The patients were anesthetized using 100% oxygen, fentanyl, and midazolam, and tracheal intubation was facilitated with succinylcholine. At least 5 min after tracheal intubation, baseline hemodynamic measurements were obtained. The patients received 0.10 mg/kg of cisatracurium (2 x ED95) or 0.10 mg/kg of vecuronium (2 x ED90) as follows: cisatracurium over 60 s (Pilot Group A, n = 5); cisatracurium over 30 s (Pilot Group B, n = 5); cisatracurium over 5-10 s (Group C, n = 30); or vecuronium over 5-10 s (Group D, n = 30). The hemodynamic measurements were repeated at 2, 5, and 10 min after cisatracurium or vecuronium injection. There were no episodes of cutaneous flushing. One patient was hypotensive before and after cisatracurium administration, and was excluded from analysis. Otherwise, there were no episodes of hypotension requiring therapy in any patient after cisatracurium. Fifteen patients overall were excluded from the analysis for one or more of the following: light anesthesia, treatment for hypotension < 10 min prior to baseline, or equipment difficulties. (ABSTRACT TRUNCATED AT 250 WORDS)


Because no information exists on the prevalence of chemical sensitivity syndromes such as multiple chemical sensitivities, a questionnaire for use in population studies was developed and tested to assess the presence or absence of chemical sensitivity. Seven hundred five individuals attending clinics answered a questionnaire asking whether each of 122 common substances caused symptoms. Results showed that patients with multiple chemical sensitivities and asthma had average total scores that were significantly different from each other and from those of each of the other diagnostic categories. Higher total scores were also reported by female patients. The instrument described here may facilitate meaningful prevalence studies of multiple chemical sensitivities. It will also allow study of chemically induced symptoms in other conditions such as asthma.


(1995) Protein-bound pyrroles in rat hair following subchronic intraperitoneal injections of 2,5-hexanediene.
Studies were initiated to ascertain whether body hair could be used to develop a biological marker for chronic exposure to industrial neurotoxicants that yield the metabolite 2,5-hexanedione (2,5-HD), that is, n-hexane and methyl n-butyl ketone. Rats were injected daily with a 50 mg/kg ip dose of 2,5-HD for 45 d. At intervals, body hair and individual vibrissae were removed (under general anesthesia) and tested for the presence of pyrrole substances with p-N,N-dimethylaminobenzaldehyde (DMAB, Ehrlich's reagent). Vibrissae and body hair were stained a reddish color that was distinctly different from that observed with the hair taken from control animals. Solubilized body hair protein from the treated animals gave a positive Ehrlich's test, while that from control animals was negative. Spectral analysis of the DMAB-treated hair from experimental animals disclosed a maximum absorbance at 530 nm, which indicated the presence of pyrrole substituents. Serial analysis of individual nose hairs taken during 2,5-HD administration showed a progression with time of the region staining positively for pyrroles, thus indicating that the process can proceed in growing hair. These findings suggest the potential utility of hair as an indicator for chronic exposure to this class of industrial chemicals possessing neurotoxicity potential. This could complement urinary analysis, which is now used to confirm recent exposure.

(1995) Correlation between the pharmacology of long-term potentiation and the pharmacology of memory.

The pharmacology of memory has been recently studied by the infusion of drugs into the hippocampus (HIP), amygdala (AMY), medial septum (MS), and entorhinal cortex (EC) at various times after training or at the time of retention testing. It was found to be remarkably similar to that of long-term potentiation (LTP). Memory and LTP are blocked early on by antagonists of glutamate N-methyl-D-aspartate (NMDA) or metabotropic receptors (mGLUs), by the antagonist of the presynaptic membrane receptor to PAF, BN 52021, by the inhibitor of heme oxygenase, ZnPP, by the inhibitor of NO synthase, N-nitro-arginine, by GABA type A receptor agonists, or by muscarinic blockers. Both memory and LTP are enhanced, at this early stage, by glutamate, mGLU agonists, GABA-A antagonists, muscarinic agonists, and norepinephrine. In the next 1-3 h, memory and LTP are accompanied by enhanced activity of protein kinases and are blocked by specific inhibitors of calcium/calmodulin dependent protein kinase II and protein kinase C. At the time of expression, memory and LTP are blocked by antagonists of glutamate AMPA receptors and are accompanied by an enhanced sensitivity of these receptors. Memories that depend on HIP are affected by drugs given into the HIP but not the MS or AMY, memories that depend on the AMY are affected by drugs given into the AMY, and memories that depend on the HIP, AMY,
and MS are affected by drugs given into the three structures. (ABSTRACT TRUNCATED AT 250 WORDS)

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7663877

---

(1995) Memory enhancement by intrahippocampal, intraamygdala, or intraentorhinal infusion of platelet-activating factor measured in an inhibitory avoidance task.

Platelet-activating factor (PAF; 1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine), which is thought to be a retrograde messenger in long-term potentiation (LTP), enhances glutamate release and LTP through an action on presynaptic nerve endings. The PAF antagonist BN 52021 blocks CA1 LTP in hippocampal slices, and, when infused into rat dorsal hippocampus pre- or posttraining, blocks retention of inhibitory avoidance. Here we report that memory is affected by pre- or posttraining infusion of the PAF analog 1-O-hexadecyl-2-N-methylcarbamoyl-sn-glycerol-3-phosphocholine (mc-PAF) into either rat dorsal hippocampus, amygdala, or entorhinal cortex. Male Wistar rats were implanted bilaterally with cannulae in these brain regions. After recovery from surgery, the animals were trained in step-down inhibitory avoidance or in a spatial habituation task and tested for retention 24 h later. mc-PAF (1.0 microgram per side) enhanced retention test performance of the two tasks when infused into the hippocampus before training without altering training session performance. In addition, mc-PAF enhanced retention test performance of the avoidance task when infused into (i) the hippocampus 0 but not 60 min after training; (ii) the amygdala immediately after training; and (iii) the entorhinal cortex 100 but not 0 or 300 min after training. In confirmation of previous findings, BN 52021 (0.5 microgram per side) was found to be amnestic for the avoidance task when infused into the hippocampus or the amygdala immediately but not 30 or more minutes after training or into the entorhinal cortex 100 but not 0 or 300 min after training. These findings support the hypothesis that memory involves PAF-regulated events, possibly LTP, generated at the time of training in hippocampus and amygdala and 100 min later in the entorhinal cortex.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7761446

---

Huff, RA and Abou-Donia, MB Journal/Neurotoxicology. 16: 281-90.
Although the neurotoxicity of organophosphorus compounds is generally attributed to inhibition of acetylcholinesterase, recent reports have indicated that direct interactions with muscarinic receptors and signal transduction may be an additional mechanism of neurotoxicity. We have previously shown that the organophosphorus insecticide O,O-diethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate (chlorpyrifos) binds directly to muscarinic receptors and inhibits adenylate cyclase of rat striatum. We have further pursued those results in this study by investigating the effect of chlorpyrifos oxon in NG108-15 neuroblastoma-glioma cells and Chinese hamster ovary cells transfected with cDNA for human m2 or m4 muscarinic receptor subtypes. At millimolar concentrations, chlorpyrifos oxon inhibited [3H]QNB binding in all cell lines. Likewise, [3H]CD binding was inhibited in NG108-15 and CHO-Hm2 cells. When the effect of chlorpyrifos oxon on adenylate cyclase was examined, the oxon was found to inhibit adenylate cyclase at millimolar concentrations. Though this effect on cyclase required greater concentrations of oxon than the comparable effect in striatal cells, it displayed the common characteristic of being atropine-insensitive, suggesting that the effect on cyclase was not muscarinic receptor dependent. The inhibition of adenylate cyclase produced by chlorpyrifos oxon was not eliminated in pertussis toxin treated cells, lending further support to the idea that it is not a receptor-mediated event, and suggesting a potential direct interaction of chlorpyrifos oxon with the adenylate cyclase molecule.


Responses to patch test substances may occur contemporaneously. Such simultaneous reactions may reflect concomitant sensitization to 2 dissimilar allergens to which concurrent exposure has taken place (e.g., ethylenediamine dihydrochloride and neomycin). It may occur when the individual has been exposed to only 1 of the substances and exhibits a response to other substances of similar chemical structure (i.e., cross-sensitization such as between para-phenylenediamine and benzocaine). Such simultaneous responses may also be chance occurrences, reflecting multiple sensitization or the result of altered response due to the "angry back syndrome". This investigation established that such concurrence of response is not uncommon and adds further documentation to the literature of these associations in patch test responses.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7634783

Individual susceptibility to lung cancer due to occupational and environmental exposures to carcinogenic agents has been shown to be modulated by host-specific factors. The underlying principle of these factors is the differences that confer sensitivity or resistance to the disease. Since the majority of chemical carcinogens are not capable of causing hazardous effects per se, the metabolism of these compounds is a crucial part of the initial host response to the environmental exposure. Disturbances in the balance between activation and detoxification may thus explain the individual variations in responses to exposures to carcinogens. Many of the metabolic enzymes have recently been shown to express genetic polymorphisms in the population, and an association has been found between cigarette smoke-induced lung cancer and CYP1A1, CYP2D6, and GSTM1 genes. In addition, GSTM1 and NAT2 polymorphisms have been associated with susceptibility to bladder cancer. Since substantial ethnic differences exist in the distribution of altered and normal alleles, and findings in one ethnic group are not necessarily applicable to others, these biomarkers are still in the validation stage. However, as more information emerges on the specific features that lead to enhanced susceptibility they can undoubtedly be used to determine risks of environmental exposures to susceptible individuals and populations.

----------------------------------------------------------------------


Diisopropyl phosphorofluoridate (DFP) produces delayed neurotoxicity (OPIDN) in hens that is characterized by peripheral and central axonal degeneration. DFP administration resulted in mCANP activity inhibition in sciatic nerve and significant decrease in total NF-H, phosphorylated NF-H, vimentin, GFAP, tubulin, and tau. The degradation of cytoskeletal proteins even in the presence of decreased CANP activity may be ascribed to the release of intracellular Ca2+, elevation of other proteinase activity, or modification of cytoskeletal proteins resulting in their increased susceptibility in OPIDN.

----------------------------------------------------------------------

Diisopropyl phosphorofluoridate (DFP) produces organophosphorus ester-induced delayed neurotoxicity (OPIDN) in humans and sensitive animal species, e.g., adult chicken. The chickens were sacrificed 18 days after a single dose of DFP (1.7 mg/kg, s.c.), which produced severe ataxia or paralysis in 10-14 days. We studied Ca²⁺ calmodulin-dependent in vitro neurofilament phosphorylation by the brain subcellular fractions of control and DFP-treated hens. There was enhanced phosphorylation of all three NF subunits by the brain supernatant of treated hens. This was accompanied by enhanced autophosphorylation of both Ca²⁺/CaM-dependent protein kinase II (CaM-kinase II) subunits and increased calmodulin binding using either 125I-CaM or biotinylated calmodulin to only alpha subunit without concomitant increase in the amount of this enzyme. This enhanced phosphorylation of neurofilament subunits was completely and partially inhibited by mastoparan and KN-62, respectively. There was no alteration in the distribution of CaM-kinase II activity in treated hens and the activity was not related to its concentration in different subcellular fractions. The difference in 125I-CaM binding to CaM-kinase II alpha subunit in the brain supernatants of control and DFP-treated hens was not altered by its phosphorylation or dephosphorylation. The increased CaM-kinase II activity in the soluble fraction of DFP-treated hen brain may be involved in the aberrant phosphorylation of axonal neurofilaments, and thus play a role in OPIDN.


The phenomenon of multiple chemical sensitivities is a peculiar manifestation of our technophobic and chemophobic society. It has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association, the California Medical Association, the American College of Physicians, and the International Society of Regulatory Toxicology and Pharmacology. It may be the only ailment in existence in which the patient defines both the cause and the manifestations of his own condition. Despite this, it has achieved credibility in workmen's compensation claims, tort liability, and regulatory actions, all of which are briefly reviewed.


The phenomenon of multiple chemical sensitivities is a peculiar manifestation of our technophobic and chemophobic society. It has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association, the California Medical Association, the American College of Physicians, and the International Society of Regulatory Toxicology and Pharmacology. It may be the only ailment in existence in which the patient defines both the cause and the manifestations of his own condition. Despite this, it has achieved credibility in workmen's compensation claims, tort liability, and regulatory actions, all of which are briefly reviewed.

---------------------------------------------------------------------


Patients with environmental somatization syndrome (ESS) believe that their symptoms are caused by exposure to tangible components of the external environment or by ergonomic stress at work. ESS is distinguishable by mental contagiousness and by the patients' focus on the external environment as cause of the illness. The presentation is often polysymptomatic, and epidemic outbreaks may appear. The patients usually refuse alternative explanations of their symptoms and discredit and reject any suggestion of a psychogenic etiology. It is important to distinguish between hygienic problems and ESS problems, particularly when poor and inadequate hygienic factors are present simultaneously with an ESS epidemic.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7871128

---------------------------------------------------------------------


To appreciate what illness means to an individual, physicians must understand that person's attitudes, views, and style of life. People react uniquely and creatively to illness and disability. Some incorporate the illness into their lives and use it to help them achieve goals that might not be obvious to the doctor. A case study presents diagnostic and therapeutic problems familiar to family physicians.

Children may be more susceptible to exposures to environmental toxins than adults and may be more vulnerable to their effects. Because of this, the health care community and those responsible for children need to be alert to possible environmental factors in identifying and responding to the health problems of children. Their focus should be on the causes of the health problem, emphasizing environmental sources, and not on simply treating the symptoms.


Although in use for more than 150 years, dental amalgam has been questioned more or less vigorously as a dental restoration material due to its alleged health hazard. Humans are exposed to mercury and the other main dental amalgam metals (Ag, Sn, Cu, Zn) via vapour, corrosion products in swallowed saliva, and direct absorption into the blood from the oral cavity. Dental amalgam fillings are the most important source of mercury exposure in the general population. Local, and in some instances, systemic hypersensitivity reactions to dental amalgam metals, especially mercury, occur at a low frequency among amalgam bearers. Experimental and clinical data strongly indicate that these and other subclinical systemic adverse immunological reactions to dental amalgam metals in humans will be linked to certain MHC genotypes, and affect only a small number of the exposed individuals. These individuals will be very difficult to detect in a mixed population of susceptible and resistant individuals, including persons with alleged symptoms due to dental amalgam fillings, where many of the individuals are likely to suffer from conditions with no proven immunological background such as multiple chemical sensitivity syndrome. Intensified studies should be performed to identify such susceptible MHC genotypes, taking advantage of the reported cases of more heavily metal-exposed humans with systemic autoimmune reactions. Further studies will also be needed to ascertain whether the combined exposure to the metals in dental amalgam may lower the threshold for adverse immunological reactions, since recent studies have shown that the metals in alloy, especially silver, may induce autoimmunity in genetically susceptible mice.
(1995) **Dextromethorphan suppresses both formalin-induced nociceptive behavior and the formalin-induced increase in spinal cord c-fos mRNA.**

The injection of dilute formalin results in a stereotyped nociceptive behavioral response. Administration of dextromethorphan (s.c.) but not saline, 30 min prior to intraplantar formalin injection prevents this nociceptive response in a dose-dependent manner. In addition, intraplantar formalin reliably induces c-fos mRNA in the ipsilateral spinal dorsal horn as assessed with quantitative solution hybridization at 30 min postinjection. No change in c-fos mRNA was detected in the contralateral spinal dorsal horn, nucleus raphe magnus, periaqueductal grey, medial thalamus, or sensorimotor cortex. Pretreatment with dextromethorphan at 60 mg/kg s.c., 30 min prior to formalin resulted in a suppression of c-fos induction, so that c-fos mRNA levels in the ipsilateral spinal dorsal horn of animals receiving dextromethorphan prior to formalin did not differ from controls. These data indicate that dextromethorphan suppresses formalin nociceptive behavior and one of the biochemical consequences of formalin nociception, i.e., induction of c-fos mRNA.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7478683

---------------------------------------------------------------

(1995) **Dextromethorphan shows efficacy in experimental pain (nociception) and opioid tolerance.**

The oral antitussive dextromethorphan is a clinically available N-methyl-D-aspartate receptor antagonist. Dextromethorphan has analgesic efficacy in the experimental formalin test, blocks the nociceptive activation of the immediate-early gene, c-fos proto-oncogene, and prevents and reverses the development of opiate analgesic tolerance in experimental models. These data suggest that dextromethorphan should be evaluated in a controlled clinical trial for analgesic efficacy in zoster-associated neuralgia.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8545027

---------------------------------------------------------------

(1995) **A preliminary investigation of chlorinated hydrocarbons and chronic fatigue syndrome.**

OBJECTIVE: To determine whether serum levels of chlorinated hydrocarbons are elevated in patients with chronic fatigue syndrome. METHODS: Chlorinated hydrocarbon levels were measured in 22 patients with chronic fatigue syndrome (CFS) (as defined by the Centers for Disease Control [CDC]); in 17 patients with CFS symptoms whose history of exposure to toxic chemicals excluded them from the research definition of CFS; and in 34 non-CFS control subjects matched for age and sex. RESULTS: DDE (1,1-dichloro-2,2-bis (p-chlorophenyl) ethene) was detected in all serum samples at levels over 0.4 ppb. The incidence of hexachlorobenzene (HCB) contamination (> 2.0 ppb) was 45% in the CFS group, compared with 21% in the non-CFS control group (P < 0.05). The CFS group had a significantly higher total organochlorine level (15.9 ppb; SEM, 4.4) than the control group (6.3 ppb; SEM, 1.1; P < 0.05). The toxic exposure group also had a higher mean organochlorine level (13.6 ppb; SEM, 6.2) than the control group, but the difference was not statistically significant. DDE and HCB comprised more than 90% of the total organochlorines measured in each of the groups. CONCLUSION: The results suggest that recalcitrant organochlorines may have an aetiological role in CFS. There were no significant differences in serum organochlorine concentrations between CFS patients and chronic fatigue patients with a history of toxic chemical exposure. Therefore, exclusion of patients from the CDC research definition of CFS on the basis of a reported history of known exposure to toxic chemicals is not valid. The role of low-level organochlorine bioaccumulation in the development of CFS symptoms requires further investigation.


This is a study of visual contrast sensitivity in a series of subjects with previously diagnosed occupational organic-solvent-induced chronic toxic encephalopathy. Contrast sensitivity was measured for 16 subjects using the Vistech VCTS 6500 chart. The results were compared with age-stratified normal data. Six of the 16 subjects (37.5%) recorded abnormal contrast sensitivity results. Monocular abnormalities were found for two (33%) of these subjects. Statistically significant abnormalities in contrast sensitivity were observed at the intermediate spatial frequencies of three cycles per degree (cpd; P < .0005), 6 cpd (P < .025), and 12 cpd (P < .01). We conclude that contrast sensitivity is abnormal in some cases of occupational organic-solvent-induced chronic toxic encephalopathy. Intermediate spatial frequency channel neurones in the visual system may be more vulnerable to solvent toxicity than those of low or high spatial frequency. Contrast sensitivity testing may be a useful adjunct in the diagnostic
process for this disease. Further research involving larger numbers of subjects is recommended.


Conditions for the induction of rat liver Ca2(+) -independent nitric oxide synthase were determined with killed Propionibacterium avidum, and compared with lipopolysaccharide endotoxin. Similar maximal induction was obtained intraperitoneally with the two types of inducers but killed Propionibacterium avidum gave a long-lasting induction while lipopolysaccharide displayed a rapid and short response. Moreover, the induction resulting from an intravenous administration of killed Propionibacterium avidum reached 60 times that of the control whereas lipopolysaccharide treatment induced a 24-fold stimulation only. It is noteworthy that with the first inducer the nitric oxide activity was stable with time whereas with the second one it dropped after 8 h. Whatever the route of administration of killed Propionibacterium avidum, some huge vacuolated Kupffer cells were found in the liver whose parenchyma was almost normal. Numerous monocytes, and unaltered Kupffer cells, were observed. Kupffer cells were identified to be responsible for the uptake of killed Propionibacterium avidum.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8748697


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7613689

(1995) Significance of individual sensitivity to chemicals: elucidation of host susceptibility by use of biomarkers in environmental health research.

Biomarker research has become the predominant theme for study of human dose-host-response relations to environmental chemicals. Increasing interest has been focused on identifying markers for host susceptibility, with mixed results. Efforts to
identify markers for host variability in carcinogenic risk, on the basis of theoretical knowledge of carcinogen metabolism, have been disappointing. New work in the area of acquired risk modifiers, such as nutritional status, is theoretically attractive, but results have been limited. Impressive achievements have been made in the area of immunological variability, which may elucidate the molecular basis of as well as provide practical biomarkers for several diseases. The problem of multiple chemical sensitivities, on the other hand, has proved refractory to biomarker research, reflecting inadequate knowledge of the mechanism and inappropriate application of biomarker methods.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7497637


We measured thresholds for eye irritation and odor in homologous series of alcohols (ethanol, 1-butanol, 1-hexanol and 1-octanol), ketones (2-propanone, 2-pentanone, 2-heptanone and 2-nonanone), and alkylbenzenes (toluene, ethyl benzene and propyl benzene). Eye irritation thresholds were well above odor thresholds for all series. Both sensory thresholds declined with carbon chain length, a trend that has implicated lipophilicity in the potency of these and related stimuli. Eye irritation thresholds were remarkably close to nasal pungency thresholds obtained previously in persons lacking olfaction (i.e. anosmics). The agreement between the two thresholds implies that, despite differences in the mucus layer at the two sites and in the epithelial tissue itself, there is remarkable similarity at the site of stimulation. As a practical matter, the eyes could serve as the sites to assess potency for induction of nasal pungency, an assessment previously limited to testing anosmics. Presumably, for our brief stimulus presentations (1-3 s), the differences between ocular and nasal mucosae have little relevance to chemical sensitivity. Studies of the ability of homologous chemical series to evoke threshold eye irritation, nasal pungency and odor not only have practical value, but also can help to define the physicochemical properties of the receptor and perireceptor biophases.

Analyses of potential dietary exposure to chlorpyrifos residues were conducted by the Department of Pesticide Regulation (DPR). Potential acute dietary ingestion of chlorpyrifos for all labelled uses was based on the 95th percentile of user-day exposures. Margins of safety (MOSs) for potential acute dietary exposure to chlorpyrifos residues were based on a no-observed-effect level (NOEL) for cholinergic signs in a human study, and ranged from 52 to 205 for all population subgroups. MOSs for potential chronic dietary exposure to chlorpyrifos residues were based on a NOEL for inhibition of brain cholinesterase activity in rats and dogs, and ranged from 2198 to 8065 for all population subgroups. The limitations on toxicity, consumption and residue data are discussed, with the assumptions necessitated by those limitations.


This article provides an overview of the control of occupational and environmental exposures. Two case studies illustrate common questions that arise in the primary care setting, regardless of specialty practice. The focus of these case studies is to offer pragmatic recommendations on how best to prevent occupational and environmental illness and injury through use of a hierarchy of controls.


The current principles of toxicology, immunology and allergy do not provide a coherent explanation of a chemical sensitivity lacking reproducible and measurable physiologic or biochemical changes. A new paradigm is needed as a scientific model for multiple chemical sensitivities.


(1995) Fibromyalgia syndrome and myofascial pain syndrome. Do they exist?

"It is in the healing business that the temptations of junk science are the strongest and the controls against it the weakest." Despite their subjective nature, these syndromes (particularly MPS) have little reliability and validity, and advocates paint them as "objective." Despite a legacy of poor-quality science, enthusiasts continue to cite small,
Methodologically flawed studies purporting to show biologic variables for these syndromes. Despite a wealth of traditional pain research, disciples continue to ignore the placebo effect, demonstrating a therapeutic hubris despite studies showing a dismal natural history for FS. In reviewing the literature on MPS and FS, F.M.R. Walshe’s sage words come to mind that the advocates of these syndromes are "better armed with technique than with judgment." A sympathetic observer might claim that labeling patients with monikers of nondiseases such as FS and MPS may not be such a bad thing. After all, there is still a stigma for psychiatric disease in our society, and even telling a sufferer that this plays only a partial role may put that patient on the defensive. Labeling may have iatrogenic consequences, however, particularly in the setting of the work place. Furthermore, review of a typical support group newsletter gives ipso facto proof of this noxious potential. The author of a flyer stuffed inside the newsletter complains that getting social security and disability benefits for "the invisible disability" can be "an uphill battle. But don't lose (sic) hope." Apparently the "seriousness of the condition" is not appreciated by the medical community at large, and "clinician bias may well be the largest threat," according to Boston epidemiologist Dr. John Mason. Sufferers are urged to trek to their local medical library and pull four particular articles claiming FS patients have more "stress," "daily hassles," and difficulty working compared with arthritis patients. If articles can't be located, patients are told to ask their lawyers for help. Although "Chronic Fatigue Syndrome" and FS are not considered by everyone to be the same malady, the "National Institute of Health (sic) has lumped these two conditions together. This could work in your favor." (A U.S. political advocacy packet is available for $8, but a list of U.S. senators with Washington, DC addresses is freely provided.) These persons see themselves as victims worthy of a star appearance on the Oprah Winfrey show. A sense of bitterness emerges; one literally bed-bound Texas homemaker writes in Parents magazine that "Some doctors may give up and tell you that you are a hypochondriac."(ABSTRACT TRUNCATED AT 400 WORDS)
120 hr after administration. Within 12 hr, the hens excreted 70% of the administered dose, and more than 99% within 48 hr. Blood, plasma, liver, and muscle contained the greatest percentage of administered dose at 4 hr after dosing. Less than 0.02% of the administered dose appeared in brain at any time. Radiolabel accumulated in the eggs, with 0.52% of the administered dose accumulated within 5 days. Binding of radiolabel to erythrocytes was minimal. Elimination of radiolabel from all tissues was biphasic. Terminal elimination half-lives for 14C were longer than 10 days, at which time less than 0.2% of the administered dose remains in the tissues. Distribution half-lives for 14C were longest for whole blood and shortest for kidney. Radioactivity in the blood and plasma reached a peak at between 4 and 12 hr. Most of this radioactivity was identified as acrylamide, which disappeared biexponentially with terminal elimination half-lives longer than 10 days. Distribution half-lives for acrylamide were longest in brain and shortest in whole blood. These results show that orally administered acrylamide is poorly absorbed and rapidly eliminated from hens and accumulates in their eggs in a nonextractable form.


BACKGROUND: Atracurium is a mixture of ten stereoisomers. 51W89, one of these isomers, is a potent nondepolarizing intermediate-duration neuromuscular blocking agent. Preclinical studies have shown 51W89 to be significantly more potent than atracurium but with a similar neuromuscular blocking profile. This study was undertaken to establish the neuromuscular blocking potency and pharmacodynamics of 51W89 in patients undergoing elective surgical procedures. METHODS: Ninety-nine ASA physical status 1 or 2 patients undergoing elective surgical procedures under nitrous oxide/opioid/barbiturate anesthesia were studied. The neuromuscular blocking effect of 51W89 was assessed after administration of bolus doses from 0.015 to 0.4 mg/kg, as well as during and after continuous infusions from 11 to 249 min in length. RESULTS: The calculated ED95 for inhibition of adductor pollicis twitch evoked at 0.15 Hz was 0.048 mg/kg. At 0.10 mg/kg, maximum block developed within 5.2 +/- 0.3 min, and recovery to 95% twitch height occurred 64.4 +/- 3.9 min after injection. At 0.4 mg kg, onset was 1.9 +/- 0.1 min, and 95% recovery developed within 121.0 +/- 5.9 min. Comparative recovery indexes from 5% to 95% or from 25% to 75% twitch heights did not differ significantly among all dosage groups from 0.1 to 0.4 mg/kg (means ranged from 29.6 to 32.3 min and from 12.6 to 14.3 min, respectively). The average infusion rate necessary to maintain approximately 95% twitch suppression was 1.35 micrograms/kg/min. Recovery indexes from infusions were 5-95% 33.2 +/- 1.8 min and 25-75% 15.0 +/- 0.6 min, not differing significantly from recovery indexes from single bolus doses. Twenty-five patients received neostigmine (0.06 mg/kg) with atropine (0.03 mg/kg) at twitch height recovery of between 6% and 21%. Antagonism to 95%
control twitch height developed within 6.8 +/- 0.3 min, and the neostigmine-accelerated 25-75% recovery index was 2.8 +/- 0.2 min. CONCLUSIONS: 51W89 is a potent nondepolarizing neuromuscular blocking agent that shows noncumulative intermediate-duration neuromuscular blocking pharmacodynamics.

(1995) Medical histories and psychological profiles of middle-aged women with and without self-reported illness from environmental chemicals.

BACKGROUND: Cacosmia, which is a predictor of cognitive deficits in industrial samples, is a core symptom of several controversial syndromes. Previous studies of cacosmic populations have considered only psychiatric but not medical or family histories of identified patients. METHOD: This questionnaire survey study examined subjective characteristics of illness from chemical odors, sensitivity to chemicals, psychological and stress profiles, and medical, psychiatric, and family health histories of 28 middle-aged women with cacosmia in self-reported poor health attributed to chemicals (MCS), 17 controls with cacosmia in good health, and 20 normal controls without cacosmia in good health. RESULTS: Those with MCS rated themselves in significantly poorer overall health with higher Pennebaker symptom scores, a larger number of chemical triggers, and greater frequency of illness from chemicals than the other two groups, even after controlling for variables on which the groups differed (i.e., education, Symptom Checklist-90 [revised] somatization, obsessive-compulsiveness, depression, anxiety, phobic anxiety, psychoticism, Barsky Somatic Symptom Amplification, and Cheek-Buss shyness). Despite increased levels of affective distress, those with MCS reported the greatest intolerance for alcohol and the lowest alcohol consumption. CONCLUSION: The data suggest that women with MCS report increased disability, multiple medical diagnoses including inflammatory and gynecologic dysfunctions, and psychological distress. The data are consistent descriptively with the phenomenology of somatization disorder. However, the persisting significance of group health rating differences after controlling for psychological variables, the lack of differences in life stress ratings between those with MCS and healthy cacosmics, the later age at onset (60% after age 30 years), and the lack of excess family psychiatric histories in this sample of women with MCS suggest a potential role for an organic factor in the evolution of poor health in certain cacosmics.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7713854

(1995) Increased limbic system symptomatology and sensitizability of young adults with chemical and noise sensitivities.
Bell, IR, Hardin, EE, Baldwin, CM and Schwartz, GE Journal/Environ Res. 70: 84-97.
We previously hypothesized that individual differences in (a) limbic system reactivity and (b) central nervous system sensitizability underlie vulnerability to environmental stimuli, not only in the controversial clinical condition multiple chemical sensitivity (MCS), but also in the general population. Earlier research has shown overlaps in the characteristics of persons who report noise and air pollutant sensitivities. This study assessed questionnaire responses of 897 young adult college students who reported high versus low frequency of illness from several environmental chemical odors and concomitantly high versus low sensitivity to environmental noise. Subjects who reported increased rates of illness from chemical odors with or without noise sensitivity scored significantly higher (P < 0.0001) on a measure of limbic system symptomatology derived from ictal sensory, somatic, mnemonic, and behavioral manifestations of temporal lobe epilepsy. The group rating high both for illness from chemicals and for noise sensitivity had characteristics predictive of heightened sensitizability from the animal research on time-dependent sensitization (progressive response amplification to repeated, intermittent stimuli over time): i.e., higher female to male ratio (gender risk factor), increased rates of drug abuse problems in blood relatives (genetic risk factor), trait shyness (hyperreactivity to novelty), and increased carbohydrate craving. Despite the increased family histories of drug abuse and levels of personal anxiety and depression, the chemical- and noise-sensitive group reported the lowest rates of current smoking or personal drug abuse problems and the highest frequency of illness from drinking a small amount of alcohol. Taken together, the findings suggest that limbic system dysfunction associates more with chemical than with noise sensitivity; that individuals with both chemical and noise sensitivity may be the most sensitzable subset of the population for prospective studies, and that, in their substance use patterns, young adults with both chemical and noise sensitivity are more similar to MCS patients than are their peers with chemical or noise sensitivity alone.


The emergence of potential treatments to slow the progression of idiopathic Parkinson's disease (PD) has increased the need for early identification of persons at risk. Although considered controversial, some prior studies indicate that PD patients may have premorbid histories of greater trait introversion or shyness as well as increased rates of disorders associated with shyness (e.g., anxiety, affective disorders, and irritable bowel syndrome). Essential features of trait shyness include (a) inhibited and avoidant behaviors and (b) physiological hyperreactivity to the novel or unfamiliar. In parallel, (a) depression in PD patients is associated with increased harm avoidance
(a possible serotonergic function), and (b) PD patients have premorbid and comorbid decreases in novelty-seeking (a possible dopaminergic function). Taken together, previous research suggests the following hypotheses: (1) given evidence for marked heritability of shyness, shy elderly should report higher rates of PD in their family members than would nonshy elderly; and (2) shy elderly without PD should exhibit psychological and biologic characteristics similar to those reported in PD. Two groups, representing the top 27% (n = 37) and bottom 31% (n = 43) of scores on a standardized shyness scale, were drawn from a larger cohort of 138 older adults (ages 50-90) living in an active retirement community. Seventeen percent of the shy versus 2% of the nonshy reported PD in a family member or self (P < .05). Shy elderly were significantly more anxious (P < .01) and depressed (P < .05) than were the nonshy. (ABSTRACT TRUNCATED AT 250 WORDS)


Human keratinocytes (HK) generate nitric oxide (NO) and proinflamatory mediators following activation with either IgE/anti-IgE immune complexes or a combination of lipopolysaccharide (LPS) and interferon-gamma (IFN-gamma). Recently, interleukin-10 (IL-10) has been shown to down-regulate various inflammatory responses and to be secreted by lymphocytes and dendritic cells during skin inflammatory reactions. We show here that IL-10 down-regulates the production of tumor necrosis factor (TNF)-alpha and IL-6 by activated HK. Also, induction of inducible nitric oxide synthase (iNOS) expression in HK by IgE/anti-IgE or LPS/IFN-gamma is significantly reduced by the addition of IL-10. This effect is dose dependent and correlates with reduction of iNOS mRNA production and enzyme level. Therefore, IL-10 down-regulates NO-mediated HK inflammatory responses and may thus participate in the regulation of the skin immune network.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7589103

Ashford, NA Journal/Am J Ind Med. 28: 611-2; author reply 629-33.
(1995) A nonconventional approach to the treatment of "environmental illness". 

Twenty patients with symptoms of "environmental illness" were subject to a controlled study of deep versus superficial acupuncture. The patients were evaluated by a detailed questionnaire concerning their occupational, environmental, and medical history. Blood samples were taken as well. Patients were randomized to deep or superficial acupuncture. Both groups improved significantly in key variables during and after treatment. There were no group differences. There were no changes in biological variables apart from a gradual and continuous increase in serum cortisol and a decrease in neuropeptide Y, which was somewhat more accentuated in those receiving deep acupuncture. This rise in cortisol may have contributed to decreased dermal symptoms among the participants. It is hypothesized that the positive treatment results observed are partly due to weakening of the conditioned response, linking bodily symptoms to environmental agents. To date, a number of different methods have been tried in the management of patients with environmental illness. However, only rarely have the treatments been evaluated in controlled studies.

(1995) [Fear of environmental poisons--justified fear or psychiatric disorder?]. 

A typical anxiety of our time is the anxiety of environmental poisons. Although some of the fears may be reasonable, anxiety diseases and somatoform disorders are important differential diagnoses. The limited value of toxicological and immunological parameters is discussed in depth, and risk factors associated with the development of environmental phobia are presented. This establishes that the concept of "clinical ecology" lacks credible scientific foundation. It must be stressed, that "clinical ecology" may seriously hinder a proper psychosomatic diagnosis and its relevant therapy.


(1995) [Multiple chemical sensitivity syndrome]. 

The multiple chemical sensitivity syndrome (MCS) is a novel constellation of symptoms in environmental medicine that has been extensively described and commented on in the USA. The main features of this syndrome are: multiple symptoms in different organ systems triggered by a variety of chemical substances, with relapses and exacerbations under certain precipitating circumstances at very low levels which do not
cause any reactions in the population at large. There are no lab markers or specific investigative findings. This paper describes the historical development of the term MCS, its diagnostic criteria and pathophysiological aspects using 10 patient histories from our hospital.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8527883


1. Organophosphorus ester-induced delayed neurotoxicity (OPIDN) is a neurodegenerative disorder characterized by the presence of swellings in the distal parts of large axons in the central and peripheral nervous systems with subsequent axonal degeneration and paralysis. 2. An early change in OPIDN is enhanced activity and autophosphorylation of Ca2+/calmodulin-dependent kinase II. 3. In OPIDN, there is also a dose- and time-dependent increase in Ca2+/calmodulin-dependent kinase mediated phosphorylation of the cytoskeletal proteins, alpha- and beta-tubulin, microtubule associated protein-2, neurofilament triplet proteins and myelin basic protein. 4. Anomalous hyperphosphorylation of neurofilaments decreases their transport rate down the axon relative to their rate of entry resulting in their accumulation. 5. Consistent with the neurochemical results is the presence of anomalous aggregations of phosphorylated neurofilaments in early stages of OPIDN. 6. These findings suggest that aberrant hyperphosphorylation of cytoskeletal proteins is a post-translational modification involved in the pathogenesis of OPIDN.

Journal/Environ Health Perspect. 103: 792-3.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7498088

Journal/Environ Health Perspect. 103: 792-3.

(1994) Multiple chemical sensitivities. Is there a scientific basis?


Not a day goes by that I don't miss my old life and the old me. To illustrate how my life has changed, I have two brief stories. In 1982, I developed a lending procedure in conjunction with Banker's Life Insurance Company that enabled commercial real estate developers to secure permanent financing for property that had not yet been developed--in essence using a permanent loan in place of a construction loan. It fixed the interest rate, at a time when new construction rates were bankrupting many projects and it allowed the developer to invest the excess funds to offset interest expenses. I received national recognition for this loan. In 1989, the police found me wandering around in 15 inches of snow, in below zero weather with no shoes or coat. The officer took me to the hospital because I was obviously disoriented. I didn't even know my name or where I lived. These stories show the disparity between my life as a successful, independent business woman and my life as someone who is chemically disabled.


Low-level chemical sensitivity is hardly a new issue in environmental toxicology. It is, in fact, the focus of risk assessment. The risk assessment process is designed explicitly to estimate the health threats posed by low exposure levels, typically by extrapolating from high experimental or environmental levels. The conventional risk assessment structure, however, was designed primarily around cancer. It is only awkwardly applicable to neurobehavioral toxicants because of the multiplicity of endpoints that have to be considered in evaluating neurotoxicity. At the same time, neurotoxic risk assessment maintains certain advantages over cancer risk assessment because of diminished uncertainties over dose extrapolation. It does not have to depart as far from the range of observable data. The main problem with extending the risk assessment model to issues such as Multiple Chemical Sensitivity (MCS) and Sick Building Syndrome (SBS) is the absence of a specific chemical whose concentration can be measured and then manipulated. A prototypical agent, however, such as a volatile organic solvent, might be selected and studied. Beyond the choice of agent, however, is the question of which behavioral criteria are likely to yield the most useful information. Although neuropsychological test batteries provide one source of data, they typically are administered in a setting other than the one allegedly provoking the syndrome. A different approach invokes what might be called a miniature work situation. Here, a test subject is evaluated in a setting that emphasizes sustained performance testing in the presence of target chemicals. Experimental design is another factor to be considered. Two features are especially critical. The most sensitive design, at least for the current stage of knowledge, would probably emphasize consistency of response, and would choose as subjects individuals who claim to be afflicted with low-level sensitivity. Consistency in a single individual may be more informative than significance tests in a large sample. In addition, consistency as a criterion helps overcome the problem that, in any such sample, only a minor proportion of the subjects may truly exhibit such sensitivity. At a later stage, a broader range of subjects might be targeted. Research on behavioral disorders evoked by food additives illustrates the importance of such questions. It also demonstrates that the methods currently used to assess the potential toxicity of many substances, including food additives, typically ignore subtle, and often sensitive, neurobehavioral measures.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778118
(1994) Activation of cardiac vagal afferents by oxygen-derived free radicals in rats.

Myocardial ischemia and reperfusion can evoke excitation of cardiac vagal afferent nerve endings and activation of a cardiogenic depressor reflex (Bezold-Jarisch effect). We postulate that oxygen-derived free radicals, which are well known to be produced during prolonged ischemia and reperfusion, contribute to this excitation. Hydroxyl radicals derived from hydrogen peroxide (H2O2) activate abdominal sympathetic afferents and produce reflex excitation of the cardiovascular system. However, it is not known whether inhibitory vagal cardiac afferents are activated by oxygen-derived free radicals. We recorded activity from 52 single vagal afferent fibers in 29 rats; the endings of these fibers were located in the walls of all four chambers of the heart. Thirty-three (63%) of these fibers were classified as chemosensitive C-fiber endings because of their irregular discharge under resting conditions, their activation in response to the topical application of capsaicin (1 to 10 micrograms) to the surface of the heart encompassing the receptive field, and their conduction velocities. Fourteen (27%) of the remaining fibers were found to be mechanoreceptors. Topical application of H2O2 to the heart activated 50% of the chemosensitive endings and did not directly affect cardiac mechanoreceptors. Activity increased by 498% at a dose of 3 mumol (P < .001). This effect was reproducible and dose dependent and was not due to [H+]. Topical application of xanthine/xanthine oxidase (20 mmol/0.03 mU) activated 8 of the 12 chemosensitive fibers tested and had no direct effect on mechanosensitive fibers. Activity increased by 287% (P < .001).(ABSTRACT TRUNCATED AT 250 WORDS)

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8156636


Myocardial ischemia and reperfusion can evoke excitation of cardiac vagal nerve endings and activation of a cardiogenic depressor reflex (Bezold-Jarisch effect). We postulate that oxygen-derived free radicals, which are known to be produced during prolonged ischemia and reperfusion, contribute to this afferent excitation. We recorded activity from 47 chemosensitive vagal afferent fibers in 31 rats; the endings of these fibers were located in the left ventricle. Chemosensitive endings were identified with topical applications of capsaicin (10 micrograms) to the surface of the heart. Reactivity of the endings to oxygen-derived free radicals was assessed by topical application of H2O2 (3 to 9 mumol). Activity of the vagal fibers was recorded during 30 minutes of occlusion of the left anterior descending coronary artery (LAD) and 10 minutes of subsequent reperfusion. The activity of chemosensitive endings within the ischemic zone increased in the first 2 minutes of LAD occlusion from 2.2 +/- 0.4 to 4.3 +/- 0.9
impulses per second (107 +/- 30% increase, P < .05). This increased activity waned after 3 to 5 minutes of occlusion. Endings outside the ischemic zone did not increase, their activity at the beginning of ischemia. Reperfusion caused a rapid elevation of activity only in chemosensitive fibers whose endings were found to respond to topical H2O2. The reperfusion-sensitive endings were located both within and outside the ischemic zone of the left ventricle. Indomethacin (5 mg/kg i.v., 20 minutes before occlusion) effectively prevented activation of chemosensitive afferent endings at the beginning of LAD occlusion regardless of their sensitivity to H2O2 but had no effect on the activation at reperfusion.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8156637


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9657704

(1994) Neurogenic vascular headaches, food and chemical triggers.

Recent evidence has demonstrated that neurogenic vascular headaches are a combination of neurological primary events and secondary vasomotor changes. The neurological events involve the hypothalamus and sensory cortex with sympathetic hypofunction and noradrenergic abnormalities. A platelet theory has been proposed but has not really been confirmed as a legitimate cause of the neurogenic vascular headaches. Food and chemicals in foods can act as a precipitating factor in the food-sensitive neurogenic vascular headache patient. In these patients evidence is now being demonstrated to confirm this, but larger patient studies are needed. The food-sensitive migraine patient and cluster headache patient must give a good history and food diary to go along with active challenges and provocative testing in order to determine the causative foods. Any concomitant allergies of inhalants or environmentals must also be treated. The treatment modalities of elimination and rotation diets or provocation neutralization may successfully control the headaches without the need for continuous medications.

(1994) Multiple chemical sensitivities.
Multiple chemical sensitivity syndrome (MCS) does not appear to fit established principles of toxicology. Social, political, and economic forces are demanding that MCS be defined medically, even though scientific studies have failed as yet to identify pathogenic mechanisms for the condition or any objective diagnostic criteria. Consequently, a working definition of MCS can only rely on a person's subjective symptoms of distress and attribution to environmental exposures rather than currently measurable objective evidence of disease. Nevertheless, patients labeled with MCS are clearly distressed and many are functionally disabled. Without reconciling the different theories of etiology of MCS discussed in Part I of this report, and recognizing that the cause of the syndrome may be multifactorial, strategies are proposed for clinical evaluation and management of patients with MCS using a biopsychosocial model of illness. The social implications of this illness are also discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7931737

Multiple chemical sensitivity syndrome (MCS) does not appear to fit established principles of toxicology. Yet social, political, and economic forces are demanding that MCS be defined medically, even though to date scientific studies have not identified pathogenic mechanisms for the condition or any objective diagnostic criteria. Consequently, a working definition of MCS can rely only on an individual's subjective symptoms of distress and attribution to environmental exposures rather than currently measurable objective evidence of disease. Nevertheless, patients labeled with MCS are clearly distressed and many are functionally disabled. In this review, four theories of causation are explored: (1) MCS is a purely biologic/physical or psychophysiological reaction to low-level chemical exposures. (2) MCS symptoms may be elicited by low-level environmental chemical exposures, but the sensitivity is initiated by psychologic stress. (3) MCS is a misdiagnosis and chemical exposure is not the cause.
The symptoms may be due to misdiagnosed physical or psychologic illness. (4) MCS is an illness belief system manifest by culturally shaped illness behavior. Areas for further research regarding the etiologies of MCS are suggested. Recognizing that the cause of the syndrome may be multifactorial, strategies are proposed for clinical evaluation and management in Part II of this manuscript using a biopsychosocial model of illness.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7931736

---------------------------------------------------------------
Sorg, BA, Hooks, MS and Kalivas, PW Journal/Toxicol Ind Health.  10:  369-86.

Time-dependent sensitization (TDS) is a phenomenon described in rodents as an enhancement in the behavioral and neurochemical responses to intermittent exposure to psychostimulant drugs. Time-dependent sensitization also occurs after repeated encounters with environmental stress. Several features of TDS parallel those of multiple chemical sensitivity (MCS) in humans, and these similarities have led to the hypothesis that MCS may be explained in part by a similar sensitization process that occurs in rodents. In the studies presented here, we discuss some of the critical features of TDS following repeated exposure to cocaine and environmental stress, including the anatomical and neurochemical pathways utilized in expressing TDS. In addition, we discuss the possible neurochemical basis for individual differences in responsiveness to stimuli, including novelty and cocaine. The striking similarities between TDS and MCS suggest it may be possible to develop an animal model of MCS, using TDS in rodents as its basis.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778104

---------------------------------------------------------------

Chemical sensitivities display a recurrent pattern on scintigraphic examinations of the brain. The pattern can include mismatching between early and late imaging, multiple hot and cold foci distributed throughout the cortex without regard to lobar distribution (salt and pepper pattern), temporal asymmetries, and sometimes increased activity in the basal ganglia. This study used Desert Shield/Desert Storm veterans who present with abnormal neurological and psychological symptoms as a model to exhibit abnormalities by brain scintigraphy. These are typical of those seen in patients with
documented exposure to neurotoxic compounds who develop a clinical syndrome that has been termed "chemical sensitivity." Exposure to cocaine, alcohol, and other substances of abuse can result in abnormal scintigrams of the brain using tracers such as [technetium-99m]hexamethylpropylenoxime. This study used techniques combining regional cerebral blood flow data with delayed distributional data after the intracellular conversion of the tracer into a hydrophilic molecule. In addition to delayed image abnormalities, a mismatch occurs in the regional activity between the two image sets of the veterans. This degree of mismatch was not seen in control subjects who were screened for avoidance of neurotoxic agents. Patterns identified from examinations performed on patients with known exposure to petroleum distillates, pesticides and other materials linked with neurotoxicity were identified in some veterans of the Desert Shield/Desert Storm operation. A single case of repeated examinations on a veteran showed a reversion of these patterns toward normal after therapy. This reversion followed independent assessments of clinical improvement.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778115


Neuropsychiatric symptoms are among the most prominent manifestations of generalized chemical sensitivity. Patients, clinicians, and researchers are in agreement that symptoms such as depression, irritability, and mood instability are prominent among the distressing and disabling symptoms occurring in response to low-level chemical exposure. Beyond that point, however, agreement is difficult. The pathophysiology and clinical management of these symptoms remain quite controversial. This paper will review available data on the prevalence and form of psychiatric symptoms among those suffering from multiple chemical sensitivity. Various models explaining the relationship of psychiatric symptoms to chemical sensitivity will be discussed. Finally, the implications of these models for clinical management and future research will be reviewed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778109


Microban, a pesticide not registered in California, was sprayed into an operating heating/ventilation/air conditioning (HVAC) unit at an elementary school in San
Francisco, California. This incident occurred on Monday, September 28, 1992, while 396 students and 67 staff members were in the school. The Microban formulation used contains ortho-phenylphenol (0.21%), a quaternary ammonium complex (di-isobutylphenoxy-ethoxy-ethylidimethylbenzyl-ammonium chloride, 0.69%), and bromine (0.04%). This study of the health effects of Microban mist exposure on the school staff was conducted as a result of legal and toxicological concerns. California registration for this formulation had been denied because of inadequate data and because there were concerns about inhalation toxicity in test animals. Predicted health effects from short-duration exposure to Microban are primarily skin and mucous membrane irritation. A self-administered health symptom questionnaire that covered the work week following the evacuation was used to determine a pattern of higher symptom risks for those who were at work on Monday and who reported that they felt they were exposed to a chemical. Symptoms, which were generally consistent with exposure to an irritating chemical, were elevated on Monday and Tuesday; the symptoms normalized by the end of the work week. No additional health effects were detected following application of chlorpyrifos to cracks and crevices for ant control 2 d following the Microban incident. Strict supervision and coordination of pesticide use in public schools are recommended to prevent adverse health effects and emotional trauma in students and staff.


Recent studies from the University of Arizona indicate that normal subjects, both college students and the elderly, can register the presence of low-intensity odors in the electroencephalogram (EEG) in the absence of conscious awareness of the odors. The experimental paradigm involves subjects sniffing pairs of bottles, one containing an odorant (e.g. isoamyl acetate) dissolved in an odorless solvent (water or liquid silicone), the other containing just the solvent, while 19 channels of EEG are continuously recorded. For the low-intensity odor conditions, concentrations are adjusted downward (decreased) until subjects correctly identify the odor bottle at chance (50%). The order of odorants, concentrations, and hand holding the control bottle, are counterbalanced within and across subjects. Three previous experiments found that alpha activity (8-12 hz) decreased in midline and posterior regions when subjects sniffed the low-intensity odors. The most recent study suggests that decreased theta activity (4-8 hz) may reflect sensory registration and decreased alpha activity may reflect perceptual registration. In a just completed experiment involving college students who were selected based on combinations of high and low scores on a scale measuring cacosmia (chemical odor intolerance) and high and low scores on a scale measuring depression, cacosmic subjects (independent of depression) showed greater decreases in low-frequency alpha (8-10 hz) and greater increases in low-frequency beta (12-16 hz) to the solvent propylene glycol compared to an empty
bottle. Topographic EEG mapping to low-intensity odorants may provide a useful tool for investigating possible increased sensitivity to specific chemicals in chemically sensitive individuals.


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778119


Male Sprague-Dawley rats were administered a daily i.p. dose of 0.70 mmol/kg body weight of acrylamide, propionamide (a non-neurotoxic structural analog of acrylamide) or deionized water. Animals were sacrificed when signs of severe neurotoxicity were apparent. Neurofilaments (NFs) and endogenous kinase were isolated from the brain and spinal cord by axonal floatation. Increased in vitro Ca2+/calmodulin-dependent phosphorylation of endogenous and exogenous NF proteins and autophosphorylation of Ca2+/calmodulin protein kinase II (CaM kinase II, EC 2-7-1-37) were observed in samples from both brain and spinal cord of acrylamide-treated animals compared with controls. There was no significant difference between samples isolated from
propionamide-treated animals and controls. Increased calmodulin binding to brain 
supernatant CaM kinase II was also observed as a result of acrylamide treatment. 
There was no significant difference observed in the amount of antibody binding to the 
alpha-subunit of brain supernatant CaM kinase II between treated or control animals. 
These results suggest that increased CaM kinase II-dependent phosphorylation of 
cytoskeletal proteins may be involved in the mechanisms of acrylamide-induced 
neurotoxicity.

(1994) Disruption of GABA-dependent chloride flux by cyclodienes and 
hexachlorocyclohexanes in primary cultures of cortical neurons. 
Pomes, A, Rodriguez-Farre, E and Sunol, C Journal/J Pharmacol Exp Ther. 271: 
1616-23.

The effect of convulsant and nonconvulsant hexachlorocyclohexane (HCH) isomers 
and cyclodienes on GABA-induced Cl- flux was studied in primary cultures of 
neocortical neurons by measuring the GABA-stimulated 36Cl- uptake. GABA induced a 
dose-dependent chloride uptake. The convulsant agents gamma-HCH and cyclodienes 
alpha-endosulfan, dieldrin and aldrin blocked this 36Cl- uptake. A total or partial 
inhibition of GABA-induced 36Cl- uptake was produced by the noncompetitive GABAA 
antagonists picrotoxinin (PTX) and pentylenetetrazol, respectively. The inhibitory 
potencies of 36Cl- uptake by the organochlorine compounds (alpha-endosulfan > 
dieldrin > gamma-HCH > aldrin) were well correlated with their inhibitory potencies of 
[35S]TBPS binding. Positive modulators of GABAergic function (flunitrazepam and 
phenobarbital) prevented the blocking of GABA-induced chloride uptake by PTX but 
not that induced by alpha-endosulfan. The depressant beta- and delta-HCH isomers 
produced a biphasic response, increasing or decreasing the GABA-stimulated chloride 
uptake, depending on the HCH isomer and GABA concentrations used. The present 
results support the idea of cyclodienes and gamma-HCH action at the GABAA receptor 
by interacting with the TBPS binding site. A different interaction of PTX and 
alpha-endosulfan in the same recognition site is also suggested. An increase of 
GABA-induced 36Cl- flux by beta- and delta-HCH can account for the depressant 
activity of these compounds. This work also demonstrates the usefulness of primary 
neuronal cultures to perform functional studies of the GABAA receptor, taking into 
account allosteric interactions between the different recognition sites of the GABAA 
receptor.

(1994) Single-breath nitric oxide measurements in asthmatic patients and 
smokers. 
343: 146-7.
Exhaled nitric oxide (NO) concentrations were measured in asthmatic outpatients and in non-smoking and smoking healthy controls. In single exhalations, NO showed a peak suggestive of airway origin in both controls and asthmatic patients. The peak NO concentration was higher in asthmatic patients and lower in smokers than in non-smoking controls (p < 0.05). The findings support a role for NO in the host defence response in asthma and suggest that NO measurements can discriminate between different types of lung disorders.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7904005


The reporting of physical symptoms is influenced to a large degree by psychological processes. Individuals are more likely to notice subtle sensations in environments lacking in stimulation than those demanding external attention. The beliefs or schemas that people hold dictate where and how they attend to their bodies as well. These normal perceptual processes help explain why people are often poor at accurately detecting internal physiological activity. Several individual differences are also related to the symptom reporting process. Females are more likely to base their symptom reports on external situational cues than are males. In addition, individuals with chronic anxiety--those high in Negative Affectivity (NA)--report more symptoms than those low in NA. Finally, individuals, who have had traumatic experiences, either in childhood or within 1-6 months prior to a major symptom reporting episode, tend to be high symptom reporters. Several recommendations are made to help researchers and clinicians distinguish between psychological or perceptual factors with presumed biological effects. One implication of this work is that MCS and allied syndromes should be viewed as both a mental and a physical health problem.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778110


Technological progress and related social processes will determine the measuring strategies of workplace air monitoring for the nineties even if the objective is dose estimation or compliance. Expectations of the lowest possible exposure, require
workplace air monitoring to be closely linked to process control in a life cycle approach. Production regularity and preventive maintenance also become important factors for strategy design. Workroom air may lose some importance as a dose estimate for the estimation of toxicological risk, as multi-factorial causes for work-related diseases become more evident and a number of syndromes of unknown aetiology become increasingly important. Cancer, cardiovascular diseases, the indoor air syndrome and multiple chemical sensitivity are given as examples. Biotechnology and the information revolution have changed the basic principles of health monitoring and surveillance. The individual worker becomes the target and the possibility of individually adjusted monitoring, surveillance and workplace design becomes important.


Substance abuse, involving drugs such as cocaine, heroin, alcohol, marijuana, nicotine, barbiturates, etc., is by far the most prevalent psychiatric disorder. Much has been learned about the abuse of these substances that may be useful to consider in designing and analyzing research concerning multiple chemical sensitivities (MCS). We review the central role of sensitization in this literature, including its definition, measurement, and expression in animals and human volunteers. Common factors among abused drugs, including sensitization, are discussed. Finally, empirical studies are delineated or proposed to test some of the notions presented in this paper.


(1994) Some preliminary thoughts on the potential contribution of epidemiology to the question of multiple chemical sensitivity.

Epidemiology has played a role in clarifying mysterious symptom complexes such as AIDS, Chronic Fatigue Syndrome, and Psychiatric Disease. Is Multiple Chemical Sensitivity a new environmental disease or another in the parade of psychosomatic syndromes which have come and gone in history. It is proposed that epidemiology can: (1) Describe quantitatively the relative frequency of presenting symptoms and natural history. (2) Work with experimental psychologists to develop double-blind protocols for the "environmental unit" where chemical challenges are said to reveal chemical etiology. (3) Develop an epidemiological definition in a clinical series. (4) Develop an epidemiological definition in cohorts recently exposed to chemicals. (5) Apply the epidemiological definitions in descriptive studies and around hazardous waste sites.

Lead poisoning, the leading environmental illness in this country, is a challenge to our health care and social systems. Because they provide routine health care in a variety of settings, including care to children from poor inner city families, who are most at risk for plumbism, nurse practitioners should be knowledgeable about this illness and prepared to care for children who have it. This article describes the role of a pediatric nurse practitioner in a specialty program who cares for children with lead poisoning and informs the general practitioner about prevention, education, treatment, coordination of care, and long-term follow-up for these children and their families.

Morrow, LA, Steinhauer, SR and Ryan, CM Journal/Toxicol Ind Health. 10: 537-44.

(1994) A toxicologic approach for evaluating cases of sick building syndrome or multiple chemical sensitivity.

The nonspecificity of symptoms and exposures commonly reported as "sick building syndrome" is very similar to that reported for the condition termed "multiple chemical sensitivity (MCS)." In many instances health care practitioners are divided on the reality of the latter. As in all scientific cases of possible cause-and-effect relationships, an organized, dispassionate approach should be used to evaluate each claim of MCS. Most obviously, known medical conditions must be ruled out before chemical "sensitivity" is proposed. Also, several questions on the toxicology of the chemical exposure must be addressed. Although temporality may be apparent (toxicity followed exposure), the time frame for the appearance of symptoms must be appropriate to the exposure conditions and chemical(s) involved. The chemical(s) must have known or reasonably inferred properties to cause the claimed effect. The dose(s) received must
be adequate to effect a response (dose-response characteristics). Alternate causation must be evaluated thoroughly, that is, are there other more logical explanations for the symptoms? In contrast to single-chemical exposures, exposure to mixtures of chemicals, as commonly found in sick buildings, is very difficult to evaluate. However, a rational, scientific approach to cause-and-effect questions will help avoid erroneous and subjective decision making.


Nearly everyone has heard something about chemical sensitivity, either from personal experience with someone who has the condition or from the media. The television series Northern Exposure recently featured a chemically sensitive attorney who lived in a geodesic dome in Alaska, and L.A. Law depicted the struggles of a Persian Gulf veteran with chemical sensitivities who lost his case against the Veterans Administration, but may appeal later in the season. Television news programs and the printed media have showcased patients living spartan existences in remote areas or in aluminum foil-lined rooms. Our views of the illness no doubt are colored by our own personal experiences of it. While some discount or make jokes about chemical sensitivity or these patients, physicians who have seen a number of them are discovering that many appear to be credible individuals with prior good work records who say they became ill following an identifiable exposure to chemicals.


Inhalation exposures can produce asthma and rhinitis by several mechanisms. Sensitization with the production of IgE specific for a substance can lead to symptoms on reexposure via mast cell degranulation and the release of inflammatory mediators. Some substances, known as environmental adjuvants, enhance the immune response to concomitant exposures with the environmental adjuvant. Respiratory irritants can lead to asthma and rhinitis through interaction with chemical irritant receptors in the airway, leading to release of substance P from sensory nerves and neurogenic inflammation. The reactive airways dysfunction syndrome is a chronic asthma-like syndrome resulting from a single acute exposure to a respiratory irritant, while the reactive upper-airways dysfunction syndrome is chronic rhinitis stemming from an irritant exposure. The dysregulation of neurogenic inflammation by chemical exposures may be an important mechanism in the toxic induction of reactive airways dysfunction.
syndrome and reactive upper-airways dysfunction syndrome and may play a role in understanding the sick building syndrome and the multiple chemical sensitivity syndrome.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7932908


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778121


2,5-Hexanedione (2,5-HD) induces central-peripheral axonopathy characterized by the accumulation of 10-nm neurofilaments proximal to the nodes of Ranvier and a Wallerian-type degeneration. It has been postulated that neurofilament crosslinking may be involved in the production of this axonopathy. A potential initiating event in this neurotoxic process may be the direct binding of 2,5-HD to neurofilament and microtubule proteins. In this study, the in vitro binding of [14C]2,5-HD to neurofilament and microtubule proteins was examined. Neurofilament proteins isolated from rat spinal cord or microtubule proteins isolated from rat brain were incubated in the presence of 2,5-HD at concentrations ranging from 25 to 500 mM. Quantitative analysis of sodium dodecyl sulfate (SDS) polyacrylamide gels revealed a dose- and time-dependent binding of 2,5-HD to both neurofilament proteins and microtubule proteins. Expressed as pmol 2,5-HD bound per microgram protein, the observed relative binding was MAP2 > NF160 > NF200 > > NF68 > tubulin. These data demonstrate the direct binding of 2,5-HD to cytoskeletal proteins including both neurofilaments and microtubules.

Kumar, R Journal/Soc Psychiatry Psychiatr Epidemiol. 29: 250-64.
The three main conditions that are associated with childbirth are the maternity blues, postnatal depression and post-partum psychosis. The prevalence of the blues, which are mild, transient and very common disturbances of postnatal mood, does not appear in a major way to be related to environmental, social or cultural factors. Postnatal depression, which has a predominantly psychosocial etiology, surprisingly does not appear to vary in incidence across different cultures in the few studies reported that permit direct comparisons. There is also no good evidence for or against the theory that postnatal depression is partly the consequence of the customs and rituals that traditionally mark the transition to parenthood being stripped away in developed Western societies. However, the lack of relevant research and limitations of method severely restrict any conclusions that can be drawn. There is much firmer evidence for a consistent incidence of post-partum psychosis across cultural and ethnic divides; this observation, together with clinical data and historical evidence of an unchanging incidence rate during the past 150 years, points to a primarily endogenous etiology for the psychoses, which may be triggered by the physiology of childbirth. The transcultural approach to postnatal psychiatric disorders provides a unique opportunity not only to test hypotheses about social and cultural contributions to the etiology of psychotic and non-psychotic reactions to childbirth, but also an opportunity to study the ways in which social factors can influence the evolution of psychopathology. It is also possible that in some cultures the family and social milieu may play a major part in buffering infants from the adverse effects of maternal postnatal illness, but the evidence is anecdotal. Systematic research across cultures will lead to better recognition of maternal illness as well as to better prevention and management.


There are three areas of my experience with chemical sensitivity that may interest you. The first is the onset of this condition and what happened to me over time as I became chemically sensitive in my work place. The second is my experience with the "medical community." The third is the effect chemical sensitivity has had on my career.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778101

(1994) Toxic encephalopathy due to 1,1,1-trichloroethane exposure.

Twenty-eight workers with long-term repetitive high exposures to 1,1,1-trichloroethane were evaluated for complaints of short-term memory loss, disequilibrium, moodiness, irritability, and decreased ability to concentrate. As a group, they had significant deficits
in memory, intermediate memory, rhythm, and speed as measured by the Luria-Nebraska Neuropsychological Battery. Platform posturography demonstrated deficits in vestibular, somatosensory, and ocular components of balance. The encephalopathic picture in these patients is similar to what has been described after exposure to other solvents.


Platelet-activating factor (PAF) is present in the brain. It enhances glutamate release and long-term potentiation (LTP) through an action on synaptic membrane receptors sensitive to the antagonist, BN 52021, and has been proposed as a retrograde messenger in the genesis of LTP. In addition, PAF has other, metabolic actions mediated by microsomal receptors sensitive to the antagonist, BN 50730. We investigated the effect on memory of the pre- or post-training infusion of BN 52021 or BN 50730 into the hippocampus and that of BN 52021 in the amygdala and the entorhinal cortex. Male Wistar rats were implanted bilaterally with cannulae aimed at these brain regions. After recovery from surgery, the animals were trained in step-down inhibitory avoidance using a 0.5-mA foot shock and tested for retention 24 h later. BN 52021 (0.5 microgram/side) was amnestic when given into the hippocampus or the amygdala either before or immediately after training but not 30 or 100 min later. BN 52021 was also amnestic when given into the entorhinal cortex 100 but not 0 or 300 min after training. Intrahippocampally administered BN 50730 had no effect on memory. The findings are compatible with the suggestion from previous findings that memory of this task depends on the generation of LTP at the time of training in hippocampus and amygdala and, 90-180 min later, in the entorhinal cortex.


It has been suggested that superior antioxidant defense systems protect promotion-sensitive (p+t) mouse epidermal JB6 clone 41 cells from excessive deleterious effects of oxidants, allowing their clonal expansion in contrast to that of promotion-resistant (p-) clone 30 cells. In support of this concept, we report that
oxidants produced by xanthine/xanthine oxidase cause more cytotoxicity, cellular
damage, and cell death in p-cells. Cell surface blebbing, an early morphological
consequence of oxidative injury, was detected in cultures grown on glass coverslips.
While a rise in cytosolic ionized calcium ([Ca2+]i) preceding bleb formation was
observed in both p+ and p- cells by digital imaging fluorescence microscopy, elevated
levels of [Ca2+]i were sustained longer in p- cells. This increase was dependent on the
levels of extracellular ionized calcium ([Ca2+]e) in p+ but not p- cells. We conclude that
the superior antioxidant defense or improved Ca2+ buffering of promotable clone 41
cells protects them from more severe deregulation of [Ca2+]i and, as a consequence,
from excessive cytotoxicity after exposure to oxidant promoters.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7945805

---------------------------------------------------------------

(1994) Chlorpyrifos oxon binds directly to muscarinic receptors and inhibits
cAMP accumulation in rat striatum.
Huff, RA, Corcoran, JJ, Anderson, JK and Abou-Donia, MB Journal/J Pharmacol Exp
Ther. 269: 329-35.

Although the acute effects of organophosphorus esters are generally ascribed to
inhibition of acetylcholinesterase, work in this laboratory and others indicates that
organophosphorus insecticides also interact directly with cholinergic receptors. The
current study verifies that the insecticide O,O-diethyl O-3,5,6-trichloro-2-pyridinyl
phosphorothionate (chlorpyrifos) and its oxon metabolite inhibits acetylcholinesterase
(AChE). The metabolite inhibits rat brain AChE three orders of magnitude more rapidly
than chlorpyrifos. In addition to their ability to inhibit AChE, these compounds were
shown to interact directly with muscarinic receptors of rat striatum. The oxon metabolite
bound at low concentrations to muscarinic receptors labeled by the muscarinic agonist
[3H] cis-methylidioxolane; chlorpyrifos oxon bound with an IC50 value of 22.1 +/- 3.6
nM. The receptors bound by chlorpyrifos oxon account for approximately 30% of
muscarinic receptors of the striatum and are of the m2 subtype. The binding of
chlorpyrifos oxon to the m2 receptor results in a covalent modification of the receptor
that does not interfere with the ability of the receptor to interact with the agonist
carbachol. This receptor modification may be responsible for the inhibition of adenylate
cyclase activity by chlorpyrifos oxon. The oxon inhibited adenylate cyclase with an IC50
of 155 +/- 78 nM. The inhibition of adenylate cyclase activity was not blocked by
atropine and was additive to that produced by carbachol. The altering of postreceptor
signal transduction by chlorpyrifos oxon may interfere with normal cellular signaling,
thereby disturbing neurological function. Direct interaction of chlorpyrifos oxon with
muscarinic receptors and associated signal transduction is a potential mechanism of
neurotoxicity that is independent of AChE inhibition.

---------------------------------------------------------------

cis-Methyldioxolane (CD) is a muscarinic receptor agonist. [3H]CD has been used to label a subpopulation of muscarinic receptors described as exhibiting high agonist affinity. Pharmacological evidence suggests that the population of receptors labeled by [3H]CD consists of m2 and/or m4 subtypes; however, no studies have directly addressed the subtype selectivity of [3H]CD. The present study characterizes binding of this ligand to individual human receptor subtypes expressed in transfected Chinese hamster ovary cells. Results indicate that [3H]CD binds with high affinity only to Hm2 receptors but not to all Hm2 receptors. Twenty-eight percent of Hm2 receptors bound [3H]CD with a KD of 3.5 +/- 0.5 nM. Binding was eliminated in the presence of guanosine 5’-O-(3-thiotriphosphate), indicating that the Hm2 receptors labeled by [3H]CD are those that are associated with GDP-bound G protein. Binding of [3H]CD by only a subpopulation of Hm2 receptors is in agreement with data generated from studies of [3H]CD binding in mammalian brain. Because muscarinic receptors have been implicated to play a role in the pathogenesis of both Alzheimer's and Parkinson's disease, as well as the neurotoxicity of organophosphorus compounds, knowledge of the binding specificity of the muscarinic agonist [3H]CD should aid research in these areas.


Exposures to neurotoxic chemicals such as pesticides, glues, solvents, etc. are known to induce neurologic and psychiatric symptomatology. We report on 41 patients--16 young patients (6 males, 10 females, age 34 +/- 8 yrs.) and 25 elderly patients (9 males, 16 females, age 55 +/- 7 yrs). Fifteen of them were exposed to pesticides, and 29 to solvents. They were studied with quantitative and qualitative analysis of regional cerebral blood flow (rCBF), performed with 30 mCi of Xe-133 by inhalation, followed by 30 mCi of Tc-HMPAO given intravenously. Imaging was performed with a brain dedicated system, distribution of rCBF was assessed with automatic ROI definition, and HMPAO was normalized to maximal pixel activity in the brain. Results of Xe rCBF are expressed as mean and S.D. in ml/min/100g, and HMPAO as mean and S.D. uptake per ROI, and compared with age-matched controls--10 young and 20 elderly individuals. table: see text] We conclude that patients exposed to chemicals present with diminished CBF, worse in the right hemisphere, with random presentation of areas of hypoperfusion, more prevalent in the dorsal frontal and parietal lobes. These findings are significantly different from observations in patients with chronic fatigue and depression, suggesting primary cortical effect, possibly due to a vasculitis process.
(1994) In vivo and in vitro effects of diisopropyl phosphorofluoridate (DFP) on the rate of hen brain tubulin polymerization.

Diisopropyl phosphorofluoridate (DFP) produces organophosphorus ester-induced delayed neurotoxicity (OPIDN) in sensitive species. We have investigated the in vivo and in vitro effects of DFP on hen brain tubulin polymerization. Hens were treated with a single dose of DFP (1.7 mg/kg, sc.), and were sacrificed after 18-21 days. Tubulin from DFP-treated hen brains showed small but significant decrease (14.42%) in the rate of polymerization and 11.05% decrease in rise in O.D. at 340 nm in 30 min. DFP in vivo treatment also resulted in decreased concentration of tau and an enhanced concentration of two peptides (45 kDa, 35 kDa) in the brain supernatant. These peptides seemed to be the degradation products of MAP-2. The decrease in the rate of brain tubulin polymerization in treated hens is consistent with neurochemical alterations and the focal degeneration and aggregation of these filamentous structures in OPIDN.


The clinical ecology model of environmental illness, or multiple chemical sensitivity (MCS), and particularly the theoretical assumptions, diagnostic procedures, and therapeutic recommendations promulgated by clinical ecologists are reviewed. No scientific evidence is found for their claims. MCS is conceptualized, instead, as a phobic disorder explicable in terms of the two-factor model of avoidance. Three cases of MCS are discussed in light of this model, and a comprehensive behavioral treatment package that includes biofeedback-assisted in vivo desensitization and cognitive restructuring is proposed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7852602

(1994) Tobacco smoke tumor promoters, catechol and hydroquinone, induce oxidative regulation of protein kinase C and influence invasion and metastasis of lung carcinoma cells.

Cigarette smoke polyphenolic agents (catechol and hydroquinone) that generate oxidants have been shown to be tumor promoters. Furthermore, oxidants can influence protein kinase C (PKC)-mediated signal transduction. Since terpenoid tumor promoters, phorbol esters, increase invasion and metastasis by activating PKC, we have determined whether polyphenolic agents present in the cigarette smoke condensate (CSC) could also influence these events. Hydroquinone (50 microM), catechol (500 microM), or CSC (50 micrograms/ml) induced an initial cytosol-to-membrane translocation of PKC in LL/2 lung carcinoma cells, followed by a later down-regulation of the enzyme. LL/2 cells treated with these CSC-related agents for a limited time (45 min) and exhibiting high membrane-associated PKC activity, when injected into mice through the tail vein, produced an increase in metastatic nodules in the lungs after 20 days. However, cells treated with CSC-related agents for a prolonged period did not exhibit an increase in metastasis. Agents that decrease the rate of production of reactive oxygen species, such as catalase either alone or in combination with superoxide dismutase, and a cell-permeable iron-chelator, o-phenanthroline, inhibited CSC-mediated membrane association of PKC and metastasis. Prior treatment of CSC with tyrosinase to modify polyphenols resulted in a partial loss of CSC stimulation of metastasis. Furthermore, a cell-permeable Ca2+ chelator and diverse PKC inhibitors, such as calphostin C, hypericin, chelerythrine, and bisindolylmaleimide, inhibited CSC-enhanced metastasis. CSC increased in vitro tumor cell adhesion to endothelial monolayers and to reconstituted basement membrane (Matrigel) and also enhanced the invasion through Matrigel coated on the polycarbonate filters in Transwells. All these CSC effects were found to be temporary and were blocked by the above mentioned antioxidant systems and PKC inhibitors. Thus, these results suggest that the oxidants generated by autooxidation of polyphenolic agents present in tobacco smoke increase tumor cell invasion and metastasis, at least in part by activation of Ca2+/PKC signal transduction. Conceivably, cigarette smoke constituents not only promote tumorigenesis but also may increase the spread of cancer in the body.


(1994) Effect of activity at metabotropic, as well as ionotropic (NMDA), glutamate receptors on morphine dependence.
1. The contribution of various excitatory amino acid (EAA) receptors (NMDA, AMPA, kainate and metabotropic) in the brain to the development of morphine dependence was examined. This was performed by measuring the severity of the precipitated withdrawal syndrome following chronic subcutaneous (s.c.) morphine and intracerebroventricular (i.c.v.) EAA antagonist treatment. 2. Continuous subcutaneous (s.c.) treatment with morphine sulphate (36.65 mumol day⁻¹) produced an intense and reliable naloxone-precipitated withdrawal syndrome. 3. Chronic i.c.v. treatment with antagonists selective for metabotropic and NMDA receptors, but not AMPA/kainate receptors, significantly attenuated abstinence symptoms. Conversely, EAA antagonists had very little effect on non-withdrawal behaviours. 4. These results suggest that, as well as changes elicited by activation of NMDA receptors, metabotropic receptors and intracellular changes in the phosphatidylinositol (PI) second-messenger system or the cyclic adenosine 3',5'-monophosphate (cAMP) second messenger system, to which EAA metabotropic receptors are linked, may be involved in the development of opioid dependence with chronic morphine treatment.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7889275


Neurological sensitization has been proposed as a model for post-traumatic stress disorder (PTSD) (Lipper et al., 1986; van der Kolk, 1987; Friedman, 1988; Post et al., 1988, 1994; Charney et al., 1993). Laboratory paradigms in which repeated exposure to a discrete stimulus is associated with progressive intensification of a neurophysiologic, behavioral, or pharmacologic response has many parallels with the sequence of events that precipitates PTSD. Investigators with other clinical interests have also been attracted to sensitization models. Specifically, Bell and associates (1992) have proposed that olfactory-limbic kindling is a very good model for understanding the etiology of multiple chemical sensitivity (MCS) syndrome. A number of articles in this volume have addressed the goodness-of-fit between this model and MCS. My major assignment is to review laboratory data and clinical observations pertinent to sensitization models of PTSD. I will show that although there are intriguing parallels between the two phenomena, one must have great respect for the complexity and polymorphism of both sensitization and PTSD before grasping for simplistic theoretical conclusions. Secondly, I will address the following question; if both PTSD and MCS can be understood as sensitization phenomena, are PTSD patients at greater risk to develop MCS and vice versa? This article is divided into four sections: a) a description of three distinct sensitization phenomena; b) a description of the symptoms of PTSD; c) a review of the applicability of sensitization models to the clinical phenomenology of PTSD; and d) a review of the hypothesis that PTSD patients might be more vulnerable to MCS.
Neurological symptoms are frequently reported by patients with multiple chemical sensitivities (MCS). Methods to compare the psychiatric, personality, and neuropsychological function of patients with MCS, chronic fatigue syndrome (CFS), and normal controls are described. Increased rates of Axis I psychiatric diagnoses are observed in the literature for MCS and CFS subjects relative to controls. Findings on the MMPI-2 and the Toronto Alexithymia Scale reveal profiles consistent with the tendency to report somatic rather than emotional symptoms in response to stress. However, many of the reported somatic symptoms also coincide with those found in neurologic disorders. The overall neuropsychological profile for MCS subjects does not reflect cognitive impairment. Relative to normal controls, the only difference in neuropsychological performance observed is reduced recognition of nontarget designs on a visual memory task. More fruitful areas for future psychological research will include measurement of the interaction between behavioral response styles and attentional processes in cognition, as well as observations under controlled challenge conditions.

Dextromethorphan attenuates and reverses analgesic tolerance to morphine.

Tolerance to the antinociceptive (analgesic) effect of morphine, a mu-opioid agonist, was developed in male CD-1 mice as assessed by a shift to the right of the analgesic (tail-flick) dose-response curves and an increase in the ED50 values. Administration of dextromethorphan at 30 mg/kg s.c., but not saline, 30 min prior to an escalating 3 times per day (t.i.d.) morphine dosing schedule prevented a 5-fold increase in the morphine ED50 value observed on treatment day 4. Concurrent administration of dextromethorphan at 12 mg/kg/24 h by s.c. infusion prevented the 6-fold increase in the morphine ED50 value that was observed in control mice that received morphine at 30 mg/kg/24 h by s.c. infusion. Implantation of two 25 mg morphine pellets resulted in a 10-fold increase in the morphine ED50 value on treatment day 4. Administration of dextromethorphan at 30 mg/kg s.c. t.i.d., but not saline, resulted in a reversal of
morphine tolerance with the almost complete return of the morphine ED50 value to the control (opioid naive) value. These results demonstrate that dextromethorphan, an NMDA receptor antagonist can modulate morphine (mu-receptor)-mediated tolerance.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7708410

(1994) Americans with Disabilities Act accommodation issues may apply to environmental illness.
Dubin, DF Journal/Healthspan. 11: 22-38.

---------------------------------------------------------------

(1994) Olfaction and multiple chemical sensitivity.
Doty, RL Journal/Toxicol Ind Health. 10: 359-68.

In this paper, a description of olfactory anatomy is presented, followed by a brief review of modern procedures for testing olfactory function. Information from the sole study which has quantitatively examined olfactory function in patients with apparent multiple chemical sensitivity (MCS) is presented. In essence, this study suggests that MCS is associated with increased nasal airflow resistance, respiration rate, heart rate, and scores on the Beck Depression Inventory, but not with significant changes in odor detection threshold sensitivity to phenyl ethyl alcohol and methyl ethyl ketone, the two target stimuli evaluated. Whether MCS patients evidence hypersensitivity to other chemicals is unknown.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7539950

---------------------------------------------------------------


Chronic fatigue syndrome (CFS) is an illness that results in debilitating fatigue as well as rheumatological, infectious, and neuropsychiatric symptoms. The present paper is a brief overview of the neuropsychological and psychiatric research on CFS. Studies from our laboratory contrasting CFS with patients with multiple sclerosis, depression, and healthy controls are detailed. Our hypothesis of neuropsychological impairments in CFS is discussed.
(1994) **Psychogenic origins of multiple chemical sensitivities syndrome: a critical review of the research literature.**

The purpose of this review was to critically evaluate research on the psychogenic origins of multiple chemical sensitivities (MCS) syndrome. Using as keywords environmental illness, multiple chemical sensitivities, and clinical ecology, two databases--PsychLit and Medline--were searched by computer; reference lists of all articles located were also searched manually. Ten articles meeting three criteria were selected for review. Five sample selection problems, seven measurement problems, and three study design problems were common in all but one of the articles reviewed. Current studies investigating psychogenic hypotheses of MCS syndrome are methodologically problematic and their conclusions questionable. Studies of psychiatric profiles observed in MCS syndrome need to be designed to differentiate between competing psychogenic and biogenic hypotheses.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7944561

(1994) **Neurasthenic fatigue, chemical sensitivity and GABAa receptor toxins.**

Following observation of fatigue syndromes in people who have been occupationally exposed to pesticides and insecticides which exert their toxicity through the GABAa receptor, we have formulated the hypothesis that fatigue syndromes in general may be secondary to altered sensitivity of the GABAa receptor. We discuss the possible involvement of organochlorine compounds which are widespread in the environment. Organophosphate compounds may have similar toxic effects through damaged cholinergic input to the dentate gyrus of the hippocampus where cholinergic and GABAergic transmission are closely linked.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7838000

(1994) **Persistent respiratory health effects after a metam sodium pesticide spill.**
Cone, JE, Wugofski, L, Balmes, JR, Das, R, Bowler, R, Alexeiff, G and Shusterman, D

STUDY OBJECTIVE: To report the occurrence of persistent respiratory disorders, including irritant-induced asthma, among adults living and working near an environmental spill of the pesticide, metam sodium, after the derailment of a tank car. DESIGN: Retrospective clinical case series. SETTING: California communities situated within one-half mile of the Sacramento River, from Mt. Shasta City to Shasta Lake. PATIENTS: 197 adults referred to a university occupational/environmental health clinic or to a private occupational/environmental health practitioner for evaluation of health problems potentially related to the spill. MEASUREMENTS AND RESULTS: History, physical examination, review of medical records, spirometry, and methacholine challenge testing revealed 20 cases of persistent irritant-induced asthma and 10 cases of persistent exacerbation of asthma. CONCLUSIONS: This is the first reported series of cases of persistent irritant-induced asthma involving both community residents and occupationally exposed individuals.


(1994) Multiple chemical sensitivity or multi-organ dysesthesia.

(1994) The utility of excitatory amino acid (EAA) antagonists as analgesic agents. II. Assessment of the antinociceptive activity of combinations of competitive and non-competitive NMDA antagonists with agents acting at allosteric-glycine and polyamine receptor sites.

The present study examined the utility of using low-dose combinations of agents acting within the NMDA receptor complex to produce analgesic effects without producing motor dysfunction. In particular, we assessed the antinociceptive activity in the formalin test of combinations of competitive (APV) and non-competitive (MK-801) NMDA receptor antagonists with agonist and antagonists acting at allosteric-glycine and polyamine receptors. Both the competitive NMDA receptor antagonist APV and the non-competitive NMDA antagonist MK-801 produced dose-dependent analgesic effects in the late, but not the early, phase of the formalin test. The antinociceptive activity of APV was significantly enhanced by combination with a non-analgesic dose of the allosteric-glycine agonist glycine, and was reduced by combination with the allosteric-glycine antagonist 7-CKA which also reversed the glycine-induced
enhancement of the antinociceptive effects of APV. The antinociceptive activity of MK-801 was significantly enhanced by combination with a non-analgesic dose of the polyamine agonist spermine, and reduced by combination with the polyamine receptor antagonist IFEN which also reversed the spermine-induced enhancement of the antinociceptive effects of MK-801. The enhancement of the antinociceptive activity of APV and MK-801 by glycine and spermine, respectively, was not accompanied by increases in motor dysfunction. Thus, by using specific combination of agents acting within the NMDA receptor complex, it was possible to produce effective antinociception in the formalin test at doses of NMDA receptor antagonists which did not produce motor dysfunction.


Oxidant carcinogens interact with multiple cellular targets including membranes, proteins, and nucleic acids. They cause structural damage to DNA and have the potential to mutate cancer-related genes. At the same time, oxidants activate signal transduction pathways and alter the expression of growth- and differentiation-related genes. Indeed, the carcinogenic action of oxidants results from the superposition of these genetic and epigenetic effects. All cells possess elaborate antioxidant defense systems that consist of interacting low and high molecular weight components. Among them, superoxide dismutases (SOD), glutathione peroxidases (GPx), and catalase (CAT) play a central role. Our studies with mouse epidermal cells demonstrate that the balance between several antioxidant enzymes rather than the activity of a single component determines the degree of protection. Unexpectedly, increased levels of Cu,Zn-SOD alone in stable transfectants resulted in sensitization to oxidative chromosomal aberrations and DNA strand breaks. However, a concomitant increase in CAT or GPx in double transfectants corrected or overcorrected the hypersensitivity of the SOD clones depending on the ratios of activities CAT/SOD or GPx/SOD. The cellular antioxidant capacity also affected oxidant induction of the growth-related immediate early protooncogene c-fos. Increases in CAT or SOD reduced the accumulation of c-fos message, albeit for different reasons. The cellular antioxidant defense also affects the action of UVB light (290-320 nm) that represents the most potent carcinogenic wavelength range of the solar spectrum. UVB light is known to exert its action in part through oxidative mechanisms. Increases in CAT and GPx protected mouse epidermal cells from UVB-induced DNA breakage. (ABSTRACT TRUNCATED AT 250 WORDS)

(1994) American Conference of Governmental Industrial Hygienists: low threshold of credibility.

(1994) Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities.

BACKGROUND: Chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivities (MCS) are conditions associated with fatigue and a variety of other symptoms that appear to share many clinical and demographic features. Our objectives were to describe the similarities and differences among patients with CFS, FM, and MCS. Additional objectives were to determine how frequently patients with MCS and FM met the criteria for CFS and if they differed in their health locus of control. METHODS: Demographic, clinical, and psychosocial measures were prospectively collected in 90 patients, 30 each with CFS, FM, and MCS. Patients were recruited from a university-based referral clinic devoted to the evaluation and treatment of chronic fatigue and three private practices. Variables included demographic features, symptoms characteristic of each condition, psychological complaints, a measure of health locus of control, and information on health care use. RESULTS: Overall, the three patient groups were remarkably similar in demographic characteristics and the presence of specific symptoms. Patients with CFS and FM frequently reported symptoms compatible with MCS. Likewise, 70% of patients with FM and 30% of those with MCS met the criteria for CFS. Health care use was substantial among patients with CFS, FM, and MCS, with an average of 22.1, 39.7, and 23.3 visits, respectively, to a medical provider during the prior year. Health locus of control did not differ among the three populations. CONCLUSIONS: In general, demographic and clinical factors and health locus of control do not clearly distinguish patients with CFS, FM, and MCS. Symptoms typical of each disorder are prevalent in the other two conditions.


Psychological, and psychophysiological sequelae were studied in a community which had experienced a railroad chemical spill of 19,000 gallons of the toxic pesticide metam sodium. Information was collected on 350 persons living in the area of the spill (spill residents) and 114 nonexposed controls, recruited using a randomized sampling strategy, from a nearby similar, but unexposed control town. Psychological measures used were the MMPI-2, POMS, IES Scale, Environmental Worry, Perceived Social Support and Perceived Control Scale. Physiological measurements were two measurements of blood pressure, pulse, and salivary cortisol level, taken both at the beginning and the conclusion of the study. Demographic and medical information was asked in a Questionnaire. Results indicate greater levels of depression, anxiety, and somatic symptoms in the spill residents in addition to greater environmental worry and lower perceived social support. Spill odor perception was related to increased psychological and physiological sequelae. The spill residents had higher blood pressure and less fluctuation of cortisol levels than the controls. Comparison of spill residents who were litigants and those who were not, indicates no differences for blood pressure, pulse, and cortisol, MMPI-2, Environmental Worry and the Control Scale. Litigants scored slightly higher on the IES, Intrusion and the POMS scales. No dose response relationship between distance to the river and evacuation status was obtained. The chemical spills was associated with a wide variety of psychological and physiological reactions.


-------------------------------------------

(1994) Psychological, psychosocial, and psychophysiological sequelae in a community affected by a railroad chemical disaster.

Psychological, psychosocial, and psychophysiological sequelae were studied in a community which had experienced a railroad chemical spill of 19,000 gallons of the toxic pesticide metam sodium. Two hundred twenty exposed residents were compared to 114 controls and paired on age, education, gender, race, and number of children. A clinical interview and physiological measurements (blood pressure, pulse, and cortisol level) were taken, the MMPI-2, IES Scale, Mood Scale, Environmental Worry, Perceived Social Support, and Perceived Control Scale and a questionnaire were administered. Results indicated greater levels of depression, anxiety, and somatic symptoms in the spill residents in addition to greater environmental worry and lower perceived social support. Spill residents had higher blood pressure and less fluctuation of cortisol levels than controls. No difference on litigation status was obtained except on the IES, Intrusion and the POMS scales. Chemical disasters are associated with a wide variety of psychological, psychosocial, and physiological distress.


I am Jacob B. Berkson, a 68-year-old resident of Hagerstown, Maryland. I was a trial lawyer for some 40 years. I am now retired and writing a book on Environmental Pollution and Environmental Illness, titled A Canary's Tale. I was invited to speak to you as a patient--one who was poisoned by an organophosphate pesticide and who subsequently developed Multiple Chemical Sensitivity (MCS, or sometimes referred to as Environmental Illness, EI).

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7539948

(1994) Sensitization to early life stress and response to chemical odors in older adults.
Bell, IR, Schwartz, GE, Amend, D, Peterson, JM and Stini, WA Journal/Biol Psychiatry. 35: 857-63.

This study examined the hypothesis that older persons who currently report illness from environmental chemical odors (cacosmia) may have experienced higher levels of stress early in life than did noncacosmic controls. The hypothesis derives from a time-dependent sensitization (TDS) model for cacosmia (Bell et al 1992) that predicts a relative interchangeability of stress and chemicals in inducing and eliciting sensitized responses in vulnerable individuals. Subjects were selected from those in the top 24% (cacosmic) and bottom 27% (noncacosmic) of a sample of 192 older adults (mean age 73.8 years) for self-reported frequency of illness form the odors of pesticide, car exhaust, paint, perfume, and new carpet. As in previous investigations, cacosmics were younger, more depressed, and more shy; cacosmics also included a higher proportion of women (83% versus 61%). As predicted, cacosmics rated themselves higher in stress for the first four decades of their lives, but not the recent past or present, even after controlling for depression, anxiety, hostility, shyness, age, and gender. Cacosmics reported increased prevalence of physician-diagnosed nasal allergies, breast cysts, hypothyroidism, sinusitis, food sensitivities, irritable bowel, and migraine headache. Only 4% of the overall sample (including 9% of the cacosmics) acknowledged the controversial physician diagnosis of "chemical sensitivity." The replicated observation of greater shyness in cacosmics is consistent with the ability of hyperreactivity to novelty to predict enhanced susceptibility to TDS from low levels of pharmacological agents in animals. The findings support a TDS model for cacosmia and suggest that cacosmia as a symptom identifies a large subset of the nonindustrial population with significant psychophysiological health problems that merit further objective examination.
(1994) Psychological characteristics and subjective intolerance for xenobiotic agents of normal young adults with trait shyness and defensiveness. A parkinsonian-like personality type?

The present study examines the psychological characteristics and self-reported responses to xenobiotic agents such as tobacco smoke and pesticide of normal young adults with personality traits similar to those claimed for Parkinsonian patients. Previous research, though controversial, has suggested that persons with idiopathic Parkinson's disease (PD) have premorbid personality traits that may include shyness and repressive defensiveness. Other epidemiological evidence indicates that PD patients may have premorbidly increased prevalence of anxiety, affective, and/or somatoform disorders; decreased rates of smoking and alcohol consumption; and elevated exposure to herbicides or pesticides. A total of 783 college students enrolled in an introductory psychology course completed the Cheek-Buss Scale (shyness), the Marlowe-Crowne Social Desirability Scale (defensiveness), Symptom Checklist 90 (revised), the Mastery Scale, a health history checklist, and rating scales for frequency of illness from alcohol and 10 common environmental chemicals. Subjects were divided into four groups on the basis of above-versus below-median scores on the Cheek-Buss and Marlowe-Crowne scales (persons high in shyness and defensiveness, those high only in shyness, those high only in defensiveness, and those low in both shyness and defensiveness). The group high in shyness but low in defensiveness had the highest, whereas the group low in shyness but high in defensiveness had the lowest, total scores on the SCL-90-R; the two shyest groups were lowest in sense of mastery.(ABSTRACT TRUNCATED AT 250 WORDS)

Bell, IR Journal/Toxicol Ind Health. 10: 277-312.

The present paper summarizes the proposed time-dependent sensitization (TDS) and partial limbic kindling model for illness from low-level chemicals; reviews and critiques prior studies on CNS aspects of multiple chemical sensitivity (MCS); and outlines possible experimental approaches to future studies. TDS is the progressive and persistent amplification of behavioral, neurochemical, endocrine, and/or immunological responses to repeated intermittent stimuli over time. Partial limbic kindling is a progressive and persistent lowering of the threshold for eliciting electrical afterdischarges, but not motor seizures, in certain brain structures such as amygdala
and hippocampus; behavioral consequences include increased avoidant behaviors. The focus of the paper is the controversial claim of altered sense of smell and illness from low levels of environmental chemicals (i.e., "cacosmia"), levels that should not have any biologically harmful effects by the rules of classical neurotoxicology. A major perspective of this paper is that the phenomenology of MCS is similar to that of time-dependent sensitization (reverse tolerance) and tolerance as studied in the substance abuse literature. The TDS model for MCS proposes that neurobiological amplification underlies the symptoms and phenomenology of these patients, including their behavioral features of heightened affective and somatic distress. It is hypothesized that MCS patients, who are mostly women, may be individuals who sensitize to substances rapidly and to the extreme, to the point of aversive symptomatology with less complete capacity for development of tolerance. Possible parallels between MCS and TDS include: (a) initiation by single or multiple intermittent stimuli; (b) lasting changes in subsequent reactivity to low levels of chemically unrelated substances; (c) cross-sensitization between the stressors and pharmacological agents; (d) greater vulnerability of individuals who are female, who have certain genetic characteristics, and/or who may be hyperreactive to novelty (cf. trait shyness); (e) lack of obvious differences between sensitized and unsensitized individuals at baseline without eliciting exposures; (f) bidirectionality (bipolarity) of sensitized responses; (g) both context-dependent (conditioned) and context-independent (unconditioned) amplification of responses. To minimize variability between studies, research in this area needs (a) consensus on a working case definition of MCS or at least of cacosmia as a specific symptom in a subset of well-defined medical and psychiatric disorders; and (b) proper design of chemical challenge studies in MCS, controlling for individual differences in sensitizability and for the properties of sensitization (e.g., repeated intermittent exposure tests) and tolerance (e.g., removal from customary ambient air exposures prior to testing).

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778100

Bell, IR Journal/Biol Psychiatry. 35: 81-3.

(1994) **Pesticides.**

(1994) **Monitoring the worker and the community for chemical exposure and disease: legal and ethical considerations in the US.**

Biomonitoring of workers and communities raises important legal and ethical concerns, but the two contexts are different. Monitoring workers is usually done by, or at the instigation of, the employer who, in law, is responsible for their health and safety. Whenever worker monitoring leads to the removal of workers, difficult issues emerge affecting labor-management relations, labor law, and discrimination law. Resulting legal and ethical questions are usually framed with the context of the employment contract or labor relationship. In contrast, public health or environmental officials may be the driving force behind biomonitoring of the community. No employer-employee relationship exists, and the doctor-patient relationship may be tenuous. The community may often request biomonitoring, but the situation is no less contentious. On the basis of an historical view of monitoring events within the US, mechanisms are suggested to promote positive interactions between employers and workers and among agencies, individuals, and groups in the monitoring of chemically contaminated communities.

(1994) **Time-dependent sensitization in animals: a possible model of multiple chemical sensitivity in humans.**
Antelman, SM Journal/Toxicol Ind Health. 10: 335-42.

It often happens in science that clues to the nature of a problem under study come from a completely different, seemingly unrelated, line of investigation. This may be the case with MCS and Time-Dependent Sensitization (TDS), a phenomenon we discovered in rats in the late 1970s and later named. TDS refers to the ability of mild stressors--whether pharmacological or environmental--to induce physiological and behavioral effects which then progress, i.e., get stronger, entirely as a function of the passage of time since stressor presentation. This strengthening is revealed when the organism is later exposed to either the original or another stressor. The characteristics
of TDS bear a remarkable resemblance to the features of MCS and that similarity is the subject of this manuscript.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778103


The balance between several components of the antioxidant defenses appears to be important for the cellular resistance to oxidative stress. While Cu,Zn-superoxide dismutase (SOD) transfectants of mouse epidermal cells JB6 clone 41 were sensitized to oxidants produced by xanthine/xanthine oxidase (X/XO) consecutive transfection with catalase corrected their hypersensitivity (Amstad, P., Peskin, A., Shah, G., Mirault, M. E., Moret, R., Zbinden, I., and Cerutti, P. (1991) Biochemistry 30, 9305-9313). We studied the effect of the transfection of bovine selenoglutathione peroxidase (GPx) on the sensitivity of JB6 clone 41 and its SOD transfectants. Sensitivity to DNA strand breakage and killing by X/XO was reversely related to the activity ratios GPx over SOD. A GPx-transfectant of JB6 clone 41 cells with a GPx/SOD ratio of 3.8 was very strongly protected. The hypersensitivity of the SOD clones with GPx/SOD ratios of 0.4 was corrected or overcorrected by secondary transfection with bovine Se-GPx resulting in increased activity ratios GPx/SOD of 1 to 2.4. Our results indicate that small deviations from the physiological activity ratios of GPx/SOD have a dramatic effect on the resistance of cells to oxidant-induced damage to the genome and cell killing.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8294405


b38d6e8d3e4dbbddd3c31ae217c5dac24

(1994) Modelling anxiety disorders following chemical exposures.
The effects of kindling and inverse benzodiazepine receptor agonist beta-carbolines on animal models of anxiety are briefly reviewed in relation to affective disorder associated with chemical exposure. Recent experimental results are described. In the present study, cats were given the inverse benzodiazepine receptor agonist, FG-7142, a powerful anxiogenic compound in humans and animals. Neural transmission in pathways involved in defensive behavior in the cat was monitored using evoked potential techniques. Change in these pathways was related to behavioral changes induced by the drug. It was found that a single dose of FG-7142 lastingly increased defensive response to rodents for at least 40 days after drug administration. Behavioral change was specific to defensive response, since approach-attack behavior remained unchanged, replicating previous studies. The benzodiazepine receptor antagonist, Flumazenil, reversed the increase in defensiveness in a drug-dependent manner, replicating previous findings. Increased defensiveness was paralleled by a delayed onset potentiation of neural transmission between the amygdala and the medial hypothalamus of the left hemisphere. Potentiation in the left hemisphere was transient, decaying between 6 and 12 days after the drug. There was a longer lasting potentiation (LTP) of activity evoked in the left and right amygdalo-periaqueductal gray pathways and in the right amygdalo-medial hypothalamic pathway. Potentiation in these pathways appeared at the time of behavioral change. Potentiation of the right amygdalo-periaqueductal gray and right amygdalo-medial hypothalamic pathways persisted until the end of the experiment. In contrast, potentiation of the left amygdalo-periaqueductal gray pathway faded by 40 days after the drug. Flumazenil decreased potentiation only in the right amygdalo-periaqueductal gray pathway. These data strongly suggest that lasting affective change is mediated by lasting changes in particular efferents of the amygdala of the right hemisphere. Behavioral and physiological effects of FG-7142 were blocked by the N-methyl-D-Aspartate (NMDA) receptor blocker, AP7. The data suggest that failure of neural inhibition induced by FG-7142 engages NMDA receptor processes to produce lasting potentiation of transmission in neural circuits that mediate defensive response with behavioral consequences. Since FG-7142 interferes with GABA mediated neural inhibition and is proconvulsant, its action might mimic the action of other environmental chemicals with similar properties, such as chlorinated hydrocarbon insecticides. The relationship of the present data to the literature on the neural and behavioral effects of insecticide exposure is discussed. The significance of these findings for multiple chemical sensitivity disorder is also briefly discussed.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7778105

-------------------------------------------------------------------------------


The Ca2+/calmodulin-dependent phosphorylation of neuronal cytoskeletal proteins was studied in brain supernatants prepared from rats exposed via inhalation to 600 to 800 ppm carbon disulfide (CS2) for 14 days. Exposure to CS2 resulted in increased phosphorylation of endogenous MAP-2 and exogenously added neurofilament triplet proteins. There also was an observed increase in the autophosphorylation of Ca2+ calmodulin-dependent protein kinase II (CaM kinase II). Slight increases in the binding of a monoclonal antibody to the alpha subunit of CaM kinase II were seen, while large increases in the binding of [125I]calmodulin to the alpha subunit of CaM kinase II also were observed. The finding of large increases in the autophosphorylation and calmodulin-binding to CaM kinase II with only slight increases in the amount of antibody-binding suggests that CS2 exposure results in increased Ca2+ calmodulin-dependent phosphorylation of proteins by inducing an increase in kinase activity.


The objective of this investigation was to examine cerebral magnetic resonance imaging (MRI) pathology and functional deficits demonstrated by neuropsychological testing in cases of toxic encephalopathy. Two subjects, occupationally exposed to toxic chemicals, were studied. As part of their neurological assessment, MRI was done and each underwent a neuropsychological battery for patients with toxic exposures (White et al. Clin. Neuropharmacol. 13(5), 392-412, 1990). In Case 1, who was exposed to inorganic mercury, MRI showed mild central and cortical atrophy. Punctiform foci (T2) were noted in both frontal regions underlying the precentral gyri and in the subcortical myelin. Neuropsychological testing showed problems in cognitive flexibility, cognitive tracking, inhibiting perseveration, fine manual motor coordination, visuospatial analysis and organization, memory, and affect and personality. In Case 2, who was exposed to 2.6-dimethyl-4-heptanone, MRI showed multiple small foci in the white matter and pons. Neuropsychological testing indicated affective changes, deficits in manual motor speed, verbal fluency, visuospatial organization, and short-term memory. Lack of aphasia in patients with toxic encephalopathy indicates that neurotoxins probably affect
subcortical and mesial temporal structures more than cortical gray matter. These MRI studies show subcortical sites of pathology.

-------------------------------------------------------------------------------------------------------------------------------

**(1993) The science of toxicology and its relevance to MCS.**

The phenomenon of multiple chemical sensitivities is a peculiar manifestation of our technophobic and chemophobic society. It has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association, the California Medical Association, the American College of Physicians, and the International Society of Regulatory Toxicology and Pharmacology. It may be the only ailment in existence in which the patient defines both the cause and the manifestations of his own condition. Despite this, it has achieved credibility in workmen's compensation claims, tort liability, and regulatory actions, all of which are briefly reviewed.

-------------------------------------------------------------------------------------------------------------------------------

**(1993) Anticonvulsant activity of delta-HCH, calcium channel blockers and calmodulin antagonists in seizures induced by lindane and other convulsant drugs.**
Tusell, JM, Barron, S and Serratosa, J Journal/Brain Res. 622: 99-104.

The anticonvulsant activity of delta-HCH and of a calmodulin antagonist, W-7 were investigated on convulsions induced in mice by lindane (ED100 100 mg/kg), by GABAergic antagonists PTZ (ED100 60 mg/kg) and PTX (ED100 4 mg/kg), by calcium channel agonist BAY-K-8644 (ED100 5 mg/kg), by two agonists of excitatory amino acid receptors, kainic acid (ED100 80 mg/kg) and NMDA (ED100 160 mg/kg and by the atypical benzodiazepine Ro 5-4864 (ED100 40 mg/kg). The anticonvulsant activity of a voltage-dependent calcium channel antagonist, nifedipine was also investigated on convulsions induced by Ro 5-4864, BAY-K-8644, kainic acid and NMDA, delta-HCH antagonized lindane- and BAY-K-8644-induced convulsions (ED50 231 (172-309) mg kg and 148 (142-154) mg/kg, respectively) and at concentrations up to 300 mg/kg failed to antagonize Ro 5-4864, kainic acid and NMDA convulsions. In contrast delta-HCH potentiated PTX-induced seizures. Nifedipine antagonized BAY-K-8644- and kainic acid-induced convulsions (ED50 6.5 (4.3-9.7) mg/kg and 30 (13-70) mg/kg but at concentrations up to 20 mg/kg failed to antagonize Ro 5-4864 and 25% of protection was observed on NMDA-induced convulsions at the highest dose (20 mg kg). The ED50 of W-7 to antagonize convulsions induced by lindane and BAY-K-8644 were 12 (8-19) mg/kg and 49 (29-85) mg/kg, respectively. Some anticonvulsant effect was observed against PTZ and NMDA but without any dose-dependent anticonvulsant activity. W-7 did not protect against PTX and kainic acid convulsions and 30% of
protection was observed against convulsions at the highest dose of W-7 (75 mg kg). (ABSTRACT TRUNCATED AT 250 WORDS)


The application of neuroimaging techniques such as cerebral blood flow (CBF), single photon emission tomography (SPECT), X-ray computed tomography (CAT), and magnetic resonance imaging (MRI) on solvent-exposed workers and patients with toxic encephalopathy results in different and somewhat inconclusive pictures. The aim of this paper is to therefore critically review the current knowledge on chronic neurotoxicity of solvent exposures with respect to neuroimaging technique. CAT measurements of 86 house or construction painters, 82 spray painters, and 81 nonpainters showed no abnormal diffuse brain atrophy due to chronic solvent exposure after controlling for confounding variables such as age, alcohol consumption, or former disease. Correlation analyses did not show any consistent, biologically plausible exposure-effect relationship. Neuropsychologic test results did not correlate significantly with CAT parameters, whereas a strong age dependency exists. It is concluded that long-term exposure to solvent concentrations not exceeding permissible occupational limit values does not cause increased brain atrophy.

(1993) Multiple chemical sensitivity: Controlled scientific studies as proof of causation.

The phenomenon of multiple chemical sensitivities is a peculiar manifestation of our technophobic and chemophobic society. It has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association, the California Medical Association, the American College of Physicians, and the International Society of Regulatory Toxicology and Pharmacology. It may be the only ailment in existence in which the patient defines both the cause and the manifestations of his own condition. Despite this, it has achieved credibility in workmen's compensation claims, tort liability, and regulatory actions, all of which are briefly reviewed.
(1993) Immunological issues in "multiple chemical sensitivities".  

The phenomenon of multiple chemical sensitivities is a peculiar manifestation of our technophobic and chemophobic society. It has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association, the California Medical Association, the American College of Physicians, and the International Society of Regulatory Toxicology and Pharmacology. It may be the only ailment in existence in which the patient defines both the cause and the manifestations of his own condition. Despite this, it has achieved credibility in workmen's compensation claims, tort liability, and regulatory actions, all of which are briefly reviewed.


Sixty-three patients with polysomatic complaints attributed to sensitivity to environmental chemicals had detailed clinical assessments and diagnostic psychologic evaluations. Objective medical parameters failed to substantiate their beliefs that multiple chemicals were the cause of their problems. A group of 64 patients with chronic medical conditions and defined psychologic disorders not attributed to chemical exposure served as controls. Approximately half the patients in each group underwent long-term psychotherapy, and in these patients, the prevalence of physical and sexual childhood abuse was significantly higher (P < .05) among the cohort of women who attributed their symptoms to environmental or chemically related illness. These data suggest that somatization may reflect sequelae of childhood abuse and may play an important role in the illness experienced by women who believe they are sensitive to environmental chemicals.

(1993) Double-blind provocation chamber challenges in 20 patients presenting with "multiple chemical sensitivity".  
A clinical algorithm was used to discriminate verifiable chemical sensitivity from psychological disorders in patients referred for evaluation of polysomatic symptoms attributed to hypersensitivity to workplace and domestic chemicals. These patients believed that they were reactive or hypersensitive to low-level exposure to multiple chemicals. Some had previously been evaluated and managed by the tenets of "clinical ecology" and diagnosed as having "multiple chemical sensitivity." Double-blind provocation challenges with an olfactory masker were performed in an environmental chamber on each of 20 patients. A variety of chemicals was employed, one or more per subject, dependent on individual clinical history. Clean air challenges with the olfactory masker were used as placebo or sham controls. As a group, probability analyses of patient symptom reports from 145 chemical and clean air challenges failed to show sensitivity (33.3%), specificity (64.7%), or efficiency (52.4%). Individually, none of these patients demonstrated a reliable response pattern across a series of challenges. Implications for future research in assessment methodology incorporating neurophysiologic and neurobehavioral measures are discussed.


Physicians who are board-certified in occupational and environmental medicine often have formal training and experience in toxicology, epidemiology, and industrial hygiene, as well as clinical medicine, human physiology, and pathology, and are well suited to be team members in the various phases of risk assessment, communication, and management. Those with several years of experience in the clinical, as well as administrative practice of occupational and environmental medicine, are engaged in the practical application of risk characterization, risk communication, and risk management on an almost daily basis. We propose that the occupational and environmental medicine physician is in a unique position to bridge the communication gap between those professionals who provide various components of the risk assessment process and those who manage those risks in society.


OBJECTIVE: To examine the role of immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity. DESIGN: Case-control comparison. SETTING: Community allergy practice (cases), university-based clinics for
musculoskeletal injuries (controls). PARTICIPANTS: Forty-one patients with chemical sensitivity and 34 control patients with chronic musculoskeletal injuries. MAIN OUTCOME MEASURES: Immunologic measures included autoantibody titers, lymphocyte surface markers, and interleukin-1 generation by monocytes. Psychological evaluation included standardized measures of anxiety, depression, and somatization. RESULTS: Immunologic testing did not differentiate patients with chemical sensitivity from controls. The only difference noted (lower interleukin-1 generation among cases) appeared attributable to laboratory methods. Patients with chemical sensitivity reported greater prevalence of current anxiety or depressive disorder (44% versus 15%, P = 0.006). This difference, however, did not appear to precede the onset of chemical sensitivity, and 25% of chemically sensitive patients showed no significant current psychological disturbance. Cases reported significantly more "medically unexplained" physical symptoms before and after the onset of chemical sensitivity. When considering only symptoms that preceded chemical sensitivity, 25% of cases (and no controls) satisfied criteria for somatization disorder. Neuropsychological testing revealed no significant case-control differences. CONCLUSIONS: Immunologic testing failed to confirm findings from earlier uncontrolled studies, militating against proposed immunologic mechanisms. The decreased memory and concentration frequently described in multiple chemical sensitivity were not confirmed by brief neuropsychological testing. Psychological symptoms, although not necessarily etiologic, are a central component of chemical sensitivity.

(1993) Multiple chemical sensitivity: respect the observations ... suspect the interpretations?

(1993) Allergen-induced airway obstruction in guinea-pigs is associated with changes in nitric oxide levels in exhaled air.

Endogenously produced nitric oxide (NO) was monitored in exhaled air from ovalbumin-sensitized and pentobarbital anaesthetized guinea-pigs. Stable levels of nitric oxide were detected in exhaled air over a 30-min control period in each experiment (9.2 +/- 1.4 parts per billion, [ppb]). Insufflation pressure and NO in exhaled air immediately increased, in a dose dependent manner, in response to challenge with nebulized allergen (Ovalbumin, 0.1-10 mg). Indomethacin (5 mg kg-1) augmented the allergen-induced increases in insufflation pressure and NO. Fifteen min after the challenge the insufflation pressure remained elevated while NO in exhaled air had dropped below control levels. The increase in insufflation pressure induced by
inhalation of PGF2 alpha (5 micrograms) was accompanied by an increase in nitric oxide in exhaled air, which however was significantly less than the increase in NO induced by allergen challenge. The results suggest a role for NO mechanisms in asthma.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8128895

---------------------------------------------------------------

(1993) Multiple chemical sensitivities syndrome: toward a working case definition.

A study was conducted to identify clinical diagnostic criteria that experts regarded as major for categorizing patients as having multiple chemical sensitivities (MCS) syndrome. A cross-sectional survey of 148 medical practitioners with an interest in, or familiarity with, the condition was performed scoreable questionnaires were returned by 60.1% of those surveyed. The following five criteria, all based on self-reports, were selected as major for diagnosing the syndrome by more than 50% of the respondents: (1) symptoms are reproducible with exposure; (2) condition is chronic; (3) low levels of exposure result in manifestations of the syndrome; (4) symptoms resolve with removal of incitants; and (5) responses occur to multiple, chemically unrelated substances. It is proposed that the major criteria accepted by the majority of survey respondents be used provisionally as the basis for categorizing cases in investigations of MCS syndrome.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8452395

---------------------------------------------------------------


Although people of color and low-income groups bear a disproportionate share of the health risks from exposure to pesticides, research attention has been meager, and data on acute and chronic health effects related to their toxic exposures are generally lacking. Increased resources are needed both to study this issue and to mitigate problems already identified. People of color should be a major research focus, with priority on long-term effects, particularly cancer, neurodevelopmental and neurobehavioral effects, long-term neurological dysfunction, and reproductive outcome. Suitable populations at high risk that have not been studied include
noncertified pesticide applicators and seasonal and migrant farm workers, including children.

(1993) Increase in nitric oxide and cyclic GMP of rat cerebellum by radio frequency burst-type electromagnetic field radiation.

1. Using rat cerebellum supernatant, the effects of radio frequency (RF) burst-type electromagnetic (EM) field radiation on the production of cyclic GMP were examined under various conditions. The radiation was generated by a generator coil, and set at a 10 MHz radiation frequency, a 50% burst time, a 10 kHz burst rate and a 5 V peak-to-peak generator voltage. 2. When the cerebellum supernatant was incubated with both exogenous L-arginine (nitric oxide (NO) donor) and NADPH, and irradiated by an RF burst-type EM field, the production of cyclic GMP was increased significantly from a level of 21-22 nmol min-1 (g tissue)-1 to 25-26 nmol min-1 (g tissue)-1. By contrast, such an effect was not found when the cerebellum supernatant was irradiated by an RF volley-type EM field. 3. When neither L-arginine nor NADPH were added to the cerebellum supernatant, the production of cyclic GMP was lowered to a level of 6 nmol min-1 (g tissue)-1 and the radiation effect was not found. When the cerebellum supernatant was chelated with EDTA, the production of cyclic GMP was lowered to a level of 7 nmol min-1 (g tissue)-1 and the radiation effect was not found. 4. Incubation with Methylene Blue, a guanylate cyclase inhibitor, lowered the production of cyclic GMP to a level of 10-12 nmol min-1 (g tissue)-1, and the radiation effect did not occur. On incubation with a NO synthase inhibitor, either NG-methyl-L-arginine or N omega-nitro-L-arginine methyl ester, the production of cyclic GMP was lowered to a level of 10-12 nmol min-1 (g tissue)-1 or 5-9 nmol min-1 (g tissue)-1 respectively, and the radiation effect was not observed. 5. Using electrochemical NO probes, the production of NO in the cerebellum supernatant was detected. The concentration of NO increased gradually after the onset of the EM field radiation. The radiation effect persisted, and reached a maximum after the cessation of the radiation. 6. In an in vivo study, the arterioles of the frog web were dilated by the radiation, and this radiation effect was almost completely abolished by the addition of a NO synthase inhibitor. This indicates that radiation activates NO synthase and ultimate induces vasodilatation.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7688808

(1993) Rhinolaryngoscopic examination of patients with the multiple chemical sensitivity syndrome.
Ten patients who met the Cullen case definition for the multiple chemical sensitivity syndrome were evaluated; a history was taken, and physical examination and fiberoptic rhinolaryngoscopy were performed. All patients had an initial chemical exposure, which was followed by multiple physical and mental complaints in response to subsequent exposure to a variety of odorous organic chemicals. Rhinitis was a prominent complaint in nine patients, but one patient denied any nasal symptoms. Rhinolaryngoscopic findings were abnormal in all patients; edema, excessive mucus, a cobblestone appearance of the posterior pharynx and base of the tongue, and mucosal injection were observed frequently. A particularly striking finding was focal areas of blanched mucosa that surrounded a prominent vessel. These results suggest that nasal pathology may be a prominent feature of this disorder.


Neurogenic inflammation as a pathway distinct from antigen-driven, immune-mediated inflammation may play a pivotal role in understanding a broad class of environmental health problems resulting from chemical exposures. Recent progress in understanding the mediators, triggers and regulation of neurogenic inflammation is reviewed. Evidence for and speculation about a role for neurogenic inflammation is established disorders such as asthma, rhinitis, contact dermatitis, migraine headache and rheumatois arthritis are presented. The sick building syndrome and mutiple chemical sensitivity syndrome has been defined as chemical entities in which exposure to chemical inhalants gives rise to disease. Current data on the existence of chemical irritant receptors in the airway and skin are discussed; neurogenic inflammation arising from stimulation of chemical irritant receptors is a possible model to explain many of the aspects of chemical sensitivities.


The author is discussing therapeutic modalities used by environmental physicians. Much emphasis is directed towards the need and methods to control the patient's environment in order to improve his/her health. Unique neutralization techniques to help patients cope with environmental exposures are presented. Importance of nutritional evaluation and correction as well as the 4-Day Rotation Diet are introduced. (The author realized that some of the foods mentioned are not on the market as yet in Poland but the idea can be adapted to available foods and a developing economy will increase diversity). The treatments should always be combined with psychological therapy and support. The paper ends with a discussion of global prophylaxis of environmental illness as it should be applied at home, school and work. All sectors of government and social institutions should be involved. Environmental medicine should be on the curriculum of medical schools.


Types I and II organophosphorus compound-induced delayed neurotoxicity (OPIDN) is characterized by axonal degeneration. Type II compounds, however, uniquely cause cell body damage. Primary cultures of bovine adrenomedullary chromaffin cells were used to investigate and assess biochemically the cell body effects of the Type II compound triphenyl phosphate (TPP). Exocytotic secretion of neurotransmitter was measured to determine whether the cytotoxic action of TPP compromised synaptic events. TPP inhibited catecholamine secretion in both a time- and dose-dependent manner. By 4 h, TPP had inhibited nicotine-induced secretion by about 85%. TPP inhibited catecholamine secretion by about 35% as early as 15 min. The IC50 for TPP was about 45 microM. TPP inhibited secretion regardless of the secretagogue used, although nicotine-induced secretion was inhibited to the greatest extent. The Type I OPIDN diisopropyl phosphorofluoridate (DFP) and the nondelayed-type neurotoxic organophosphorus compound O,O-diethyl-O-4-nitrophenyl phosphate (paraoxon) did not inhibit catecholamine secretion from these cells. In contrast, when high potassium was used to induce secretion, significant stimulation was observed in the presence of DFP and paraoxon. Since Ca2+ homeostasis plays a key role in both exocytosis and neuronal necrosis, its uptake into the cells was measured radiometrically in the presence of TPP or DFP. Incubation with 100 microM TPP for 4 h resulted in the inhibition of 45Ca2+ uptake evoked either by nicotine or K+. No significant inhibition of 45Ca2+ uptake was observed in the presence of DFP. TPP and DFP produced 95% and 88% inhibition, respectively, of the activity of the neurotoxic esterase enzyme (NTE), a putative target for OPIDN. Results suggest that these changes in the secretory mechanisms of the cell may be involved in the TPP-induced pathological alterations in chromaffin cells.
(1993) **Brain autopsy in organic solvent syndrome.**

General autopsy findings, brain weight and brain pathology were studied in 98 men and five women who had been exposed occupationally to organic solvents over several years and assessed by the Danish National Board of Industrial Injuries for chronic toxic encephalopathy. The findings were compared with a forensic control material and a hospital control material. As in the general population, the most common causes of death among the exposed workers were heart failure and other vascular diseases. Due to the composition of the material (forensic cases), the number of suicides and violent deaths was high. Atherosclerosis was the most common CNS finding, but in comparison with the two control materials, no increase in the frequency of atherosclerosis or of Alzheimer's disease was found. Brain weights of the exposed workers corresponded closely to brain weights in the control materials, after correction for body height, body weight and age. Chronic alcoholism was correlated with slightly reduced brain weight.

(1993) **Symptoms, syndrome, and semantics: multiple chemical sensitivity and chronic fatigue syndrome.**

(1993) **Toxic encephalopathy due to 1,1,1-trichloroethane.**

(1993) **Role of the amygdala, hippocampus and entorhinal cortex in memory consolidation and expression.**

1. Experiments using localized microinfusions of specific agonists and antagonists of neurotransmitter receptors have shown that the amygdala, hippocampus, medial septum and entorhinal cortex are involved in memory consolidation, storage and
expression. The data are consistent with observations derived from lesion studies suggesting a role for these structures in memory processes, but permit many additional conclusions concerning the mechanisms involved and their timing. 2. Memories are initially processed by glutamatergic N-methyl-D-aspartate (NMDA) receptors in amygdala, hippocampus and medial septum, which are sensitive to amino-phosphonovalerate (AP5). Memory of inhibitory avoidance is processed by the three structures; memory of habituation to a novel environment is processed only by the hippocampus. At the time of consolidation, immediately after training, gamma-aminobutyrate type A (GABA-A) receptors, modulated by endogenous benzodiazepines, play an inhibitory role, and cholinergic muscarinic and beta-noradrenergic transmission play a modulatory role. 3. From 90 to 180 min after training, memories are blocked by cyano-nitro-quinoxalinedione (CNQX) given into the amygdala, septum and hippocampus. CNQX blocks non-NMDA glutamatergic receptors. Also between 90 and 180 min after training, memory of the habituation and inhibitory avoidance tasks is blocked by the infusion of AP5 or of the GABA-A agonist, muscimol, into the entorhinal cortex. This late post-training intervention of the entorhinal cortex is essential for the integration of successively acquired memories, and occurs in response to the simultaneous activation of CNQX-sensitive synapses in amygdala and hippocampus. 4. The expression of memory is blocked by the infusion of CNQX, at the time of testing, into the amygdala and hippocampus (inhibitory avoidance), into the hippocampus but not the amygdala (habituation), or into the entorhinal cortex (for the two tasks). Since consolidation is blocked by AP5 infused into these structures (see above), the data agree with the hypothesis that memories are mediated by (or actually consist of) long-term potentiation (LTP) in these areas of the brain. LTP induction is blocked by AP5 and LTP expression is blocked by CNQX. It is possible that, at the time of memory expression, the entorhinal cortex is an output of the amygdala and hippocampus.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7504967

(1993) Successful management of patients with "multiple chemical sensitivities" on an inpatient psychiatric unit.

BACKGROUND: Much controversy exists over the diagnosis, etiology, and treatment of "multiple chemical sensitivities" also known as "environmental illness." The experience of multiple nonspecific reactions to numerous environmental agents leads to these diagnoses. Due to skepticism surrounding the validity of these patients' complaints, they are often referred for psychiatric evaluations, but successful management on a psychiatric inpatient unit can be complicated because of their unique presentations. METHOD: The approach taken by a university psychiatric inpatient unit to the evaluations of three such patients is presented along with a literature review of etiologic theories and treatment recommendations. RESULTS: Each of the three patients presented with severe disability from their "sensitivities," but
each improved significantly over the course of a 17-day hospitalization. CONCLUSION: These patients benefited greatly from a serious, nonjudgmental, comprehensive approach to the evaluation of their multiple complaints. Despite the absence of any positive organic findings, each felt that her experiences had been validated, and each subsequently improved. When evaluating similar patients, clinicians should be aware of useful, effective management strategies and should avoid overt skepticism and confrontation.


Diisopropyl phosphorofluoridate (DFP) produces type I organophosphorus ester-induced delayed neurotoxicity in humans and sensitive animal species. This is accompanied by enhanced Ca2+/CaM-dependent protein kinase II (CaM-kinase II) activity, and [125I]calmodulin binding to CaM-kinase II in DFP-treated hen brain supernatant without increase in the enzyme quantity. We have purified CaM-kinase II from control and DFP-treated hen whole brains and compared various physical and biochemical properties. The two enzymes exhibited similar properties in many respects. However, there was a decrease in calcium-independent protein kinase II activity after autophosphorylation, and an increase in $K_{0.5}$ for free calcium and calmodulin of enzyme purified from DFP-treated hen brains. This change in kinetic parameters may result in greater percentage of total CaM-kinase II present in unphosphorylated form, which is consistent with the increased autophosphorylation of CaM-kinase II and [125I]calmodulin binding in the brain supernatant of DFP-treated hens.


The phenomenon of multiple chemical sensitivities is a peculiar manifestation of our technophobic and chemophobic society. It has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association, the California Medical Association, the American College of Physicians, and the International Society of Regulatory Toxicology and Pharmacology. It may be the only ailment in existence in which the patient defines both the cause and the manifestations of his own condition. Despite this, it has achieved credibility in workmen's compensation claims, tort liability, and regulatory actions, all of which are briefly reviewed.

The phenomenon of multiple chemical sensitivities is a peculiar manifestation of our technophobic and chemophobic society. It has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association, the California Medical Association, the American College of Physicians, and the International Society of Regulatory Toxicology and Pharmacology. It may be the only ailment in existence in which the patient defines both the cause and the manifestations of his own condition. Despite this, it has achieved credibility in workmen's compensation claims, tort liability, and regulatory actions, all of which are briefly reviewed.

(1993) [The frequent screams].

Functional analysis is a research process that links problem behavior, its surrounding elements and the resulting consequences. The goal of this study was to decrease repetitive shouting of an elderly patient diagnosed with Alzheimer-like dementia. The analysis provided the following data: BEHAVIORS: Repetitive shouting by the patient lasting 80-115 seconds per 30 minutes during specific times of the day--accompanied by licking of the lips to moisten them. Environmental factors: Constant loud noise in the patient's room; the use of loud voices by staff and visitors; familiar objects out of the patient's reach. Individual factors: Diagnosis of the patient's blindness and auditory hypersensitivity; side-effects of psychotropic medications; a lack of social activities; inactivity because of the patient being bedridden 22 hours per day and the use of restraints when positioned in a chair. SURROUNDING ELEMENTS: The patients was isolated in a private room; psychotropic medication was increased; staff and other patients were less disrupted and the number of visitors to the patient was decreased. CONSEQUENCES: The above data enabled the formulation of four hypotheses (with specific interventions for each) that assisted staff in planning the patient's care for a 10-day period; a reduction of anxiety; a reduction in discomfort; sensory hypostimulation; verbal hypostimulation. Following the application of these interventions for a 10-day period, a second set of data was gathered and the results showed a decrease in shouting by 40 per cent in the morning and 51 per cent in the afternoon.(ABSTRACT TRUNCATED AT 250 WORDS)
(1993) **pS2--a new cytosolic protein recognized by monoclonal antibodies as a marker of hormone sensitivity in breast cancer.**

Using a new immunoradiometric assay (ELSA pS2 Cis-France), a total of 200 cytosols obtained from primary breast tumors were examined for pS2 content, which is an estrogen-regulated protein actually studied as a marker of hormone sensitivity and favorable prognostic factor in breast cancer. In our patient group, the median pS2 value corresponding to 5.3 ng/mg of cytosolic proteins was used as cutoff. pS2 content was not related to menopause status, tumor size, or nodal involvement, whereas a positive correlation was found between pS2 and ER/PgR status. Moreover, the association of pS2 with steroid receptors seems to identify subgroups of patients better than ER/PgR alone.


(1993) **Potent analgesia induced in rats by combined action at PCP and polyamine recognition sites of the NMDA receptor complex.**

The present study was performed to examine the analgesic effects of the intrathecal administration of agents acting at various sites in the N-methyl-D-aspartic acid (NMDA) receptor complex on the nociceptive responses to s.c. formalin injection in rats. Both the competitive NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (APV) and the non-competitive NMDA antagonist dizocilpine maleate (MK-801) produced dose-dependent analgesic effects in the late, but not the early, phase of the formalin test. The polyamine antagonist ifenprodil, and the strychnine-insensitive glycine antagonists DCQX and 7-chlorokynurenic acid, failed to produce any analgesic effects in either the early or the late phase of the formalin test. The analgesic effects of APV were enhanced slightly by combined administration with a non-analgesic dose of glycine, and the analgesic effects of MK-801 were dramatically potentiated by combined administration of a non-analgesic dose of the polyamine spermine. The results indicate that much more potent analgesia can be produced in the formalin test by a combination of open channel blockers (such as MK-801) with agonists acting at the polyamine site, than by a single treatment with antagonists to either glycine allosteric or polyamine sites within the NMDA receptor complex.

Cassileth, BR and Drossman, DA Journal/Psychother Psychosom. 59: 131-43.

Gastrointestinal (GI) illnesses represent a paradigm of psychosomatic medicine. Nearly half of patients seen in GI practice present with functional illnesses, and patients commonly complain of symptoms that have coexisting organic and functional etiologies. This chapter addresses the connected nature of psychosocial factors and GI function, disease and outcome in the context of the biopsychosocial model, which allows illness to be examined from the encompassing perspective of interacting system, from the cellular to the environmental. This perspective also helps explain why biologic events such as oncogene alteration can produce heterogeneous clinical and biological responses. Links between gut and brain, involving neuroendocrine associations of the enteric nervous system and its connections with the spinal, autonomic and central nervous systems, are well documented. Neural connections allow information to affect GI secretion and motility. Disturbances in one component of the system can lead to brain-gut effects, such as dysmotility and mood disturbance. Appropriate diagnosis and treatment require clear understanding of biologic, psychologic, and social contributory events. In chronic unexplained GI illnesses, the appropriate clinical approach may be to suspend the search for structural disease, and work instead to assess and treat the physical symptoms and psychosocial problems at hand.

-------------------------------------------------------------------


Thirty-three workers, ages 24 to 63, developed clinical toxic encephalopathy after exposure to neurotoxins and were studied by SPECT brain scans. Five were exposed to pesticides, 13 were acutely exposed to mixtures of solvents, 8 were chronically exposed to mixtures of hazardous wastes that contained organic solvents, 2 were acutely exposed to phosgene and other toxins, and 5 had exposures to hydrogen sulfide. Twenty-nine had neuropsychological testing and all had a medical history and physical. Of the workers who had a clinical diagnosis of toxic encephalopathy, 31 (93.9%) had abnormal SPECT brain scans with the most frequent areas of abnormality being temporal lobes (67.7%), frontal lobes (61.3%), basal ganglia (45.2%), thalamus (29.0%), parietal lobes (12.9%), motorstrip (9.68%), cerebral hemisphere (6.45%), occipital lobes (3.23%), and caudate nucleus (3.23%). Twenty-three out of 29 (79.3%) neuropsychological evaluations were abnormal. Other modalities when performed included the following percentages of abnormals: NCV, 33.3%; CPT sensory nerve testing, 91.3%; vestibular function testing, 71.4%; olfactory testing, 89.2%; sleep EEG analysis, 85.7%; EEG, 8.33%; CT, 7.14%; and MRI brain scans, 28.6%. The complex
of symptoms seen in toxic encephalopathy implies dysfunction involving several CNS regions. This series of patients adds to the previous experience of brain metabolic imaging and demonstrates that certain areas of the brain are typically affected despite differences in toxin structure, that these lesions can be globally defined by SPECT/PET brain scans, that these lesion correlate well with clinical and neuropsychological testing, and that such testing is a useful adjunct to previous methods. EEG and structural brain imaging such as CT and MRI are observed to have poor sensitivity in this type of patient. Additional metabolic imaging studies need to be done to explore dose, time, and specific toxin effects as well as mechanisms of toxicity and olfactory migration.


The authors report on measures of distress in 26 subjects who had been diagnosed with environmental illness (EI) by a "clinical ecologist." EI subjects were more likely than control subjects to meet criteria for one or more personality disorder diagnoses assessed with the Structured Interview for DSM-III Personality Disorders and exhibited more somatic, mood, and anxiety symptoms assessed with the Symptom Checklist-90-R and the Illness Behavior Questionnaire. The authors conclude that subjects receiving this diagnosis may suffer from unrecognized psychological distress, which may account for some or all of the symptoms that had resulted in a diagnosis of EI.


A fringe group of medical practitioners called clinical ecologists believes that hypersensitivity to common foods, chemicals, and organisms can disrupt the immune system and lead to diverse medical or psychiatric problems. They believe this condition, frequently referred to as environmental illness (EI), can be diagnosed on the basis of a patient's history of exposure, and the results of provocation testing and
elimination diets. They advise treating the condition with avoidance of the offending agent(s), special diets, and symptom neutralization. Other treatments are often recommended. Clinical ecology beliefs and practices have been criticized by mainstream medical practitioners who have urged that EI not be recognized as a clinical syndrome. Research has shown that individuals receiving a diagnosis of EI frequently have common psychiatric or medical disorders, which are usually unrecognized and untreated. Thus, the clinical ecologists are misinterpreting common signs and symptoms of illness and failing to prescribe appropriate and proven therapies. The advice and recommendations of a clinical ecologist can lead to iatrogenic social and occupational disability.


The phenomenon of multiple chemical sensitivities is a peculiar manifestation of our technophobic and chemophobic society. It has been rejected as an established organic disease by the American Academy of Allergy and Immunology, the American Medical Association, the California Medical Association, the American College of Physicians, and the International Society of Regulatory Toxicology and Pharmacology. It may be the only ailment in existence in which the patient defines both the cause and the manifestations of his own condition. Despite this, it has achieved credibility in workmen's compensation claims, tort liability, and regulatory actions, all of which are briefly reviewed.


The present paper summarizes key features of time-dependent sensitization (TDS) in neuropharmacology (progressive amplification of behavioral, neuronal, endocrine, and or immune responses to repeated intermittent exposures to an environmental agent or cross-sensitizing agents) as a possible model for cacosmia (subjective sense of feeling ill from low levels of environmental chemical odors) in nonindustrial and industrial populations; and extends previous cacosmia research in nonpatient populations to an elderly sample. This study examined the symptom and psychological profiles of 263 older adults (aged 60-90 y, 71% women, 29% men); 57% reported that at least one chemical and 17% reported that at least four of five chemicals (pesticide, automobile exhaust, paint, new carpet, perfume) made them feel ill. Cacosmia ratings correlated weakly and negatively with age (r = -0.19, p = .001) over the whole sample. Cacosmia
correlated significantly with self-reported illness from foods that may mobilize or
generate opioid peptides (wheat, dairy, eggs) \( (r = 0.32, p < .0001) \) and with illness from
opiate drugs \( (r = 0.23, p < .0001) \). When the sample was divided into four cells on the
basis of above-versus below-median total chemical-induced illness score (CI) and total
food-induced illness score (FI), the high CI and high FI, high CI only, and high FI only
groups had more frequent indigestion, and the high CI group had more frequent
difficulty concentrating than the groups below median for illness from both chemicals
and foods (NOILL), even after covarying for age and anxiety. The most cacosmic
subjects noted higher prevalence of physician-diagnosed allergies and irritable bowel
than did noncacosmic subjects. In contrast with previous young adult cohort studies,
the older illness groups did not differ with regard to sex distribution, depression,
shyness, or repressive defensiveness. When considered with prior surveys of young
adults, the present findings are consistent with the presence of previously established,
time-dependent sensitization to multiple xenobiotic agents in susceptible individuals for
whom psychological variables do not explain the symptom of cacosmia. If cacosmia is
a symptom of TDS, then the neuropharmacology literature suggests the possibility of
excitatory amino acid, hypothalamic-pituitary-adrenal axis, dopaminergic, and/or opioid
involvement. Prospective studies with objective measures testing the possible
induction of TDS to specific chemicals are indicated.

(1993) Self-reported illness from chemical odors in young adults without clinical
syndromes or occupational exposures.
Bell, IR, Schwartz, GE, Peterson, JM and Amend, D Journal/Arch Environ Health. 48:
6-13.

The present survey of young adult college students investigated the prevalence of
self-reported illness from the smell of the five following common environmental
chemicals (cacosmia): (1) pesticide, (2) automobile exhaust, (3) paint, (4) new carpet,
and (5) perfume. Sixty-six percent of 643 students reported feeling ill from one or more
of the five chemicals; 15% identified the smell of at least four chemicals as making
them ill. Ratings of illness from pesticide correlated weakly but significantly with ratings
for the largest number of individual symptoms (9 of 11); daytime tiredness and daytime
grogginess both correlated at high levels of significance with illness ratings (on a
5-point scale) for four of the five chemicals. The most cacosmic group (CS) included
significantly more women (79%) than the noncacosmic group (NS) (49%); women
overall were more cacosmic than men \( (p < .001) \), even with the significant covariate of
depression. Ratings of cacosmia correlated only weakly with scores for depression \( (r =
0.16) \), anxiety \( (r = 0.08) \), and trait shyness \( (r = 0.18) \) in the total sample. On stepwise
multiple regression with cacosmia score as the dependent measure, shyness
accounted for 5.8% of the variance, while depression, anxiety, sense of mastery, and
repression did not enter the equation. Histories of physician-diagnosed hay fever, but
not asthma, were more frequent in the CS (16%) than in the NS group (5%). Without
the confounds of chronic illness or specific treatment programs, these data are similar
to patterns described clinically for a subset of patients with multiple chemical sensitivities (MCS), including previous data on increased nasal resistance in MCS. (ABSTRACT TRUNCATED AT 250 WORDS)

(1993) Symptom and personality profiles of young adults from a college student population with self-reported illness from foods and chemicals.

Despite much debate over a presumptively somatic vs psychological etiology of nonatopic food and chemical sensitivities, little systematic research has addressed the issues. The present study investigated self-reported illness from several common foods (wheat, dairy, eggs) and chemicals (pesticide, car exhaust, paint, perfume, new carpet), symptom patterns, and psychological profiles of a sample of young adult college students (n = 490, age 19.4 +/- 2.4, 52% female/48% male). Subjects were divided into 4 groups on the basis of sample medians for frequency of illness from the foods (FI) and chemicals (CI); high FI with high CI (FI/CI), high FI alone, high CI alone, and NOILL (low FI and CI). FI was associated with more defensiveness (denial of negativity) while CI was linked with more shyness (avoidance of novelty). Women outnumbered men in all groups (FI/CI: 61%; FI: 80% CI: 55%) except the NOILL (40% women). Nevertheless, the FI/CI, FI, and/or CI groups still had significantly higher total symptom scores as well as more indigestion, headache, and memory trouble than did the NOILL group, even after depression, anxiety, shyness, defensiveness, and gender were covaried. The illness groups reported significantly more limitation of foods that mobilize endogenous opioids or generate exogenous opioids (sweets, fats, bread) as well as more illness from opiate drugs, small amounts of beverage alcohol, and late meals. Nasal symptoms from pollens or animals were more common in the FI/CI (42%) and CI (42%) than in FI (26%) or NOILL (28%) groups. Premenstrual tension syndrome and irritable bowel were also more common in the FI/CI group. The findings indicate that young adults outside the clinical setting who are relatively higher in FI and/or CI have distinctive symptom and psychological patterns. Covariate analyses suggest that important symptoms in FI and CI individuals such as indigestion, headache, and memory problems may occur in addition to rather than as simply part of emotional distress. The data are consistent with a previously hypothesized role of olfactory-limbic and hypothalamic pathways and with a time-dependent sensitization model for illness from foods and chemicals.

We studied relationships between shyness and health during a health screening survey of older adults (ages 50-88) living in an active retirement community in the southwestern United States (n = 232). As in previous studies of infants, older individuals with hay fever, insomnia and constipation were more shy than those without these problems. Shy persons overall showed higher sitting systolic blood pressure and a larger fall in orthostatic systolic blood pressure on standing; shy men had a greater prevalence of hypertension histories than did low-shy men. Shy subjects of both sexes had lower HDL cholesterol and higher triglycerides than did low-shy subjects; shy women tended to have higher LDL cholesterol than did low-shy women. In contrast with findings of elevated salivary cortisol in extremely inhibited children of both sexes, only shy women had higher 24 h urinary free cortisol excretion than did low-shy women; men showed the opposite pattern, possibly related to suppression of aggression. Shy men also tended to report a higher prevalence of thyroid disease history than did low-shy men (20% versus 6%). Notably, autoimmune thyroiditis has previously been linked with panic and depression, disorders which in turn have been associated with shyness. Taken together with previous work in shy children and their families, the data raise the possibility of (a) increased risk for arteriosclerotic vascular disease; and (b) increased risk of adrenal- and/or thyroid-related diseases in certain shy older adults.

(1993) Polysymptomatic syndromes and autonomic reactivity to nonfood stressors in individuals with self-reported adverse food reactions.

This study compared symptom reports and cardiovascular reactivity of a group of 24 individuals recruited from the community who reported a cognitive or emotional symptom caused by at least one food (food-sensitivity reporters, FSR) vs those of 15 controls (C) without a history of food, chemical, drug, or inhalant sensitivities. The main findings were: 1) FSR indicated sensitivities not only to foods, but also to environmental chemicals, drugs, and natural inhalants, as well as significantly more symptoms than C in multiple systems; 2) more FSR than C noted recent state depression and anxiety, as well as higher trait anxiety on the Bendig form of the Taylor Manifest Anxiety Scale; 3) however, on multiple regression analysis, not only depression, but also the number of sensitivities (foods, chemicals, drugs, inhalants), accounted for part of the variance in total number of symptoms (38 and 17%, respectively), whereas none of the affective measures accounted for any of the variance in total number of sensitivities over all subjects; 4) after controlling for depression and anxiety, FSR still showed a trend toward poorer performance on a timed mental arithmetic task (p = 0.16); and 5) FSR and C showed opposite patterns of
heart rate change to two different stressful tasks (mental arithmetic and isometric exercise) (group by task interaction, p < 0.05). The data are discussed in terms of a time-dependent sensitization (TDS) process that predicts a cross-sensitizing and cross-reactive role for xenobiotic agents (e.g., foods, chemicals, drugs, and inhalants) and for salient psychological stress in the expression of psychophysiological dysfunctions of FSR. As in other chronically ill populations, negative affect in food-sensitive individuals may explain greater symptom reporting, but not necessarily account for the illness itself. For either a food or a psychological stimulus to begin to elicit sensitized responses, e.g., marked physiological differences from C, FSR may require multiple, intermittent exposures spaced over 5-28 days rather than on only 1 day.

(1993) Memory deficits, sensory impairment, and depression in the elderly.
Bell, IR, Amend, D, Kaszniak, AW and Schwartz, GE Journal/Lancet. 341: 62.


This study estimates the extent of work-related chronic disease fatalities in Oklahoma. Occupational cancer, pneumoconiosis, and chronic respiratory, cardiovascular, renal, and neurological diseases are addressed specifically. Also, the costs of chronic occupational illness are estimated. Because many cases of work-related disease find their way to the primary care physician, an individual who often has little formal training in the recognition and diagnosis of occupational or environmental illness, the education of primary care physicians and medical students in occupational disease recognition and prevention is encouraged.


Life-threatening organophosphate-induced delayed polyneuropathy with transient bilateral vocal cord paralysis occurred in a 3-year-old child. Recovery was slow after prolonged ventilatory support. Patients who recover from serious organophosphate intoxications should be closely monitored for the development of organophosphate-induced delayed polyneuropathy.

Diisopropyl phosphorofluoridate (DFP) produces Type I organophosphorus compound-induced delayed neurotoxicity (OPIDN) in adult female chickens. We have proposed that calcium/calmodulin protein kinase II (CaM kinase II) plays a role in the development of OPIDN by increasing the phosphorylation of cytoskeletal proteins. We investigated in vivo the effects of treatment of DFP on CaM kinase II-dependent phosphorylation. In isolated brain supernatants from DFP-treated hens, calmodulin binding increased concurrent with increases in CaM kinase II-dependent autophosphorylation and phosphorylation of cytoskeleton proteins. There were no changes in the relative amounts of the enzyme based on immunobinding studies of antibodies to the CaM kinase II. In the absence of any exogenously added substrate, CaM kinase II and microtubule associated protein-2 (MAP-2) exhibited substantially increased phosphorylation, 833 and 275%, respectively, over brain supernatants from untreated hens. Moreover, isolated brain supernatants from treated hens with exogenously added cytoskeletal proteins and myelin basic protein (MBP) exhibited significant increases in phosphorylation over control, 233, 332 and 60%, for MAP-2, tubulin, and MBP, respectively. 125I-Calmodulin binding studies revealed a 136% increase in calmodulin binding to CaM kinase II in treated hens when compared to control groups. The data suggest that in vivo DFP treatment increases the percentage of unphosphorylated, active CaM kinase II resulting in increased calmodulin binding and subsequent enhanced phosphorylation of cytoskeletal proteins that leads to their aggregation and the production of axonal degeneration.


Acrylamide (2-propenamide) monomer produces central-peripheral distal axonopathy in humans and some animal species. Its neurotoxicity is characterized by abnormal sensation, decreased motor strength, and ataxia. Acrylamide forms adducts with glutathione, proteins, and DNA. Recent studies demonstrated that acrylamide is metabolized to its epoxide, glycidamide (2,3-epoxy-1-propanamide). We studied the neurotoxicity potential of glycidamide in male Sprague-Dawley rats. Animals (groups of
were injected ip daily with either aqueous acrylamide or glycidamide at an acrylamide-equivalent dose of 50 mg/kg (0.70 mmol/kg). Both treatments resulted initially in the rats circling, which was followed by the onset of ataxia at 7-9 d and hindlimb paralysis at 12-14 d. Treated animals showed muscle wasting. At termination, acrylamide- and glycidamide-treated rats weighed 105% and 86% of initial weight, respectively, compared to 145% for controls. Animals were anesthetized and perfused with 10% neutral phosphate-buffered formalin 12 or 14 d after beginning of treatment. Both treatment groups exhibited similar neuropathologic changes in the central and peripheral nervous systems. More severe lesions were produced by glycidamide. A marked increase in the number of affected Purkinje cells in the cerebellum, which exhibited changes ranging from pyknosis to cell death, were present. The brainstem exhibited axonal degeneration with chromatolytic necrosis in midbrain medial and lateral reticular nuclei. The spinal cord was characterized by spongy form changes with vacuoles of different sizes in various levels. These results suggest that glycidamide is an active neurotoxic metabolite of acrylamide.


Although the immediate action of organophosphorus esters is the inhibition of acetylcholinesterase, some of these compounds also produce a neurodegenerative disorder known as organophosphorus ester-induced delayed neurotoxicity (OPIDN). Tri-o-cresyl phosphate (TOCP) first produced this condition in humans and later in sensitive animal species. OPIDN is characterized by a delay period prior to onset of ataxia and paralysis. The neuropathologic lesions are Wallerian-type degeneration of the axon and myelin in the distal parts of the large tracts in both the central and peripheral nervous systems. In the past decade we have demonstrated that the pathognomonic features of OPIDN are an aberrant increase in autophosphorylation of calcium/calmodulin kinase II (CaM kinase II) and an increase in phosphorylation of cytoskeletal proteins, i.e., MAPs, tubulin, neurofilament triplet proteins, and myelin basic protein. Protein kinase-mediated phosphorylation of cytoskeletal proteins plays a critical role in regulating the growth and maintenance of the axon. We hypothesize that, in OPIDN, hyperphosphorylation of cytoskeletal proteins and axonal swelling are causally linked. Hyperphosphorylation of cytoskeletal proteins decreases their transport rate down the axon relative to their rate of entry into the axon, thus leading to their accumulation. Consistent with this hypothesis is our finding of the anomalous accumulation of phosphorylated neurofilament aggregates in the central and peripheral axons of hens treated with TOCP.
(1992) Illness from chemical "odors": is the health significance understood?

---------------------------------------------------------------

(1992) Multiple chemical sensitivity: treatment and followup with avoidance and control of chemical exposures.
Ziem, GE Journal/Toxicol Ind Health. 8: 73-86.

Reducing unnecessary chemical exposures, particularly pesticides and other petrochemicals, shows promise for reducing illness episodes in the chemically sensitive. Because similar types of exposures have been associated with the onset of chemical sensitivity, such precautions could have wider preventive value for the rest of society as well. Many uses of chemicals have dubious social benefits, and reduced use should be achievable. The chemical industry will likely bitterly contest the reduced use of chemicals because it stands to lose substantial sales. Compensation and liability insurance carriers also stand to lose if the environment is found problematic, rather than individual psychology, for example. Professionals should also recognize conflicts of interest for the chemical and insurance industries by openly acknowledging funding sources for research. The author believes that research on chemical sensitivity that blames the psyche of the victim rather than the chemical will more likely be funded by the insurance or chemical industry than will other research. Study designs should be developed in an atmosphere removed from financial conflicts of interest. This means a substantially larger role for government funding of research on chemical sensitivity to avoid biasing the knowledge base by financially interested parties. The time is critical for government funding of research on chemical sensitivity because the illness is being defined and characterized. If preliminary research is flawed by improper design and focus, our understanding of the problem could be delayed for years.

---------------------------------------------------------------

Young, DB and Van Vliet, BN Journal/Headache. 32: 24-34.

Two hypotheses have dominated attempts to understand the etiology of migraine with aura or classic migraine; the vascular spasm model proposed by Wolff and colleagues, and the spreading cortical depression hypothesis. Neither can provide a fully satisfactory explanation for the syndrome, however. We propose that classic migraine is both spreading cortical depression and localized ischemia linked in a vicious cycle by potassium induced vasoconstriction. The cycle can be initiated by any event which raises the local cortical ECF potassium concentration to approximately 20 mM. Such an event could be a localized burst of activity of a group of cells, localized metabolic
impairment, or a transient reduction in blood flow to a region of the cortex. Once this level of potassium concentration is reached, it may result in localized depolarization of neurons, releasing more potassium into the ECF. Glial siphoning can distribute the potassium preferentially toward the blood vessels in the area, leading to an elevation in potassium concentration in the ECF surrounding the vascular smooth muscle of the arterioles. Above approximately 15 mM, vascular smooth muscle increases its tension in response to elevations in potassium. Therefore, as cortical ECF potassium concentration rises above 15 to 20 mM, localized vasoconstriction occurs, thereby reducing both the supply of oxygen for aerobic metabolism and the removal of potassium in the blood. Under these conditions, the effectiveness of the mechanisms which control potassium concentration is impaired and unable to prevent additional elevations in potassium. As the concentration continues to rise, vasoconstriction becomes more intense, perpetuating the cycle that results in localized depression of cortical neuronal activity and ischemia. The condition is propagated to adjacent regions of the cortex by diffusion and glial-mediated spread of potassium. In many respects, the hypothesis unites the vascular spasm and spreading depression models. If verified, it may provide insight into the causes of classic migraine as well as give direction toward development of effective therapies.

---------------------------------------------------------------

Welch, LS and Sokas, R Journal/Toxicol Ind Health. 8: 47-50.

Investigation of this outbreak raises some important points for future research. Although for various reasons the case ascertainment for MCS was not complete, the three MCS patients described here all had preexisting conditions that may have put them at risk. In addition, one person among the 20 described had chronic fatigue syndrome but did not develop MCS. Many of the persons described here continue to have ongoing complaints that are not MCS. Significant exacerbation of preexisting allergic disease and new onset of asthma occurred among those patients. As a group, they did not recover completely after the outbreak; several are no longer working in the building but in alternative work spaces. An important distinction should be made between individuals who met the definition used here for MCS and others who had significant exacerbation of some better-defined illness brought on by building conditions. New onset of MCS was a partial but not complete explanation of the clinical course for this group of 20 persons.

---------------------------------------------------------------

(1992) Effect of different convulsants on calmodulin levels and proto-oncogene c-fos expression in the central nervous system.
In the present study, a relationship between convulsant activity and two cellular events, changes in calmodulin (CaM) concentration and proto-oncogene c-fos expression has been considered. c-fos has been found activated after the administration of the organochlorine insecticide lindane, the Ca2+ channel agonist Bay K, and N-methyl-D-aspartate (NMDA). The administration of the voltage-dependent Ca2+ channel antagonist nifedipine was able to block the expression elicited by lindane. The effect of lindane on c-fos expression could not be blocked by prior administration of MK-801, a non-competitive antagonist of the NMDA receptor. These results suggest a possible role for the voltage-dependent Ca2+ channels in the mechanism of action of lindane. By means of in situ hybridization, the different patterns of c-fos expression after the administration of the mentioned compounds have been described. A possible modification of the levels of CaM has also been investigated. Among all the subcellular fractions considered, only levels of nuclear CaM appeared to be affected after the different treatments. The changes observed seemed to follow a similar pattern to that described for c-fos induction. Calcium entry through these voltage-dependent calcium channels would be the link between membrane depolarizing events and expression of c-fos and/or increase in nuclear CaM.


Twenty toluene-exposed rotogravure printers, without signs of solvent-induced toxic encephalopathy, had lower median plasma levels of follicle stimulating hormone (FSH) (3.2 vs. 4.9 IU/L; p = .02) and luteinizing hormone (LH) (6.4 vs. 7.2 IU/L; p = .05) and also lower serum levels of free testosterone (7.8 vs. 86.8 pmol/L; p = .05), respectively.
than 44 unexposed referents. The individual time-weighted toluene levels in air were 36 (median; range 8-111) ppm. The printers' median toluene levels in blood were 1.7 (1.0-6.6) mumol/l, and in subcutaneous adipose tissue 5.7 (2.5-21) mg/kg fat. There was a negative association between blood toluene and plasma levels of prolactin. In eight printers, the levels of FSH and LH increased during a 4 week vacation, while the levels of thyroid stimulating hormone, free triiodothyronine, and free thyroxine decreased during the same period. The results indicate a slight, reversible effect of toluene on the cortical level or on the hypothalamic-pituitary axis at exposures well below the permissible levels, possibly mediated through an effect on catecholamine neurotransmission.


1. Male rats received cannula implants above the nucleus accumbens for monitoring extracellular concentrations of dopamine via in vivo microdialysis. 2. Daily injections with cocaine led to an augmentation in both the behavioral response and the neurochemical response (i.e. cocaine-induced increase in extracellular dopamine within the nucleus accumbens) to this drug. 3. Pertussis toxin injections into the A10 region led to sensitized behavioral and neurochemical responses to an acute injection of cocaine. 4. Prior exposure to footshock stress augmented the cocaine-induced increase of motor activity and of extracellular dopamine within the nucleus accumbens. 5. These data suggest that treatments which lead to behavioral sensitization also lead to sensitization within the mesolimbic dopamine system as measured by an augmented dopamine release in the nucleus accumbens.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1579639


A questionnaire survey of health, social, and performance indices related to shiftwork among masters, mates, and pilots of a State Ferries System was performed in response to a joint request from labor and management. The questionnaire results for the group as a whole resembled those reported for other groups of shiftworkers. Significantly more sick days, dissatisfaction with work schedules, poor sleep patterns, physician consultations for insomnia, and reports of errors of judgement and near
misses attributed to fatigue were reported on the ferry run with one of the most erratic schedules compared to all other runs, suggesting the need for further study.

Slesinger, DP Journal/J Rural Health. 8: 227-34.

Migrant farmworkers lead a hard life filled with strenuous work, stress, and anxiety about employment; live under substandard conditions; and rarely get the health care they require. Preventive care is a luxury they cannot afford. Year-round nutritious meals are rarely possible, due to long working hours, traveling, and living in housing without adequate cooking and refrigeration facilities. Children may attend up to six or more schools during the course of a school year. Crowded housing conditions support the invasion of parasites, infectious diseases, and viral infections. Dermatological conditions from working around a wide variety of plants, dirt, and in the sun are frequent. Exposure to pesticides, herbicides, and other chemical additives creates the likelihood of acute reactions, such as headaches and rashes, and also puts workers at risk of developing chronic diseases as the level of exposure rises because of accumulation and mix of various chemicals. Yet, we know little about the health status of this population. We are unable to estimate crude death rates, age-specific death rates, or prevalence rates of most common causes of death, such as heart disease, cancer and stroke. There is no information about occupational accident rates, infectious disease rates, or even postneonatal mortality. We do know that when migrants go to a clinic, they are often likely to have the chronic conditions of hypertension or diabetes. They present symptoms of acute conditions such as dental problems, dermatitis, otitis media among children, and acute upper respiratory infections. Women frequently need obstetrical care, reflected (ABSTRACT TRUNCATED AT 250 WORDS)


Despite the controversy and uncertainty surrounding the causes of the MCS syndrome, psychiatric treatments may provide some relief to MCS patients. These approaches may help patient and physician focus on the most important goals: relief of symptoms and improvement of function. Success requires that physician and patient establish a collaborative relationship and negotiate a treatment plan. Behavioral treatments are most effective at reducing disability and promoting a return to active life. When directed at appropriate target symptoms, psychopharmacologic treatments may reduce some of the most distressing symptoms of chemical sensitivity.


The nonlinear mixed-effects modeling (NONMEM) computer program was used to investigate the variability in the duration of doxacurium-induced neuromuscular block in 408 patients enrolled in phase II and phase III clinical trials of doxacurium. Spontaneous recovery data in the 10% to 90% block range from all patients were pooled and fitted to a linear model. Two parameters were estimated: (1) the slope, which is related to the pharmacokinetics and to the steepness of the dose-response curve, and (2) the intercept, which is linearly related to dose but has no physiologic meaning. The primary goal was to determine the factors affecting the slope by use of univariate and multivariate analyses techniques. Estimates of the slope ranged from 0.67% to 1.1% block/min (interindividual variability, 39%). Factors with clinically significant effects on the slope included the following: age, obesity, and anesthesia type. Thus these factors influence the time course of doxacurium-induced block and may require individualization of dose.


Although no one has all the answers to the mystery of chemical sensitivity, the reality of this condition, most recently called multiple chemical sensitivities, is not in doubt. Evidence is increasing of its possible physiologic mechanisms, which will be discussed
later in this volume. From the evidence and from personal and professional experience, the author believes that chemical sensitivity is not a diagnosis of exclusion, and that fixed-name diseases may have environmental triggers or complicating factors (Rea, 1990b). With appropriate preparation and environmental controls, MCS can be investigated and diagnosed in a scientific and reproducible manner.

Ross, GH Journal/Cmaj. 147: 397.

Ross, GH Journal/Toxicol Ind Health. 8: 87-94.

The essential features of treatment for chemical sensitivity are: 1) Encouraging the provision of clean air, food, water, and surroundings. 2) Identifying substances to which the patient is sensitive, with subsequent a) enhanced avoidance, or b) specific immunotherapy to reduce the patient's reactivity to those substances. 3) Assessing and enhancing the patient's nutritional status to maximize the body's ability to detoxify and to minimize the free-radical production and oxidative stress of xenobiotics. 4) Addressing concurrent problems such as infections, immunosuppression, and other medical conditions in an appropriate fashion. 5) Evaluating the patient's psychologic status and addressing any social and emotional problems in a compassionate manner. The author believes that multiple chemical sensitivity is a real condition with documented physiologic abnormalities. It is not a functional or psychologic illness or a belief system of the patient. Second, this condition is diagnosable and treatable by various means. These treatment options not only make common sense but usually result in significant improvement for these unfortunate patients, who deserve the very best efforts of their health care providers.

The immunotoxic effects of anticholinesterase (antiChE) agents were reviewed. The general characteristics of immunotoxicology were discussed, considering topics such as the mechanism of immune response generation, nonspecific immunity, the
consequences of immunomodulatory processes such as immunostimulation and immunosuppression, and suggested assays for evaluating immunotoxicity. Epidemiological studies investigating the general toxic effects of organophosphates (OPs) have shown that they may also affect the immune system. Induction of allergic reactions following 3 to 4 months exposure, decreases in the number of rosette forming T-cells, increases in the number of B-cells, decreases in leukocyte phagocytic activity, and increases in susceptibility to colds and the number of subjective health complaints have been reported. The results of studies investigating the specific immunotoxic effects of parathion (56382) and malathion (121755) were discussed. Parathion, the most extensively studied OP, has been shown to be immunosuppressive in a number of in-vitro and in-vivo systems. Peroral treatment of mice infected with a cytomegalovirus with parathion caused a significant increase in mortality. In-vitro exposure of human peripheral blood leukocytes to methyl-parathion (298000) decreased their chemotactic activity. In-vivo studies with malathion have shown that it can either suppress or enhance immune responses depending on the route, magnitude, or frequency of administration. Studies of the effects of impurities in OP pesticides have shown that impurities such as O,O,S-trimethylphosphorothioate (152205) or O,O,O-trimethylphosphorothioate (152181) in malathion, acephate (30560191), fenitrothion (122145) and other pesticides can modulate immune responses. Carbamates such as carbaryl (63252) have been shown capable of suppressing immune function, modulating humoral immune responses, macrophage function, and hematologic parameters such as erythrocyte and platelet counts, and lowering resistance to parasitic, bacterial, and viral infections.

Rest, KM Journal/Toxicol Ind Health. 8: 51-65.

(1992) Advancing the understanding of multiple chemical sensitivity (MCS): overview and recommendations from an AOEC workshop.

Rea, WJ  Lewis Publishers. 1:
(1992) **Otoneurologic disturbances caused by solvent pollution.**

Subjects exposed to industrial solvents may experience vertigo and nausea. Solvents are usually volatile hydrocarbon compounds, which are important parts of everyday life in a modern society. They may also cause neurastenia, personality changes, and reduced intellectual capacity. The syndrome that may develop was formerly named psycho-organic syndrome (POS), but in modern terminology it is called chronic toxic encephalopathy (CTE). The syndrome develops slowly, and during the first years no pathological findings will be found using various test batteries. Somewhat later, when the syndrome still might be reversible, psychometric, auditory, and otoneurologic testing may well unveil disturbances within the posterior fossa structures. Animal experiments suggest one site of effect for solvents to be within the cerebellum and brainstem regions with close relationship to the gamma-amino-butryc acid (GABA) transmission. In the otoneurologic test battery, visual suppression and smooth pursuit are of extreme value, as are some auditory tests such as discrimination of interrupted speech and cortical response audiometry using frequency glides as stimuli. Dynamic posturography and magnetic resonance imaging (MRI) have recently proved valuable in the diagnosis. Research is needed concerning the most efficient test battery for early detection of solvent-induced lesions. During further research it is important to unveil other toxic agents, like heavy metals and alcohol, and their damage to the central nervous system and to make comparisons between these substances and the lesions caused by hydrocarbon solvents.

(1992) **Toxicologic data--sorry, wrong number.**


(1992) **Possible models for multiple chemical sensitivity: conceptual issues and role of the limbic system.**

Conceivably, chemicals contacting olfactory nerve projections in the nose could either be transported into or relay electrical signals to the limbic region, leading to a vast array
of symptoms. Likewise, thought processes and mood states may trigger or interrupt pre-existing limbic activity. At present, however, no evidence suggests that limbic activity triggered by environmental exposures can be entirely overcome by psychologic interventions. One important ramification of a limbic hypothesis, if true, is that no convenient biologic marker for multiple chemical sensitivity may exist at the present time. Ten years from now, we may finally confirm the existence of multiple chemical sensitivities (by careful, blinded challenges) but still have no single mechanism to explain it; that is, after all avenues of biochemical and immunologic inquiry have been exhausted, no single cause or marker for this disorder may be apparent. The theory that adaptation plays a role in MCS is based on the observed responses of patients in a deadapted state who have been housed in an environmental unit. Although adaptation is only an observation at this time, not a mechanism, biologic limits might regulate how much an organism can adapt. Such limits could be highly individual and vary by orders of magnitude. Certainly adaptation occurs at all levels of biologic systems, from enzyme systems to cells, tissues, organs, and even behavior (Fregly, 1969). Theoretically, a major insult or the accumulation of lower-level injuries within these systems could lead to a kind of "overload" or "saturation" effect with respect to adaptive capacity. This might cause an individual to have environmental responses, which, instead of being flexible and fluid, would become fragile and overly responsive. Many MCS patients report that years, and in some cases decades, after the onset of their problems, they have recovered only a portion of their former energies and tolerance for their environment. Their descriptions seem to suggest the loss of an intangible capacity to adapt, parts of which may be temporary and recoverable and other parts of which may not. Perhaps our patients have been telling us the diagnosis.


Mitochondrial DNA (mtDNA) was isolated from leukocytes contained in whole blood of cattle. Leukocyte membranes except the nuclear envelope were solubilized in a buffer that contained 1% Triton X-100. After sedimentation of cell nuclei, mtDNA was purified from the cell lysate by organic solvent extraction and ethanol precipitation. Approximately 5 micrograms of mtDNA was recovered from 400 ml of whole blood, a quantity sufficient for routine DNA cloning procedures or for detailed restriction mapping studies. mtDNA isolated with this method is a suitable substrate for several DNA-modifying enzymes. Thus, preparation of mtDNA from blood by detergent lysis provides a noninvasive alternative to tissue biopsy for characterization of mitochondrial genotypes in studies of evolutionary genetics and population dynamics.
(1992) Biases in perception and reporting following a perceived toxic exposure.
Lees-Haley, PR and Brown, RS Journal/Percept Mot Skills. 75: 531-44.

Reactions to chemical exposures often include fears of future illness, cancerphobia, reports of multiple chemical sensitivity, and other ill-defined complaints. Frequently, these complaints occur at levels of exposure not known to cause physiological harm. Although frequently dismissed as hysterical or hypochondriacal reactions, these complaints, along with other indefinite symptoms, may be better understood in terms of biases in perception and reporting. In this paper, we outline various sources of perceptual and response biases including prior beliefs, the media, influential others, reconstructed personal histories, self-perceptions, and the forensic environment. It is recommended that a thorough understanding of symptom-reporting and psychological distress following a chemical exposure involves consideration of these issues.


Calcium- and calmodulin-regulated protein phosphorylation has been suggested to play a role in the pathogenesis of organophosphorus compound-induced delayed neurotoxicity (OPIDN). This condition is characterized by ataxia that progresses to paralysis concurrent with a central-peripheral distal axonopathy after a delay period of 1-2 weeks following exposure to an organophosphorus compound causing delayed neurotoxicity, such as tri-o-cresyl phosphate (TOCP). Calcium/calmodulin (CaM) kinase II is involved in the increased phosphorylation of brain microtubule and spinal cord neurofilament triplet proteins following treatment of animals with organophosphorus compounds that are capable of producing OPIDN. In this study, chickens were given a single oral neurotoxic dose of 750 mg TOCP/kg body weight and killed after 1, 6, 14 or 21 days following treatment. Protein kinase-mediated phosphorylation of cytoskeletal proteins was studied in proximal and distal parts of sciatic nerves of control and treated hens. Peripheral nerve proteins were phosphorylated in vitro using [gamma-32P]ATP as a phosphoryl group donor. Phosphorylated proteins were separated by one- and two-dimensional sodium dodecyl sulfate polyacrylamide gel electrophoresis. Protein phosphorylation was detected by autoradiography and quantified by laser microdensitometry. The extent of Ca2+-calmodulin dependent phosphorylation of five cytoskeletal proteins was significantly increased in TOCP treated animals, particularly at 1 and 6 days after treatment, in both the proximal and distal portion of the nerve. The identity of these proteins was confirmed by 2-D PAGE as tubulin, the neurofilament triplet proteins and microtubule associated protein-2 (MAP-2). These results confirm earlier observation of
the close temporal relationship between increased cytoskeletal protein phosphorylation and the development and OPIDN.

(1992) Triphenyl phosphite-induced ultrastructural changes in bovine adrenomedullary chromaffin cells.

Primary cultures of bovine adrenomedullary chromaffin cells were treated with the phosphorus acid ester triphenyl phosphite (TPP), a chemical capable of producing Type II organophosphorus compound-induced delayed neurotoxicity (OPIDN), and the morphological changes were assessed by transmission electron and scanning microscopy. Following a 24-hr incubation with 100 microM TPP nearly all mitochondria were either disrupted or swollen and glycogen buildup within the cytoplasm was evident. The viability of cells treated with TPP and cultured on coverslips for scanning electron microscopy was very low. By scanning electron microscopy, the filopodia of these cells appeared contracted. The surface texture was very irregular and giant globular bodies were evident. Parallel studies were carried out with the cholinergic compound O,O-diethyl 4-nitrophenyl phosphate (paraoxon) and the Type I delayed neurotoxicant O,O-diisopropylphosphorofluoridate (DFP). Transmission and scanning electron microscopy revealed that treatment with these organophosphorus compounds did not produce the ultrastructural effects that were seen with TPP. The morphological data were confirmed biochemically by assessing the viability of the mitochondria via measurement of [3H]adenosine incorporation into ATP. Treatment with 100 microM TPP for 4 or 24 hr caused a marked inhibition (90% relative to controls) of adenosine incorporation. Neither 100 microM paraoxon nor 100 microM DFP had an inhibitory effect on incorporation. The effect of TPP was time-dependent with significant biochemical effects as early as 60 min. In contrast, ultrastructural changes were not seen until 24 hr. Morphologically, the 60-min incubations showed no perturbation in mitochondrial integrity. Our results support a specific effect of the triphenylphosphite, TPP, a Type II OPIDN compound, not a general toxic effect of organophosphorus compounds since the cholinergic agent paraoxon and the Type I delayed neurotoxic compound DFP did not alter the cells ultrastructurally or compromise the mitochondria biochemically. The apparent target for TPP toxicity is the mitochondria.

Anti-histamine and anti-PAF effects of epinastine were tested in rats, guinea pigs and rabbits. Epinastine showed a potent histamine H1-blocking effect, but the potency was slightly less than that of ketotifen in histamine-induced contraction of guinea pig ileum and histamine-induced cutaneous reactions in rats. In histamine-induced dye leakage into the nasal cavity tested in rats, the drug was slightly more potent than ketotifen and azelastine. Epinastine as well as ketotifen suppressed rabbit platelet aggregation induced by PAF at higher concentrations compared with WEB 2086, a specific PAF-antagonist. In the bronchospasm induced by PAF in guinea pigs, epinastine was more effective than ketotifen in inhibiting the bronchoconstriction, while it showed no remarkable effect on the hypotension induced by PAF. Epinastine caused a potent antagonistic effect on LTC4-induced contraction of isolated guinea pig trachea. In conclusion, the potent anti-histamine, anti-PAF and anti-LT effects of epinastine may significantly contribute to its antiallergic activity.

----------------------------------

(1992) Sick hospital, sick doctor: Halifax hospital tries to cope with "environmental illness".  
Jones, D Journal/Cmaj.  146:  2056-7, 2060-1.

----------------------------------


----------------------------------


Previous biochemical studies demonstrated a dramatic increase in phosphorylation of cytoskeletal proteins that occurs early in organophosphorus ester-induced delayed neurotoxicity (OPIDN). In this report we present immunohistochemical evidence that there is anomalous aggregation of phosphorylated neurofilaments within central and peripheral axons following organophosphate exposure. The morphology, location, and time of appearance of these aggregations are consistent with the hypothesis that the aberrant phosphorylation of cytoskeletal elements is an antecedent to the focal axonal swelling and degeneration characteristic of OPIDN.
(1992) Smell or taste disturbances, neurological symptoms, and hydrocarbon exposure.

A total of 264 workers participated in a cross-sectional study concerning the toxicity of hydrocarbons. The clinical examination shows an increased prevalence of smell and/or taste disturbances in the heavily exposed group. These symptoms appear to be generally transitory and reversible. They seem to be due to concentration peaks rather than to a long exposure duration. They are associated with acute depressor effects and not with symptoms which could belong to a hydrocarbon-induced chronic toxic encephalopathy.


Ca2+/calmodulin-dependent protein kinase II (CaM-kinase II) has been purified from hen whole brain. The enzyme was purified 3000-fold using phosphocellulose and calmodulin-Agarose column chromatography. The specific activity was 200 nmol/min mg protein. Microtubule associated protein-2 (MAP-2) was used as a substrate to assess the activity of the enzyme during purification and for its characterization. CaM-kinase II consisted of alpha and beta/beta' subunits of molecular weights 46,000 and 55,000/52,000, respectively. The ratio of alpha to beta/beta' subunits was 3:1 in the enzyme purified from the whole brain. The enzyme exhibited broad substrate specificity and phosphorylated myelin basic protein, MAP-2, histone II, histone VIII, casein, tubulin, myosin light chains, glycogen synthase, and phosvitin in decreasing order. Phosphorylase b was phosphorylated at a negligible rate. Autophosphorylation of CaM-kinase II for 10 min in the presence of calcium and calmodulin decreased its total activity to 33%, and calcium/calmodulin-independent activity reached 30% after 1 min and then dropped to 14% after 10 min of autophosphorylation. The Km value of ATP was 19 +/- 1.3 microM, and the K0.5 values of calcium and calmodulin were 4.4 + - 0.5 and 3.0 +/- 0.5 microM, respectively. The latter were determined using myelin basic protein as the substrate. CaM-kinase II exhibited great differences in the calmodulin requirement for phosphorylation of MAP-2, histone II and myelin basic protein. MAP-2 required the least amount of calmodulin for its phosphorylation. Autophosphorylation of CaM-kinase II resulted in decreased mobility of the alpha-subunit but apparently not of the beta/beta' subunits in sodium dodecyl
sulfate-polyacrylamide gel. Antiserum was raised against the CaM-kinase II alpha subunit and used for testing cross-reactivity of hen brain enzyme with that of other species. The antiserum which reacted with both alpha and beta subunits of hen brain CaM-kinase II cross-reacted with only the alpha subunit of rat, mouse, rabbit, cat, dog, pig and human brain samples. The purified hen brain CaM-kinase II is a multifunctional enzyme and resembled rat brain CaM-kinase II in several properties. Immunocross-reactivity suggested that there was similarity in the alpha but not the beta subunits of the hen brain enzyme and the brain enzyme of other species.

(1992) Ethanol-inducible microsomal aniline hydroxylase activity and cytochrome P-450 isozymes in adult hen liver.

1. Cytochrome P-450 was induced in adult hen liver by administering 15% ethanol in drinking water and compared with other inducers such as phenobarbital and beta-naphthoflavone. 2. Aniline was the only substrate whose turnover was induced by ethanol treatment when measured in the presence of 100 microM alpha-naphthoflavone. 3. The inhibitor alpha-naphthoflavone differentiated aniline and p-nitrophenol hydroxylase activities, while p-hydroxyphenyl imidazole and SKF differentiated p-nitrophenol hydroxylase activity between ethanol- and beta-naphthoflavone-induced microsomes. 4. Ethanol treatment also slightly induced some P-450 isozymes related to phenobarbital and beta-naphthoflavone inducers.


The research reviewed in the present paper indicates that vasopressin and oxytocin cells in the human HNS constitute an extremely stable population of neurons throughout the human life span. Increases in the activity of these cells, which are probably related to maturation of the system were observed during fetal development and probably extend well beyond term. During senescence an increase in the activity
of the vasopressin cells in the human HNS was observed which is probably a compensation for age-related changes in kidney function. These data do not support a role of declining vasopressin secretion in age-related memory decline. Although there is some evidence for an impairment of vasopressin synthesis and release in Alzheimer patients, vasopressin cell numbers in Alzheimer's disease do not fall below values observed in young controls. Furthermore, peripheral administration of vasopressin or vasopressin analogues to AD patients have not yielded consistent results.

(1992) Acquired intolerance to solvents following pesticide/solvent exposure in a building: a new group of workers at risk for multiple chemical sensitivities?

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1412491

(1992) The role of NMDA receptor-operated calcium channels in persistent nociception after formalin-induced tissue injury.

The contribution of intracellular calcium to central sensitization and persistent nociception in response to tissue injury in rats was examined following the subcutaneous injection of formalin into the hindpaw. Formalin injury-induced nociceptive behaviors were enhanced by intrathecal pretreatment with the calcium ionophore A23187 or the calcium channel agonist Bay-K8644. Conversely, formalin nociceptive responses were reduced by intrathecal pretreatment with the calcium chelator Quin 2 or the calcium channel antagonists verapamil and nifedipine. Each of these agents affected the tonic, but not the acute, phase of the formalin response. The enhancement in formalin nociceptive behavior in rats treated with L-aspartate or L-glutamate was reversed by combined pretreatment with the noncompetitive NMDA antagonist MK-801, but not by nifedipine or the non-NMDA excitatory amino acid antagonist 6-cyano-7-dinitroquinoxaline-2,3-dione. In rats not treated with excitatory amino acids, the analgesic effect of MK-801 was also significantly greater than that produced by nifedipine. Furthermore, combining nifedipine with MK-801 did not produce a significantly greater analgesic effect than MK-801 alone. The results suggest that central sensitization and persistent nociception following formalin-induced tissue injury are dependent on the influx of calcium through predominantly NMDA receptor-operated (and to a lesser extent voltage-gated) calcium channels.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1326611

Growth promotion by oxidants is observed with cultured human and mouse fibroblasts as well as epidermal cells. It is expected to play a role in inflammation, fibrosis, and tumorigenesis. Indeed, oxidants trigger (patho)physiological reactions that resemble those induced by growth and differentiation factors. For example, active oxygen activates protein kinases, causes DNA breakage, and induces the growth competence-related protooncogenes c-fos and c-myc. The cellular antioxidant defenses affect the consequences of oxidant exposure. Transfectants of mouse epidermal cells that overproduce Cu,Zn-superoxide dismutase (SOD) were sensitized to the toxic effects of an extracellular burst of O2- plus H2O2, whereas overproducers of catalase (CAT) were protected. Transfection of SOD overproducers with CAT corrected their hypersensitivity. Inducibility of the protooncogene c-fos by oxidants was diminished in SOD and CAT overproducers, albeit probably for different reasons. It is concluded that a fine balance of the multiple components of the antioxidant defense determines the growth response of cells to oxidative stress. In studies of the mechanism of the transcriptional induction of c-fos by oxidants, we identified the joint DSE-AP1 elements (dyad symmetry element, DSE) as major enhancer motifs in the 5'-upstream regulatory sequences of c-fos. Oxidants also increased the de novo synthesis of protein factors that bind to the fos-AP1 enhancer motif. Protein kinase and ADPR transferase inhibitors suppressed the transcriptional induction of c-fos as well as the increase in factor binding to fos-AP1. We conclude that protein phosphorylation and protein polyADP-ribosylation are required for the transcriptional induction of c-fos and the synthesis of protein factors that bind to fos-AP1. It is likely that the FOS and JUN proteins are among these factors and that they participate in the regulation of c-fos expression by oxidants.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1482049


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1412483
(1992) Multiple chemical sensitivities--fact or myth.
Brautbar, N, Vojdani, A and Campbell, AW Journal/Toxicol Ind Health.  8: v-xiii.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7570617

(1992) Multiple chemical sensitivities--fact or myth [editorial].
Brautbar, N, Vojdani, A and Campbell, AW Journal/Toxicol Ind Health.  8: v-xiii.

(1992) Roles played by music as revealed during countertransference facilitated transference regression.

Clinical and experimental investigations have demonstrated that music may serve subtle and complex psychological functions, the sounds per se serving more primitive roles than the themes and lyrics. The present study offers data obtained during the psychoanalysis of a musically talented man who had suffered life-threatening croup and asthma until the age of 5 or 6. Regression that was achieved as the result of interpretations based on the analyst's countertransferential responses revealed that the analysand was unable to achieve psychological separation from his mother and that music served predominantly the function of retaining a life-supporting connexion with her. Presumably as the result of a complex elaboration of respiratory and auditory introjection, music came to symbolize the noise of air-flowing through tubes into the steam tents and blood coursing through the umbilical cord, conceptualized as connecting him with his mother and making them permanently interdependent. The early ego defect was overcome through a transference-countertransference interaction that is delineated in detail. Then, the less primitive meanings and psychological uses of musical themes and lyrics were elucidated, again in response to interpretations based on countertransference reactions.


Little is known about the causes of health complaints associated with work with video display units (VDUs). The symptoms are to a large degree similar to those of "multiple chemical sensitivity." We observed 47 white-collar employees with and without VDU-associated skin complaints during a regular workday and a day of leisure. VDU workers with skin symptoms had higher levels of the stress-sensitive hormones thyroxin and prolactin compared with employees without symptoms. They also had lower levels of the anabolic hormone testosterone during work. VDU workers with skin complaints also reported more occupational mental strain. A model is proposed in which physiological signals act as unconditioned stimuli and the VDU environment as the conditioned stimuli.

Low thyroxine levels in female psychiatric inpatients with riboflavin deficiency: implications for folate-dependent methylation.

Intermediates in the folate-dependent methylation pathways may play a role in the etiology and treatment of such mental disorders as major depression. These pathways include a step dependent on a riboflavin (B2)-derived coenzyme, flavin adenine dinucleotide (FAD), which is reportedly sensitive to thyroid status and to phenothiazine and tricyclic drug exposure. In a sample of 52 male and female acute psychiatric inpatients, 17% (n = 9) showed B2 deficiency (i.e., insufficient FAD activity) on a functional red blood cell enzyme assay, but only one B2-deficient individual showed deficiency in another B-complex vitamin (folate). All patients with B2 deficiency were women, who were also significantly younger than the rest of the sample. The B2-deficient women had significantly lower thyroxine levels, even when controlling for sex and covarying for age. B2-deficient patients exhibited a nonsignificant trend toward more unipolar depression (44% vs 14%), but not toward bipolar or schizophrenic disorders. As in a previous study, drug exposure did not show a relationship to riboflavin deficiency in this sample. The findings suggest that B2 (FAD) activity may serve as a sensitive marker of thyroxine status in certain female psychiatric inpatients and that B2 deficiency may play an etiological role in defects of the methylation pathways in a subset of mentally ill individuals.
Bell, IR, Miller, CS and Schwartz, GE Journal/Biol Psychiatry. 32: 218-42.

This paper reviews the clinical and experimental literature on patients with multiple adverse responses to chemicals (Multiple Chemical Sensitivity Syndrome-MCS) and develops a model for MCS based on olfactory-limbic system dysfunction that overlaps in part with Post's kindling model for affective disorders. MCS encompasses a broad range of chronic polysymptomatic conditions and complaints whose triggers are reported to include low levels of common indoor and outdoor environmental chemicals, such as pesticides and solvents. Other investigators have found evidence of increased prevalence of depression, anxiety, and somatization disorders in MCS patients and have concluded that their psychiatric conditions account for the clinical picture. However, none of these studies has presented any data on the effects of chemicals on symptoms or on objective measures of nervous system function. Synthesis of the MCS literature with large bodies of research in neurotoxicology, occupational medicine, and biological psychiatry, suggests that the phenomenology of MCS patients overlaps that of affective spectrum disorders and that both involve dysfunction of the limbic pathways. Animal studies demonstrate that intermittent repeated low level environmental chemical exposures, including pesticides, cause limbic kindling. Kindling (full or partial) is one central nervous system mechanism that could amplify reactivity to low levels of inhaled and ingested chemicals and initiate persistent affective, cognitive, and somatic symptomatology in both occupational and nonoccupational settings. As in animal studies, inescapable and novel stressors could cross-sensitize with chemical exposures in some individuals to generate adverse responses on a neurochemical basis. The olfactory-limbic model raises testable neurobiological hypotheses that could increase understanding of the multifactorial etiology of MCS and of certain overlapping affective spectrum disorders.

--------------------------------------------------------------------------------


Depression among elderly people with reversible cognitive loss often manifests with concomitant vascular disease and can also precede the development of nonvascular degenerative dementia. Little is known about etiological factors for reversible or irreversible dementias in older depressed people. The amino acid homocysteine (HC), which is both a vascular disease risk factor and a precursor of the excitotoxic amino acids cysteine and homocysteic acid, could play a role in the pathophysiology of such individuals. Twenty-seven depressed elderly acute inpatients by DSM-III-R criteria had significantly higher plasma homocysteine levels and lower cognitive screening test scores than did 15 depressed young adult inpatients. HC was highest in the older
patients who had concomitant vascular diseases \( (n = 14) \). HC was lowest in the older depressives who had neither vascular illnesses nor dementia \( (n = 8) \), comparable to the young adult depressives. Higher HC correlated significantly with poorer cognition only in the nonvascular geriatric patients \( (r_s = -0.53) \). The findings extend earlier work showing higher HC in vascular patients from general medical populations, and also suggest a possible metabolic factor in certain dementias associated with late-life depression.

(1992) Brief communication. Vitamin B1, B2, and B6 augmentation of tricyclic antidepressant treatment in geriatric depression with cognitive dysfunction.

This was a 4-week randomized placebo-controlled double-blind study to assess augmentation of open tricyclic antidepressant treatment with 10 mg each of vitamins B1, B2, and B6 in 14 geriatric inpatients with depression. The active vitamin group demonstrated significantly better B2 and B6 status on enzyme activity coefficients and trends toward greater improvement in scores on ratings of depression and cognitive function, as well as in serum nortriptyline levels compared with placebo-treated subjects (Ss). Without specific supplementation, B12 levels increased in Ss receiving B1/B2/B6 and decreased in placebo Ss. These findings offer preliminary support for further investigation of B complex vitamin augmentation in the treatment of geriatric depression.

(1992) Multiple chemical sensitivity: a respiratory disorder?
Bascom, R Journal/Toxicol Ind Health. 8: 221-8.


A previously healthy 45 years old carpenter suffered a whiplash injury in a road accident on July, 18th, 1990. He continued to work in spite of occipital headache, episodic sweating and slight hypersomnia. On August, 8th, 1990 while parking his car into the deck of a ferry-boat he was found slightly confuse and markedly amnestic. A post-traumatic subdural haematoma was suspected. As a CT-scan of the brain was
normal, a toxic encephalopathy or an hysterical amnesia were proposed. However, a MRI performed on August, 22th, 1990, apart from a small infarct in the white matter of the left occipital lobe, showed two small bilateral paramedian thalamic infarcts. The last lesions usually follow a thrombotic or embolic occlusion of the "basilar communicating artery" (BCA) belonging to the vertebro-basilar system. The possible etiologic relationship between this syndrome and the previous whiplash injury has been considered. Six months later, while a control MRI showed a reduction of the brain lesions, a neuropsychological examination revealed a slight improvement of memory dysfunction evident also at a distance of further 6 months. This case is interesting because it tests the high sensitivity of MRI in amnestic syndromes and because of the possible role of a whiplash injury in the etiology of BPTI.

Baker, P and Selvey, D Journal/Vet Hum Toxicol. 34: 156-60.

More than 100 people, including firefighters, police officers, paramedics, nurses and physicians responded to reports that students at an elementary school had been exposed to an unknown and possibly toxic substance; 296 students were transported to eight hospital emergency departments. None were diagnosed as acutely ill. The substance was subsequently identified as approximately 22 ml of malathion, diluted in 15 L of water and applied by means of a hand-held sprayer approximately 100 m from the school. The odor apparently drifted to the school in 19 to 24 km/h winds. The episode was determined to be epidemic hysteria, possibly triggered by the malathion odor, but perpetuated by the stress of the emergency response. Hallmarks of epidemic hysteria are discussed, and recommendations for dealing with similar events are offered.


At two scientific conferences in 1985, one in Copenhagen sponsored by the Nordic Council of Ministers and the World Health Organization (WHO), the other in Raleigh, NC, it was concluded that chronic toxic encephalopathy may develop following long-term occupational exposure to organic solvents (1,2). The terms organic affective syndrome, mild and severe chronic toxic encephalopathy were suggested for this condition describing increasing severity. In May 1990, a conference on organic solvents and the nervous system was held in Copenhagen sponsored by the Commission of the European Communities and the Danish Ministry of the Environment
(3). Scientists and representatives from the governments, industries, and labour organisations from the EEC and US participated.

(1992) Is there evidence of an immunologic basis for multiple chemical sensitivity?


http://www.sciencedirect.com/science/article/B6T4S-485CWDV-28/2d636a68e8ce7b2ad8596cc3690771cd6


Building-related illness ranges from mild rhinitis to potentially life-threatening hypersensitivity pneumonitis and legionellosis. Sick-building syndrome, consisting of headache, mucous membrane irritation, and fatigue, may be present in 30% of all office workers. Hypersensitivity pneumonitis, asthma, and legionellosis are less common, and it is difficult from existing studies to estimate the incidence of these more severe illnesses. There are even fewer data on an illness now being called multiple chemical sensitivity and its relationship to indoor environments. New studies are
needed to estimate the frequency of all building-associated illnesses, and case
definitions for these disorders must be delineated.

(1991) Chronic neuropsychological and neurological impairment following acute
exposure to a solvent mixture of toluene and methyl ethyl ketone (MEK).
Toxicol. 29: 435-45.

A 38 year-old laborer experienced solvent intoxication during each of two spray
paintings of a dump truck and other heavy equipment in an enclosed, unventilated
carage. The paint base consisted primarily of toluene and methyl ethyl ketone.
Nausea, headaches, dizziness, respiratory difficulty and other symptoms began after
exposures. Over the next several days he developed impaired concentration, memory
loss and cerebellar signs including an intention tremor, gait ataxia and dysarthria. MRI
of the brain and EGG early in the work-up were normal, although later MRIs
demonstrated fluid collection over the left parietal area. Examination by a toxicologist
and neurologist revealed likely toxic encephalopathy with dementia and cerebellar
ataxia. Three formal neuropsychological assessments over 2 1/2 years quantified
cognitive, motor and behavioral changes. Despite similar findings in chronic exposure
to these solvents, lasting sequelae following acute exposure have not been widely
reported.

(1991) Depression and panic attacks related to phenol-formaldehyde composite
material exposure in an aerospace manufacturing plant.
Sparks, PJ, Ayars, GH, Simon, GE, Katon, WJ, Altman, LC and Johnson, RL Journal
Allergy Proc. 12: 389-93.

In a case series study we evaluated 53 composite-materials workers in an aerospace
plant who filed workers’ compensation claims for illness allegedly related to
phenol-formaldehyde resin exposure. Symptoms ranged from mucosal and skin
irritation to depression and cognitive impairment. Certain health practitioners implying
they had immunologic dysfunction and organic brain injury, led workers to believe they
were chemically poisoned. Industrial hygiene evaluation failed to show levels of
chemicals above permissible levels. Thorough evaluation by our multidisciplinary panel
failed to find significant objective abnormalities by physical exam and laboratory
testing. Thirty-nine percent of the workers had sensory irritation and/or skin complaints
that generally resolved rapidly with removal from exposure. Psychiatric diagnoses
(including major depression and/or panic attacks) were made in 74% of the workers,
but only 26% of these had antecedent disease. Fourteen (26%) had multiple somatic
complaints that generally persisted despite removal from exposure, but they also had
long histories of significant pre-existing psychological illness. Detailed neuropsychologic testing failed to show any definite evidence or organic brain dysfunction in any of the workers tested. We speculate that sensory irritation from low-level volatile organic compounds with autonomic arousal, reinforced by the belief they were "chemically poisoned," led to psychogenic illness.


The onset and development of testicular lesions following tri-o-cresyl phosphate (TOCP) dosing have been documented through light and electron microscopic morphological studies. Male Fischer 344 rats (190-210 g body weight) were administered 150 mg TOCP/kg/day in corn oil for 1, 3, 5, 7, 10, 14, and 21 days. Vehicle-treated rats served as the control group. Sections of formaldehyde- and glutaraldehyde-fixed, methacrylate-embedded testes showed, by Day 5, numerous spermatid heads apparently detached from tails lying at oblique angles near the basement membrane of the seminiferous tubules. Columnar and spherically shaped vacuoles of the epithelium, radiating from the basement membrane to the lumen of the tubules, were also observed. Electron micrographs revealed that these were localized in Sertoli cells. Widespread dilation of Sertoli cell smooth endoplasmic reticulum was also noted. By 7 days of treatment, residual body abnormalities were noted in stage VIII tubules, along with spermatocyte-derived multinucleated giant cells. The lesion progressed with increased vacuolation of the epithelium and numbers of abnormal residual bodies and giant cells, together with spermatid karyorrhexis (Days 10, 14, and 21). There was also an apparent decrease in sperm density/tubule with continued exposure: 90% of the seminiferous tubules were devoid of sperm by Day 14. These morphological results indicate an initial effect of TOCP on Sertoli cells. Spermatogenesis is affected as seen by the decrease in sperm density and increase in necrotic spermatids.


Assessment of nasal patency by the recording of nasal symptom scores was compared with an objective method of determining nasal airway area using a fiberoptic rhinoscope. Sixty patients with active allergic rhinitis and nasal congestion requiring
treatment were studied. Nasal symptoms were recorded and nasal airway area was measured before and at fixed time intervals after administration of either pseudoephedrine or oxymetazoline. Both methods detected a decongestant response to both drugs, and the symptom of congestion correlated with the measured nasal airway area. Rhinoscopic measurement of cross sectional nasal airway area is an objective method that may be used to complement other methods for evaluation of nasal patency.


A model of external- and middle-ear function is described that uses existing data to quantify the flow of sound power from the environment to the cochlea of humans, cats, and chinchillas. This model estimates the sound power produced at the entrance of the cochlea by an environmental sound stimulus, and can be used to predict the shape of the auditory threshold function and the relative potency of various traumatic acoustic stimuli. The shapes of the predicted and measured threshold functions in the three species are similar in best frequency, bandwidth, and low-frequency slope, and the model accurately predicts the hypersensitivity of the middle-frequency regions of the cochlea to acoustic trauma. The model assumes that the mechanics of the middle-ear system are linear even at high stimulus levels and does not include the effects of either middle-ear or cochlear efferent loops. The effects of these simplifications on the model are discussed as are the implications of the model results for hearing protection and damage risk criteria.


Fifty chemically sensitive patients with vascular, asthmatic and arthritic signs, ranging in age from 21 to 61, were exposed to double-blind challenges of ambient doses of
inhaled toxic chemicals in a specially designed booth in an Environmental Control Unit (ECU). Primary signs and symptoms were recorded before and after challenge with five chemicals and three placebos. Inhaled challenges included phenol (less than .0025 ppm), petroleum-derived ethyl alcohol (less than .5 ppm), formaldehyde (less than .2 ppm), chlorine (less than .3 ppm), and pesticide (2, 3-D at less than .0034 ppm). Placebos were water or saline. A set on testing criteria were evaluated for maximizing the likelihood of well-defined, reproducible information from these ambient-dose double-blind challenges. For best results, these testing criteria include: Before testing, the patient must be housed in a chemically less polluted environment. The individual must have been de-adapted to food, air, and water pollutants by means of a water fat for three to four days. At the time of the challenge, the patient must be on food and water previously determined to be safe. An enclosed non-pulluted challenge booth must be used for these chemical exposures. Sign and symptom scores appropriate for that patient must be recorded, before and after challenge. Appropriate doses of the chemical in question (determined by air concentration and length of exposure) are necessary to investigate a particular problem. The conclusion of the study is that in these patients, chemical sensitivity clearly does exist (pulse rate differences between positive responses and placebo - p .001).(ABSTRACT TRUNCATED AT 250 WORDS)


By the nature of their work environment, physicians may be exposed to potentially toxic substances that can trigger chemical sensitivity. Nineteen physicians with chemical sensitivity were evaluated at the Environmental Health Center - Dallas regarding: type of specialty, history of chemical exposure, symptoms produced, food and water tolerance, immune parameters and double-blind chemical inhalation challenge. Food and chemical sensitivities were demonstrated in these physicians by oral, intradermal and inhalation challenges. After treatment, fifteen of the nineteen physicians were able to resume medical practice. Potential sources of chemical exposure in medical environments are evaluated.

(1991) Food and chemicals as environmental incitants.

Susceptibility to environmental incitants such as air, food and water components is becoming an increasingly recognized health problem. These sensitivities and reactions can induce a spectrum of symptoms affecting smooth muscle, mucous membranes
and collagen in the respiratory, gastrointestinal, genitourinary and vascular systems. These reactions may be mistaken for hypochondriasis, but actually are due to reactions to foods and chemicals found in the patient's home and work environments. Careful clinical histories should alert the nurse and physician, who can confirm suspicions by eliminating and challenging the patient with potentially offending agents under controlled circumstances.


In this study, different modes of therapy for the removal of toxic chemicals from the human body have been assessed and compared. This consisted of: 1) thirteen inpatients in an environmentally controlled area in a hospital, 2) forty-one outpatients with home environmental control and work area change, and 3) fifteen outpatients in a physical therapy/sauna program with a good environmental control. Attention to manipulation of food, food contaminants, water and air pollution as well as nutritional therapy was important in all groups. Each modality seemed efficacious in its own right; 100% inpatients, 80% sauna/physical therapy patients, and 70% outpatients improved their signs and symptoms. Inpatient therapy in a finally controlled environment was far superior to the other two modalities in clearing of symptoms, as well as in clearing of organic chemicals. Outpatient and sauna/physical therapy are efficacious for less ill patients.


The purpose of the present study was to see if chemically sensitive individuals had aliphatic hydrocarbon solvents as part of their total body load. This was done by measuring blood levels from 85 chemically sensitive patients. These were measured by a purging trap method with gas chromatography/mass spectrometry (GCC/MS) by the methods of Laseter. Thirteen patients had blood levels below the detection limit of less than 1 ppb and 72 were above the detection limit. An average of three solvents, out of seven measured, including n-pentane, 2,2-dimethylbutane, cyclopentane,
2-methylpentane, 3-methylpentane, n-hexane, n-heptane, was found in 85% of the patients' blood on the 1 to 299 ppb range. The means were as follows: n-pentane 14.7 ppb, 2,2-dimethylbutane 2.5 ppb, cyclopentane 9.0 ppb, 2-methylpentane 16.7 ppb, 3-methylpentane 28.0 ppb, n-heptane 5.5 ppb. The most frequently found of the above solvents was 2-methylpentane (found in 68.1% of the patients), 3-methylpentane (62.5%), n-hexane (61.1%), and pentane (40.3%).

Ott, L, Young, B, Phillips, R, McClain, C, Adams, L, Dempsey, R, Tibbs, P and Ryo, UY

Most patients with moderate to severe head injury initially do not tolerate enteral feedings postinjury. This intolerance is more prolonged than that found in patients suffering other types of trauma. The authors prospectively evaluated 12 patients with moderate to severe head injury (Glasgow Coma Scale score between 4 and 10) throughout their hospitalization for liquid gastric emptying as a possible mechanism for intolerance to enteral feeding. During Week 1, the majority of patients displayed a delay in gastric emptying. Patients also displayed an abnormal biphasic response (gastric emptying faster than normal during the early stage but prolonged later). By Week 2, many patients still had delayed and abnormal biphasic responses to gastric emptying. By Week 3, an improvement was observed with the majority of patients exhibiting rapid gastric emptying, but delays and abnormal biphasic responses were still seen. Patients who initially had rapid or normal gastric emptying tolerated full-strength full-rate feedings significantly earlier compared with those who experienced delayed gastric emptying (8.5 +/- 0.5 days vs. 13.7 +/- 3.2 days, p less than 0.001). All patients tolerated full-strength full-rate feedings by Day 16 postinjury (range 7 to 16 days) except the two patients who displayed delayed gastric emptying for prolonged periods of time (mean 25 days). This is the first study to longitudinally evaluate gastric emptying following head injury. The authors suggest that patients with moderate to severe head injury often experience alterations in gastric emptying which may affect their ability to tolerate enteral feedings.

Ornstein, E, Matteo, RS, Weinstein, JA, Halevy, JD, Young, WL and Abou-Donia, MM

STUDY OBJECTIVE: To determine whether a drug interaction exists between doxacurium and anticonvulsants. DESIGN: Open-label controlled study. SETTING:
Inpatient neuroanesthesiology service at a university medical center. PATIENTS: Three groups of nine patients each, consisting of those chronically receiving carbamazepine, phenytoin, or no anticonvulsant therapy. INTERVENTION: Intravenous administration of doxacurium 60 micrograms/kg during anesthesia with nitrous oxide (N2O), fentanyl, and droperidol. MEASUREMENTS AND MAIN RESULTS: The adductor pollicis mechanical response to single 0.2-millisecond supramaximal pulses delivered to the ulnar nerve at 0.15 Hz was recorded. Patients receiving phenytoin or carbamazepine recovered neuromuscular function more quickly than did the control group. The times from doxacurium injection to 50% recovery of mechanomyographic response, for example, were as follows: control group, 161 +/- 55 minutes (mean +/- SD); phenytoin group, 76 +/- 31 minutes; and carbamazepine group, 66 +/- 27 minutes (p less than 0.05). The time for recovery from 75% to 25% blockade (recovery index) was decreased by 53% in the phenytoin group and by 67% in the carbamazepine group as compared with the control group (41.0 +/- 18.0 minutes and 28.6 +/- 8.6 minutes vs 86.4 +/- 45.2 minutes, respectively). CONCLUSION: Chronic treatment with anticonvulsants results in more rapid recovery from neuromuscular blockade produced by doxacurium.

(1991) Organic cognitive impairment?


This study examined neuropsychological prognosis following organic solvent exposure. Twenty-seven persons with evidence of "mild toxic encephalopathy" were evaluated on two separate occasions with a standard neuropsychological test battery and the Minnesota Multiphasic Personality Inventory. Ratings by experienced clinicians revealed that 50% of exposed persons had improved neuropsychological performance at the second evaluation. The other 50% were rated as having no change or a decline in neuropsychological tests scores. While the majority of persons in the good-outcome group were working at the time of the follow-up evaluation, none of the persons in the poor-outcome group was actively employed. Persons rated as having shown no improvement were significantly more likely to have had a peak exposure--an episode in which they were briefly exposed to a larger than normal amount of solvent. In addition, persons in the poor outcome group reported higher levels of psychological distress, both initially and at the follow-up evaluation. Results from this study suggest that the
presence of certain risk factors, namely a peak exposure and psychological distress, may be particularly detrimental for long-term neuropsychological outcome in persons with a history of organic solvent exposure.


1. When the web of the anaesthetized Xenopus laevis was perfused with Ringer solution maintained at 20 degrees C, radio frequency (RF) burst-type electromagnetic (EM) field radiation not only dilated arterioles of the web which had been preconstricted with noradrenaline, but also dilated arterioles under non-stimulated conditions. The EM field-induced vasodilatation increased slowly and reached a plateau 60 min after the onset of radiation. After the cessation of radiation, vasodilatation remained for 10-20 min, then slowly subsided. 2. When a 10 MHz, 1 V (peak to peak) generator voltage induced a 7.3 milliGauss, 2.19 V cm-1 EM field, the vasodilatory effect was optimum when bursts were applied 50% of the total time at 10 kHz burst rate. 3. The vasodilatory effect was not secondary to dielectric heat in the web, because the EM field was too weak to have produced enough heat to dilate the arterioles and heat would have been constantly conducted away by the perfusion solution. 4. During perfusion with Ringer solution warmed to 30 degrees C, no vasodilatation was found, but perfusion with Ringer solution warmed to 35 degrees C induced only 11% vasodilatation. Perfusion with Ringer solution warmed to 37 degrees C induced irreversible vasoconstriction. The pattern of vasodilatation induced by warm Ringer solution was different from the vasodilatory effect of weak EM field radiation. 5. The extent of the vasodilatory effect was influenced by Ca2+ concentration of the perfusion medium. Under normal Ca2+ conditions arterioles dilated to 126% of the control diameter, while under Ca(2+)-free conditions arterioles dilated to 131% of the control value and under high-Ca2+ conditions (twice the normal level) arterioles dilated to 111% of the control value. This suggests that the vasodilatory effect may be caused by facilitation of Ca2+ influx, and the extent of this flow may settle down to the equilibrium level of countercurrent flux between Ca2+ influx and outflow. 6. The vasodilatory effect was not inhibited under perfusion with Na(+)-free Ringer solution, suggesting that Na(+)-Ca2+ exchange system may not be involved in the vasodilatory effect. The vasodilatory effect was inhibited by vanadate, an inhibitor of Ca(2+)-ATPase, and was abolished by Methylene Blue, an inhibitor of guanylate cyclase. The evidence suggests that the mechanism of the vasodilatory effect may depend on an increase in Ca2+ influx through the plasma membrane of the smooth muscle and/or an increase in Ca2+ influx into the sarcoplasmic reticulum.(ABSTRACT TRUNCATED AT 400 WORDS)


Although known neurotoxins with potential ophthalmotoxic properties are commonly used in microelectronics assembly, there has been no systematic study of visual disturbances among past or present workers in this industry. The objective of the present study was to compare visual functions, using a matched-pair design, between former workers from a microelectronics plant and a local reference population. From an initial population of 180 former workers and 157 potential referents, 54 pairs were matched for age (+/- 3 y), education (+/- 2 y), sex, ethnic origin, and number of children. Near and far visual acuity, chromatic discrimination, and near contrast sensitivity were assessed monocularly. Paired comparisons (Signed-rank Wilcoxon test) revealed that the former microelectronics workers had significantly lower contrast sensitivity, particularly in the intermediate frequencies, independently of near visual acuity loss. There were no differences for far visual acuity in both eyes. Even though near visual acuity and color vision were compromised among the former workers, the differences were only significant for one eye, as was the prevalence of acquired dyschromatopsia (chi-square for matched pairs, p less than .001). These findings suggest a pattern of contrast sensitivity deficits consistent with impairment to foveal and/or neuro-optic pathways among these former microelectronics workers. Exposure to ophthalmotoxic chemicals is proposed as the most probable risk factor.


Chronic fatigue is a common and disabling problem in primary care practice. The differential diagnosis of chronic fatigue is extensive and includes medical disorders, altered physiologic states (eg, pregnancy, exertion), psychiatric disorders, lifestyle derangements, drugs, and controversial entities (eg, chronic candidiasis, food allergies, environmental illness, and chronic fatigue syndrome). The most common diagnoses are psychiatric disorders, including mood, anxiety, and somatoform disorders. A comprehensive approach to diagnosis and management is necessary, including structured psychiatric interviewing, functional assessment, and elicitation of the patient's diagnostic beliefs. Patients often believe they are suffering from an organic medical disorder (eg, viral or immunologic) and resist psychiatric labelling of their symptoms and referral to mental health practitioners. Establishing and maintaining rapport, having a flexible approach, and demonstrating a personal concern for the
patient is essential. Drug therapy for specific psychiatric and medical illnesses and cognitive-behavioral approaches for enhancing coping mechanisms are effective.

----------------------------------------

(1991) **Chronic toxic encephalopathy investigated using dynamic posturography.**

Seven male patients previously exposed to industrial solvents and diagnosed with chronic toxic encephalopathy (aged 38 to 69 years; mean age, 56 years) were investigated by dynamic posturography and compared with healthy, age-matched male control patients. Dynamic posturography comprises two phases: a sensory organization (SO) phase, in which the support surface and visual surround are either stable or referenced to the patient's sway, with eyes open or closed, and a movement coordination (MC) phase, in which the platform makes active movements. In SO testing, the patient group showed significantly impaired equilibrium performance compared with the control group in most test conditions. The MC test revealed no differences between groups. A relationship was found between the equilibrium score resulting from SO testing with stable support and visual surround and the sway area of the confidence ellipse elicited 3 years previously by static posturography with eyes open. We conclude that patients with chronic toxic encephalopathy have impaired equilibrium, as demonstrated by dynamic posturography testing.

----------------------------------------

(1991) **Persistent alterations of calmodulin kinase II activity in chickens after an oral dose of tri-o-cresyl phosphate.**

Calmodulin kinase II has been found to be involved in the increased phosphorylation of brain microtubule and spinal cord neurofilament triplet proteins following treatment of animals with organophosphorus compounds that are capable of producing organophosphorus compound-induced delayed neurotoxicity (OPIDN). In this report, chickens were given a single oral neurotoxic dose of 750 mg/kg tri-o-cresyl phosphate (TOCP), and killed after 1 or 21 days of treatment. Crude calmodulin kinase II from brain cytosol as well as phosphocellulose-purified microtubules were prepared from control and treated animals. Phosphorylation reactions were started by adding protein into the phosphorylation buffer in the presence of Mg2+, Ca2+, calmodulin or trifluoperazine, and [gamma-32P]ATP. Proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and subjected to autoradiography. The extent of the calmodulin kinase II autophosphorylation as well as the Ca2+ calmodulin-dependent phosphorylation of the purified microtubules was investigated.
The enzyme activities isolated from control and treated animals were compared. Autophosphorylation of calmodulin kinase II was found to be higher in both 1-day and 21-day TOCP-treated animals than in control animals. The activity of the kinase to phosphorylate exogenous substrates such as tubulin and microtubule-associated protein-2 (MAP-2) was also higher in the treated hens than in the controls. The increased activity of the kinase was noted at day 1 following treatment when no clinical signs were observed and persisted until day 21 when the animals were paralyzed completely. This finding supports the significance of altered calmodulin kinase II in the pathogenesis of OPIDN.

(1991) Induction of cytochrome P450 isozymes by simultaneous inhalation exposure of hens to n-hexane and methyl iso-butyl ketone (MiBK).

Chickens were exposed simultaneously to the industrial hexacarbon solvents n-hexane and methyl iso-butyl ketone (MiBK). n-Hexane has been shown to be neurotoxic in both humans and other vertebrates. While MiBK is not neurotoxic, it has been shown to greatly synergize the clinical appearance of neurotoxicity in animals exposed to both of these solvents. Groups of hens were exposed for 29 days in inhalation chambers to 1000 ppm n-hexane in combination with 10, 100, 250, 500, or 1000 ppm MiBK. Other groups received either 1000 ppm n-hexane, 1000 ppm MiBK, or ambient air and served as controls. A dose-dependent decrease in body weight and an increase in clinical effects were noted for the highest exposure groups (1000 ppm n-hexane combined with 1000, 500 or 250 ppm MiBK). There was an MiBK dose-dependent increase in cytochrome P450 content and benzphetamine N-demethylase activity, but there was no distinct pattern for ethoxyresorufin O-deethylase or cytochrome c reductase activities. Mixed-function oxidase levels and activities (cytochrome P450 content and benzphetamine N-demethylase) were elevated significantly (P less than 0.05) over controls even in the lowest MiBK group (10 ppm), although there were no clinical signs of neurotoxicity. Four different isozymes of cytochrome P450 were measured immunologically. There was a dose-dependent increase in three of the isozymes, two of which were phenobarbital inducible and one of which was induced by beta-napthoflavone. Quantitatively, the largest increase was in the PB-A isozyme, a phenobarbital-inducible isozyme which accounted for approximately 70% of the cytochrome P450 present in animals treated with MiBK. The results suggest that MiBK selectively induces cytochrome P450 isozymes leading to the metabolic activation of the weak neurotoxicant n-hexane to the potent neurotoxicant 2,5-hexanedione (2,5-HD).

Critical to a more definitive human health assessment of the potential health risks from exposure to complex mixtures in indoor air is the need for a more definitive clinical measure and etiology of the health effects of complex mixtures. This panel overview highlights six of the eight presentations of the conference panel discussion and features a number of the major topical areas of indoor air concern. W. G. Meggs assessed clinical research priorities with primary focus on the role of volatile organic chemicals in human health, recognizing the areas where definitive data are lacking. By recognizing many types of chemical sensitivity, it may be possible to design studies that can illuminate the mechanisms by which chemical exposure may cause disease. The critically important topic of multiple chemical sensitivity was discussed by N. A. Ashford, who identified four high risk groups and defined the demographics of these groups. P. A. Schulte addressed the issue of biological markers of susceptibility with specific considerations of both methodological and societal aspects that may be operative in the ability to detect innate or inborn differences between individuals and populations. Three case studies were reviewed. H. Anderson discussed the past and present priorities from a public health perspective, focusing on those issues dealing with exposures to environmental tobacco smoke and formaldehyde off-gassing from materials used in mobile home construction. J. J. Osborne described several case studies involving wood smoke exposure to children, with emphasis on the significantly greater occurrence of chronic respiratory symptoms and acute chest illness for children from homes heated with woodburning stoves.(ABSTRACT TRUNCATED AT 250 WORDS)

-----------------------------------------------

Gerken, GM, Solecki, JM and Boettcher, FA Journal/Hear Res. 53: 101-12.

Temporal integration functions were measured, before and after a sound-induced hearing loss, in 5 cats using trains of electrical pulses applied to auditory nuclei in the brainstem. The 8 stimuli ranged from 1 pulse (0.25 ms duration) to 16 pulses (0.25 ms pulses spaced over 240 ms). The stimuli were applied to inferior colliculus or cochlear nucleus via permanently implanted electrodes. One electrode was tested extensively in each animal to obtain 10 sets of behaviorally-measured electrical detection thresholds counterbalanced across stimuli. The animal was then exposed to a 110 dB SPL, 2 kHz tone for 48 h and pre- and post-exposure audiograms were measured. The mean permanent threshold shift for acoustic stimuli was 48.5 dB. Another 10 thresholds for each of the 8 electrical stimuli were then measured. In the normal hearing animals, the mean slope of the temporal integration function for electrical stimulation was -7.6 dB.
per factor of 10 pulses. Alternatively, the mean time constant was 139 ms. In the hearing impaired animals, the slope was reduced to -1.5 dB per factor of 10 pulses, which corresponded to a mean time constant of 17 ms. In addition, the hearing impaired animals showed a decreased threshold for the electrical stimuli (stimulation hypersensitivity) as well as reduced variability across electrical stimulation thresholds. The results suggest that a major contribution to temporal integration occurs in inferior colliculus or higher. In addition, the results suggest that the reduction in temporal integration that follows hearing impairment is a peripherally-induced, central effect.

(1991) *Multiple chemical sensitivity and environmental toxicology.*

(1991) *Development of dermal and respiratory sampling procedures for human exposure to pesticides in indoor environments.*

No standard methods presently exist for measuring air and surface residues in indoor environments following pesticide applications. Four studies of chlorpyrifos broadcast applications for flea control were conducted to test preliminary sampling guidelines developed by Health and Welfare Canada. Air and wipe samples were collected for 24 hr following 0.5% or 0.48% chlorpyrifos applications. Ventilation from open doors or windows reduced air concentrations substantially. Air concentrations also varied with sampler height; i.e., greater near the floor than at one m above the floor. Wipe sampling from aluminum foil exhibited high precision (less than 10% coefficient of variation), and wipe sampling of carpets and other surfaces did not show variability in excess of the variability in initial pesticide deposits produced by the application procedures. Residues recovered from treated surfaces decreased by 60-70% over 24 hr, while residues on untreated surfaces increased 200-300% over this period. The Guidelines for Assessment of Indoor Occupant Exposure to Pesticides developed by Health and Welfare Canada have been revised in light of these findings, and provide a set of standard procedures for monitoring indoor air and surface residues. Further studies will be required to determine human exposures and health risks resulting from indoor pesticide applications.

(1991) *Multiple chemical sensitivities (MCS).*

(1991) Lawn chemicals on school grounds: are they safe?


The literature on the important indoor air pollutants, their sources, their effect on human welfare, and methods for controlling their presence is reviewed. The review is chiefly concerned with the air in homes, offices, schools, and public buildings, rather than in industrial facilities.

(1991) Pharmacokinetics and pharmacodynamics of doxacurium in normal patients and in those with hepatic or renal failure.

We determined the pharmacokinetics and duration of action of a bolus dose of doxacurium (15 micrograms/kg) in 27 patients anesthetized with isoflurane and nitrous oxide. Nine patients had normal renal and liver functions and were undergoing a variety of surgical procedures, nine were undergoing cadaveric kidney transplantation because of end-stage renal disease, and nine were undergoing cadaveric liver transplantation because of end-stage hepatocellular disease. Plasma concentrations of doxacurium were measured for 6 h after administration using a sensitive and specific capillary gas chromatographic assay. Plasma concentration versus time data were analyzed by a noncompartmental method based on statistical moments. Neuromuscular blockade was assessed by measuring the electromyographic evoked response of the adductor pollicis muscle to train-of-four stimulation of the ulnar nerve. The degree of neuromuscular blockade after doxacurium administration was described as the percent of control of the first train-of-four response. The pharmacokinetic variables were (normal vs hepatic failure vs renal failure, respectively): volume of distribution at steady state (220 +/- 110 vs 290 +/- 60 vs 270 +/- 130 mL/kg [mean +/- SD]), plasma clearance (2.7 +/- 1.6 vs 2.3 +/- 0.4 vs 1.2 +/- 0.7 mL.kg-1.min-1), mean
residence time (95.2 +/- 57 vs 129.4 +/- 30 vs 270 +/- 210 min), and elimination half-life (99 +/- 54 vs 115 +/- 31 vs 221 +/- 156 min). Plasma clearance and mean residence time differed significantly between patients with renal failure and control patients.(ABSTRACT TRUNCATED AT 250 WORDS)


People assess the quality of the air indoors primarily on the basis of its odors and on their perception of associated health risk. The major current contributors to indoor odorants are human occupant odors (body odor), environmental tobacco smoke, volatile building materials, bio-odorants (particularly mold and animal-derived materials), air fresheners, deodorants, and perfumes. These are most often present as complex mixtures, making measurement of the total odorant problem difficult. There is no current method of measuring human body odor, other than by human panel studies of expert judges of air quality. Human body odors have been quantitated in terms of the "olf" which is the amount of air pollution produced by the average person. Another quantitative unit of odorants is the "decipol," which is the perceived level of pollution produced by the average human ventilated by 10 L/sec of unpolluted air or its equivalent level of dissatisfaction from nonhuman air pollutants. The standard regulatory approach, focusing on individual constituents or chemicals, is not likely to be successful in adequately controlling odorants in indoor air. Besides the current approach of setting minimum ventilation standards to prevent health effects due to indoor air pollution, a standard based on the olf or decipol unit might be more efficacious as well as simpler to measure.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1821378


A neurotoxic organophosphate, tri-o-cresyl phosphate (TOCP) is also a testicular toxicant. Histopathologic damage in the testis is first seen in Sertoli cells. TOCP and its activated metabolite saligenin cyclic-o-tolyl phosphate (SCOTP) were evaluated for effects on rat Sertoli cells in primary culture. SCOTP, but not TOCP, caused minor morphologic effects on the cells and increased levels of lactate in the spent medium with no change in pyruvate levels, synthesis of cellular or secreted proteins, or the cyclic AMP response to FSH stimulation. SCOTP was the metabolite of TOCP that
produced the largest decrease in nonspecific esterase activity in Sertoli cells (up to 80%), when tested in the concentration range found in vivo. This decrease is consistent with previous in vivo evidence. These in vitro experiments replicate previously observed in vivo biochemical effects and suggest that SCOTP is the metabolite responsible for at least some of the biochemical effects seen in the testis after TOCP exposure.


Environmental illness, a hypothesized disease caused by exposure to substances such as combustion products, pesticides, food additives, and Candida albicans, is discussed. The case of a patient with environmental illness and systemic candidiasis for six weeks with ketoconazole, liver enzyme concentrations increased. One month after discontinuation of ketoconazole, the liver enzyme concentrations decreased; however, over the next five months, liver enzymes and bilirubin increased. The patient developed encephalopathy and eventually was transferred to a medical center for possible liver transplant. A review of the literature pertaining to ketoconazole hepatotoxicity is also presented.


The production and manufacture of microelectronic components, carried out primarily by women workers, require extensive use of organic solvents. Affective and personality disturbances frequently have been associated with organic solvent toxicity. A group of women, former microelectronics workers (N = 70), primarily of Hispanic origin (77.1%) but raised in the United States, were evaluated for affective and personality disturbance with the MMPI. Profiles were analyzed, and diagnostic classification was performed blind. Results showed that (1) 85.7% of the profiles indicated abnormally
high clinical elevations; and (2) MMPI profile classification revealed four clinical diagnostic groups: somatoform (24.3%), depression (15.7%), anxiety (28.6%), and psychotic (14.3%). These findings indicate significant psychopathology among these women, who formerly had worked in a microelectronics plant. The patterns of impairment present similarities to previous reports of organic solvent toxicity.


Although chemicals posing potential neurotoxic hazards are commonly used in the microelectronics industry, there has been no systematic study of possible chronic nervous system effects in microelectronics workers. The objective of the present study was to assess neuropsychological functions of a group of former microelectronics plant assembly workers and a group of referents, using a matched pair design. During employment, the former microelectronics workers had been exposed to multiple organic solvents, including trichloroethylene, xylene, chlorofluorocarbons and trichloroethane. Referents were recruited from the same geographic region. From a pool of 180 former workers and 157 referents, 67 pairs were matched on the basis of age, sex, ethnicity, educational level, sex and number of children. Comparison of results on the subtests of the California Neuropsychological Screening Battery-Revised (CNS-R) revealed significantly lower performance by the former microelectronics workers on tests of attention/concentration, verbal ability, memory functions, visuospatial functions, visuomotor speed, cognitive flexibility, psychomotor speed, and reaction time (t-test for pairs or Wilcoxon Signed Rank p less than 0.05). No significant differences were observed for performance on tests assessing mental status, visual recall, tactile function and learning. This overall pattern of impairment is consistent with organic solvent-related chronic toxic encephalopathy, and possible early stages of dementia. These findings underline the need for more studies among workers currently or previously employed in microelectronics industries.


The possible association between depression and type I allergies (i.e. immunoglobulin E-mediated hay fever, asthma, eczema, hives) was examined in a nonclinical sample of 379 college students. Measures included self-reports of depression, tiredness,
fearfulness, allergic disorders, and environmental allergens and irritants. Seventy-one percent of the subjects who had ever received a professional diagnosis of depression also indicated a history of allergy: those with greater self-rated current depression overall reported a significantly higher prevalence of asthma (p less than 0.05). Type I allergic (43%) and nonallergic subjects did not differ in self-rated frequency of depression, fatigue, or anxiety. However, type I subjects reported significantly worse mood after the flu than did nonallergic subjects (p less than 0.001). The data support the hypothesis that individuals prone to clinical depression have more allergies than nondepressives. Allergics may experience more postflu mood worsening but not current depression in comparison with nonallergics.

----------------------------------------------------------------------

(1991) B complex vitamin patterns in geriatric and young adult inpatients with major depression.

This study compared the B complex vitamin status at time of admission of 20 geriatric and 16 young adult non-alcoholic inpatients with major depression. Twenty-eight percent of all subjects were deficient in B2 (riboflavin), B6 (pyridoxine), and/or B12 (cobalamin), but none in B1 (thiamine) or folate. The geriatric sample had significantly higher serum folate levels. Psychotic depressives had lower B12 than did non-psychotic depressives. Poorer blood vitamin status was not associated with higher scores on the Hamilton Depression Rating Scale or lower scores on the Mini-Mental State Examination in either age group. The data support the hypothesis that poorer status in certain B vitamins is present in major depression, but blood measures may not reflect central nervous system vitamin function or severity of affective syndromes as measured by the assays and scales in the present study.

----------------------------------------------------------------------

Ashford, NA Journal/Toxicol Ind Health. 7: 335-45.

----------------------------------------------------------------------

(1991) Lack of interaction between prior succinylcholine administration and doxacurium-induced neuromuscular block.

The joint neurotoxic action of simultaneous exposure to vapors of n-hexane and methyl iso-butyl ketone (MiBK) and dermally applied O-ethyl O-nitrophenyl phenylphosphonothioate (EPN) was studied in groups of five adult hens. Four groups of hens were concurrently exposed to a dermal 2.5 mg/kg of EPN, 1000 ppm of n-hexane and 100, 250, 500 or 1000 ppm of MiBK. Two groups were each exposed to binary mixtures of a dermal dose of 2.5 mg/kg of EPN and 250 ppm of MiBK or 1000 ppm of n-hexane. Another three groups of hens were exposed to either 250 ppm of MiBK, 1000 ppm of n-hexane or a dermal dose of 2.5 mg/kg of EPN. A Group of hens was kept untreated. All hens were terminated after 30 days of treatment. Hens exposed to MiBK or n-hexane vapor did not exhibit any toxicity signs. In contrast, hens treated with EPN alone or in combination with n-hexane and/or MiBK developed acute cholinergic and delayed neurotoxicity signs. Hen brain acetylcholinesterase and neurotoxic esterase activities were inhibited in hens treated concurrently with EPN, n-hexane and MiBK. MiBK alone or in combination with EPN and n-hexane induced liver microsomal cytochrome P-450 content and phenobarbital-inducible cytochrome P-450 enzyme activities. Microsomes from hens treated with EPN, n-hexane, MiBK or mixtures of EPN, n-hexane and MiBK significantly enhanced the biotransformation of EPN to the more neurotoxic oxidation metabolite O-ethyl O-4-nitrophenyl phenylphosphonate.(ABSTRACT TRUNCATED AT 250 WORDS)


(1990) Old wine in new bottles: neurasthenia and 'ME'.
Wessely, S Journal/Psychol Med.  20:  35-53.

The history of neurasthenia is discussed in the light of current interest in chronic fatigue, and in particular the illness called myalgic encephalomyelitis ('ME'). A comparison is made of the symptoms, presumed aetiologies and treatment of both illnesses, as well as their social setting. It is shown that neurasthenia remained popular as long as it was viewed as a non-psychiatric, neurological illness caused by environmental factors which affected successful people and for which the cure was rest. The decline in neurasthenia was related to the changes which occurred in each of these views. It is argued that similar factors are associated with the current interest in myalgic encephalomyelitis. It is further argued that neither neurasthenia nor 'ME' can be fully understood within a single medical or psychiatric model. Instead both have arisen in the context of contemporary explanations and attitudes involving mental illness. Future understanding, treatment and prevention of these and related illnesses will depend upon both psychosocial and neurobiological explanations of physical and mental fatigability.

(1990) Challenges from the environment.

Suwita, E and Abou-Donia, MB Journal/Arch Toxicol.  64:  237-41.

Hens were given a single oral dose of 50 mg (4.6 microCi)/kg [14C] tri-o-cresyl phosphate (TOCP). Four groups of three hens each were killed after 0.5, 1, 2, and 5 days. The half-life of 14C in plasma was 2 days. TOCP and its metabolites in the plasma, liver, kidneys, and lungs were analyzed by high-performance liquid chromatography and liquid scintillation counting. TOCP reached its highest concentration in plasma between 0.5 and 1 day after administration. Under these experimental conditions, the disappearance of TOCP from the plasma followed monoexponential kinetics with a half-life of 2.2 days. Appreciable concentrations of saligenin cyclic-o-tolyl phosphate, the active neurotoxic metabolite, were detected in the plasma as well as in the liver, kidneys, and lungs at all time points and had half-lives of 2.06, 1.36, 1.11 and 4.44 days, respectively. The presence of this active metabolite of TOCP might contribute to the sensitivity of the hen to TOCP-induced delayed neurotoxicity. Other hydrolytic and oxidative products of TOCP were also identified in tissues.
(1990) Neuropsychophysiology during relaxation in generalized, universal 'allergic' reactivity to the environment: a comparison study.

Comparisons were made among a group of patients presenting with universal 'allergic' intolerance to environmental chemicals (universal reactor, n = 58), a group of control subjects without psychologic symptoms (control, n = 55) and a group of outpatients from a psychology practice (psychologic, n = 89) on neuropsychophysiological measures during relaxation. The measures were electroencephalographic (EEG) spectral category for frequencies below 15 Hz, EEG beta activity, scalp electromyography (EMG), peripheral temperature (TEMP), and skin resistance level (SRL). The distributions of subjects in each group across eight EEG spectral categories were significantly different, with the distribution for universal reactors the same as that of the psychologic patients (p = 0.22), and both different from the distribution of controls (p less than 0.001). High levels of EEG beta activity were observed in more universal reactors and psychologic patients than in controls (p = 0.04). High levels of EMG scalp activity were observed in a greater number of universal reactors than in subjects in the other two groups (p less than 0.001). The three groups did not differ in TEMP and SRL. Implications of neuropsychophysiologic stress profiling for the diagnosis and treatment of psychosomatic illness are discussed.


A multispecialty panel of physicians evaluated a case series of 53 composite-materials workers in a large aircraft manufacturing facility who filed workers' compensation claims for illness labeled by the media as the "aerospace syndrome." Possible skin and respiratory tract exposures included formaldehyde, phenol, particulates, epoxy resins, and trace organic solvents, but measured concentrations were well below all regulatory and consensus standards. Most workers had histories of transient skin or respiratory tract irritation consistent with the known potential toxicity of these materials. None of the workers tested had immunoglobulin IgG or IgE antibodies to human serum albumin complexed with formaldehyde. A majority (74%) met DSM-III-R [Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised] criteria for major depression, panic disorder, or both. Most of these psychiatric disorders were of a recent onset, correlating in time with the use of phenol- and formaldehyde-impregnated composite material. Psychosocial factors were thought to have played a major role in the high prevalence of illness in this group and should be evaluated directly in well-controlled epidemiologic studies of similar crisis-building situations in the future.
(1990) The 'aerospace syndrome'.

(1990) Disposition, elimination, and metabolism of tri-o-cresyl phosphate following daily oral administration in Fischer 344 male rats.
Somkuti, SG and Abou-Donia, MB Journal/Arch Toxicol. 64: 572-9.

The disposition, elimination, and metabolism of 50 mg/kg (1.36 μCi/animal) of tri-o-cresyl [phenyl-U-14C] phosphate after ten daily oral doses was investigated in adult male Fischer 344 rats. Groups of three treated animals were killed at intervals of 24, 48, 72, and 96 h after the last administrations. Generally, the highest concentrations of radioactive material were excreted via the gastrointestinal tract and the bladder, particularly at the earlier time points. Liver, adipose, epididymis, sciatic nerve tissues; plasma; and red blood cells also contained high concentrations of radioactivity. The lowest concentrations were found in brain, spleen, testes, and heart. Four days after the last dose, the rats had excreted approximately all of the cumulative dose in either urine (63.1%) or feces (36.1%). TOCP and its metabolites in urine, feces, plasma, brain, testes, kidneys, and liver were analyzed by high-performance liquid chromatography and liquid scintillation. Metabolism studies performed 24, 48, 72, and 96 h after administration of the last dose showed that TOCP was the major compound identified in brain, testes, kidneys, plasma, and liver. Liver, additionally, had high levels of di-o-cresyl hydrogen phosphate and o-cresol. TOCP and o-cresol were the predominant compounds in feces; only trace amounts of TOCP were detected in urine. The major metabolites in urine were di-o-cresyl hydrogen phosphate, o-cresol, and o-hydroxy benzoic acid. Testes in rats given ten doses had significantly more TOCP and saligenin cyclic-o-tolyl phosphate than those from rats given a single dose. These results may account for testicular toxicity in rats given daily oral administrations of TOCP but not following a single oral dose.


Environmental illness is an increasingly frequent and medically unexplained syndrome of "allergy" to common environmental agents. A recent outbreak of chemical-induced illness allowed study of psychological factors in environmental illness. Thirty-seven
symptomatic plastics workers completed structured diagnostic interviews and self-report measures of somatization and psychopathology. The 13 subjects who developed environmental illness scored higher on all measures than those who did not. The greatest differences were in prior history of anxiety or depressive disorder (54% versus 4%) and number of medically unexplained physical symptoms before exposure (6.2 versus 2.9). These findings suggest that psychological vulnerability strongly influences chemical sensitivity following chemical exposure.


A 35-year-old furniture refinisher came to the occupational medicine clinic with complaints of upper respiratory irritation, fatigue, and lightheadedness occurring on a daily basis after using a methylene chloride-containing paint stripper. Determinations of blood carboxyhemoglobin (COHb) on three occasions showed an apparently linear elevation of COHb as a function of hours worked on the day of sampling. COHb levels predicted from spot industrial hygiene measurements were in close concordance with those observed in the patient, indicating the potential usefulness of COHb monitoring in estimating airborne exposure levels. Methylene chloride (or dichloromethane) is an organic solvent that has found wide use as a degreaser, paint remover, aerosol propellant, and a blowing agent for polyurethane foams, and as a solvent in food processing, photographic film production, and plastics manufacturing. Discovery of its unusual metabolic fate--conversion to carbon monoxide in vivo--has earned the compound a special place in the solvent toxicology literature. Demonstration of oncogenicity in experimental animals has occasioned a reconsideration of exposure limits, with emphasis upon stricter controls. In some workplaces, conditions prevail in which controls are inadequate to prevent even acute toxicity, much less long-term exposure risks.


Case reports and chart reviews of patients asserting environmental illness suggest that they suffer from psychiatric difficulties, typically somatization disorder. We assert that....
viewing these patients solely as somatizers or hysterical characters searching for a
nurturant relationship will undermine the doctor-patient relationship. Rather, many of
these patients are obsessive/paranoid characters searching for a medical explanation
to their physical symptoms. This distinction is highlighted by contrasting the clinical
presentations of hysteric/somatizing patients with those environmental illness patients
demonstrating an obsessive/paranoid style. Further illustration is provided by a case
report with psychological test data. Finally, treatment recommendations based upon
this distinction are delineated.

(1990) Modulation of Respiratory Burst Activity and Mitogenic Response of
Human Peripheral Blood Mononuclear Cells and Murine Splenocytes and
Peritoneal Cells by Malathion.
Rodgers, KE and Ellefson, DD Journal/Fundamental and Applied Toxicology, Vol. 14,
The differences between in-vivo and in-vitro exposure to malathion (121755) was
studied in female C57B1/6-mice. Malathion was preincubated with a crude liver
enzyme system (the supernatant of a 9000g centrifugation) with cofactors to
regenerate NADPH. The effect on human peripheral blood mononuclear cells (PBMC)
of in-vitro exposure to malathion was also considered. Significantly elevated
proliferative responses of murine splenocytes to mitogens were reported following
in-vivo exposure to malathion. Adherent splenocytes from treated mice were able to
elevate the proliferative responses of nonadherent splenocytes from control levels.
In-vitro exposure of murine splenocytes or human PBMC to either malathion or
malathion metabolized by a liver enzyme system suppressed or did not change,
respectively, the proliferative responses to mitogens. Nonadherent splenocytes and
PBMC were affected by in-vitro exposure to malathion. The production of
hydrogen-peroxide by murine peritoneal cells following stimulation with
phorbol-myristate-acetate was also elevated by malathion in in-vivo exposure. The
respiratory burst activity of murine peritoneal cells was suppressed following exposure
to malathion but elevated following exposure to malathion metabolized by a liver
enzyme system. The ability of human PBMC to produce hydrogen-peroxide was
enhanced following in-vitro malathion exposure.

(1990) Neuromuscular and cardiovascular effects of mivacurium chloride (BW
B109OU) during nitrous oxide-narcotic, nitrous oxide-halothane and nitrous
oxide-isoflurane anesthesia in surgical patients.
Pearson, KS, From, RP, Choi, WW, Abou-Donia, M and Sokoll, MD Journal/Middle
East J Anesthesiol. 10: 469-78.
One hundred seventeen adult surgical patients were studied to compare neuromuscular and cardiovascular effects of mivacurium chloride during nitrous oxide-narcotic (BAL, n = 45) nitrous oxide-halothane (HAL, n = 27) and nitrous oxide-isoflurane (ISF, n = 45) anesthesia. Anesthesia was maintained with nitrous oxide (60%-70%) and oxygen (30%-40%) with end-tidal concentrations of halothane or isoflurane to yield a total MAC of approximately 1.25, or with supplemental fentanyl and thiopental as clinically indicated. Twitch response of the adductor pollicis muscle was elicited by supramaximal square wave pulses of 0.2 msec duration at a frequency of 0.15 Hz (Grass S44 stimulator) to the ulnar nerve and quantitated by a Grass FT10 transducer. Nine patients in each of the HAL and ISF groups received one of four doses of mivacurium (0.03, 0.05, 0.10 or 0.15 mg/kg). Ninety patients in the balanced anesthesia group received one of seven doses of mivacurium (0.03, 0.04, 0.05, 0.08, 0.15, 0.20, 0.25 mg/kg). The ED50, ED75 and ED95 of mivacurium in each group were estimated from linear regression plots of log dose versus probit of maximum percentage depression of twitch height. The ED50, ED75 and ED95 for halothane and isoflurane are 0.040, 0.053 and 0.081 and 0.037, 0.043 and 0.053, respectively. The ED50, ED75, and ED95 for the balanced group are 0.039, 0.050, and 0.073 mg/kg respectively. There was no significant difference between the slopes of the HAL and BAL inhalation anesthetic dose-response curves. The slope of the ISF group was significantly than the slope of the BAL group. Intercepts of the HAL and BAL curves were not different. The isoflurane curve's intercept was significantly less than the other groups' intercepts, lying above the halothane curve, but below the BAL curve. For the 0.05 mg/kg dose, maximum block was greater in the ISF group (89.1 +/- 2.7%, n = 9) than in the HAL (70.3 +/- 7.6%, n = 9) or BAL (67.7 +/- 6.4%, n = 9) groups. At higher doses of mivacurium, isoflurane produces a greater potentiation of neuromuscular block than halothane or balanced anesthesia. There were no significant cardiovascular changes seen in any group following mivacurium doses up to 0.15 mg/kg (approximately 2xED95).


Limbic encephalitis as a distinct clinicopathological entity is becoming increasingly familiar to neurologists. However, despite its classical clinical presentation of mental status changes and behavioral abnormalities, the disorder is not well known in the psychiatric literature and premortem diagnosis is rare. We recently participated in the care of a patient who spent two months on a psychiatric service and in whom a medical disorder was consistently suspected but not confirmed until autopsy revealed paraneoplastic limbic encephalitis and two primary systemic malignancies. A detailed neuropsychiatric description of this clinical entity is provided from presentation to autopsy with review of the literature.
(1990) **Chemical mediators in hypersensitivity reactions.**

The study of chemical mediators is essential in clarifying the mechanism of hypersensitivity reactions. Recent advances in this field have been made particularly with the arachidonic acid metabolites, several of which strongly contract smooth muscle, attract granulocytes to inflammatory foci and lead to increased vascular permeability. These functions play a crucial role in allergic reactions. Furthermore these mediators might work to modulate the intracellular network which mediates the complicated inflammatory process of hypersensitivity reactions.

(1990) **Occupational phenoxyethanol neurotoxicity: a report of three cases.**

2-Phenoxyethanol, used as an anesthetic for handling small fish at a salmon hatchery, caused three women to experience headache and symptoms of intoxication during use, followed by diminished sensation and strength of hands and fingers, worse in the preferred hand. Persistent neuropathy did not develop in any of them. After 1 to 2 years of exposure, the women manifested gradual onset of symptoms of cognitive impairment with an inability to work. Neuropsychologic testing verified that all three had focal cognitive impairments that persisted. One also had documented labyrinthine hypofunction, which originated during this exposure. The immediate and delayed effects of 2-phenoxyethanol on the central nervous system resemble those of the other organic solvents.

(1990) **Cerebrospinal fluid proteins and free amino acids in patients with solvent induced chronic toxic encephalopathy and healthy controls.**

The concentrations of protein, albumin, IgG, and free amino acids in the cerebrospinal fluid of 16 patients with chronic toxic encephalopathy due to organic solvents were measured. The patient group consisted of all patients with this diagnosis in a neurological department in 1985. The diagnosis was based on neuraesthetic symptoms, pathological psychometric performance, and verified exposure to neurotoxic organic solvents. A control group of 16 patients with myalgias or backache, or both, and no signs of disease was used for comparison. The purpose was to study possible changes in the cerebrospinal fluid that might contribute to understanding the
aetiology of solvent induced chronic toxic encephalopathy. A rise in protein, albumin, and IgG was found in the patient group compared with the control group, as well as reduced concentrations of phosphoethanolamine, taurine, homocarnosine, ethanolamine, alpha-aminobutyric acid, and leucine. Using a stepwise multiple regression analysis, taurine was negatively correlated to exposure to solvents. These findings may indicate membrane alterations in the central nervous system related to exposure to organic solvents.

(1990) Vascular responsiveness to norepinephrine in sympathicotonic orthostatic intolerance.

Sympathicotonic orthostatic intolerance (hypotension, tachycardia, or both) is associated with normal or excessive orthostatic increases in plasma norepinephrine concentration and is reversible by the inflation of a military anti-shock trouser suit enveloping the lower limbs and abdomen. These facts suggest that one possible mechanism of the disorder might be a defect in alpha-adrenergic receptor or postreceptor responsiveness of the veins or arterioles. We have investigated in 11 patients and 15 healthy controls the blood pressure and heart rate responses to increasing rates of intravenous norepinephrine infusion (1 to 16 micrograms/min), the dorsal hand vein contractile responses to increasing rates of norepinephrine infusion (1 to 256 ng/min) with a linear variable differential transformer, and the platelet alpha 2-adrenergic receptor densities and dissociation constants. No statistically significant difference in any of these parameters was found between the normal subjects and nine of the 11 patients with orthostatic intolerance. The venous contractile response to norepinephrine was excessive in one patient and was virtually absent in another. Because supersensitivity of the hand veins to norepinephrine suggests up-regulation of alpha 2-receptors resulting from postganglionic autonomic insufficiency, this finding in one patient with sympathicotonic orthostatic hypotension might have been caused by venous denervation. The venous unresponsiveness to norepinephrine in the other patient presumably resulted from a defect in the venous receptors or smooth muscle function. It is evident that norepinephrine responsiveness and the innervation of the arterioles and hand veins was normal in the other nine patients, in whom the defect must have been mediated by some other mechanism.

Mergler, D, Bowler, R and Cone, J Journal/Neurotoxicol Teratol. 12: 669-72.
Test performance on a neurobehavioural battery was examined with respect to acquired colour vision loss among patients with a history of neurotoxin exposure. The study group included 14 men and 7 women with clinically diagnosed neuropsychological impairment (mean age: 41.3 +/- 8.1 years; mean educational level: 13.4 +/- 1.4 years). Verbal and visual ability, memory and psychomotor function were assessed with the California Neuropsychological Screening Battery. Colour vision was assessed with the Lanthony D-15 desaturated colour arrangement panel. Acquired dyschromatopsia was present in 17 patients (80.9%), 11 of whom manifested patterns of Type II colour vision loss. Simple regression analysis of neuropsychological test performance with respect to colour vision loss, using age-adjusted Z-scores, revealed significant relationships (p less than or equal to 0.05) solely for tests which rely heavily on the visual system. Significant differences in visual task test scores were also observed with the type of dyschromatopsia (Kruskal-Wallis, p less than or equal to 0.05). These findings suggest that poor performance on visual tasks and colour vision loss may both result from damage to neuro-ophthalmic pathways or that loss of integrity of the peripheral visual pathways may affect visual task performance. The authors propose that visual testing should be incorporated into neurobehavioural test batteries.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2255314


Triallate (S-2,3,3-trichloroallyl diisopropylthiocarbamate) was tested for the potential to produce delayed neurotoxicity. Hens were given single oral doses ranging from 312.5 to 2500 mg/kg of triallate, 750 mg/kg tri-o-cresyl phosphate (TOCP), or empty gelatin capsules on Days 1 and 21 and were killed on Day 42. In a second experiment, animals were administered daily oral doses of 25-300 mg/kg triallate or 10 mg/kg TOCP for 90 days. In a third experiment, animals were given single oral doses of 2500 mg/kg triallate, 750 mg/kg TOCP, or empty gelatin capsules and killed after 24 hr. Delayed neurotoxicity was observed only in TOCP-treated animals. Animals given daily doses of 300 mg/kg triallate became moribund after 30 days; however, histological examination revealed no lesions characteristic of organophosphorus-induced delayed
neurotoxicity. Neurotoxic esterase was not significantly altered in triallate-treated animals while it was 95% inhibited in TOCP-treated animals. Plasma butyrylcholinesterase increased significantly 24 hr after treatment with triallate in a dose-dependent manner. In summary, triallate, a thiocarbamate, did not produce neurotoxicity which has been previously reported for some dithiocarbamates.


Previous introductions of new technologies have frequently resulted in unanticipated occupational and environmental illness. Prevention of such illness in the twenty-first century requires stringent application of two fundamental principles of public health: evaluation of new technologies before their introduction, and surveillance of exposed persons after the introduction of new technologies. Failure to establish these basic preventive mechanisms in advance will inevitably result in the development of new toxic diseases in the twenty-first century.


Several experiments were conducted to validate the use of a two-channel microprocessor-based electroencephalographic (EEG) device for detecting changes in EEG background rhythm in the clinic or at the bedside. The reliability of background measures in healthy individuals was evaluated by obtaining EEG data on 20 control subjects on two occasions separated by at least 1 day. The sensitivity to an experimental toxic encephalopathy was evaluated using measures of EEG and the Buschke Memory Selective Reminding Test after the administration of scopolamine hydrobromide, 0.86 mg subcutaneously, to three healthy volunteers. Postdrug measures of the EEG showed significant group differences from controls at 1 and 2 hours for relative alpha and relative theta power. The drug-induced change for each individual exceeded the predicted range calculated from data on control subjects. These findings suggest the feasibility and the potential utility of this method. This approach was extended to the elderly with measures on 102 subjects (average age, 85 years) living in an institutional setting. EEG measures in the population were of acceptable reliability and were significantly correlated with Mini-Mental State Examination (MMSE) scores ($r = -.375$ for theta and .357 for beta). Preliminary findings suggest that this method may detect metabolic encephalopathies in the elderly. The
study demonstrates the potential value of this approach and suggests the need for further research.

(1990) Effects of diisopropyl phosphorofluoridate (DFP) on CA3 and CA1 responses in rat hippocampus.

Diisopropyl phosphorofluoridate (DFP), an insecticide, is a potent anticholinesterase that binds essentially irreversibly to acetylcholinesterase, resulting in severe, acute neurologic pathology, and less severe, but longer-lasting, delayed neuropathy. We report here on the short-term effects of bath-applied DFP on extracellularly recorded responses from CA3 and CA1 of rat hippocampus. Exposure to 10 microM DFP evokes low amplitude, spontaneous bursts in CA3 generally within 10 minutes, and the bursting does not reverse with washing. The CA1 neuronal population usually bursts synchronously with CA3, but the population events are of low amplitude and sometimes not detectable, implying a differential sensitivity to DFP. These effects were partially blocked by the muscarinic antagonist atropine, while the cholinergic antagonist gallamine had little effect. Also, the reversible anticholinesterase physostigmine could, within temporal limits, protect slices from DFP's effects, implicating the cholinergic system as the probable mediator in the first stages of DFP-induced epileptogenesis.


BACKGROUND. Some claim that food sensitivities can best be identified by intradermal injection of extracts of the suspected allergens to reproduce the associated symptoms. A different dose of an offending allergen is thought to "neutralize" the reaction. METHODS. To assess the validity of symptom provocation, we performed a double-blind study that was carried out in the offices of seven physicians who were proponents of this technique and experienced in its use. Eighteen patients were tested in 20 sessions (two patients were tested twice) by the same technician, using the same extracts (at the same dilutions with the same saline diluent) as those previously thought to provoke symptoms during unblinded testing. At each session three injections of extract and nine of diluent were given in random sequence. The symptoms evaluated included nasal stuffiness, dry mouth, nausea, fatigue, headache, and feelings of disorientation or depression. No patient had a history of asthma or anaphylaxis. RESULTS. The responses of the patients to the active and control injections were indistinguishable, as was the incidence of positive responses: 27
percent of the active injections (16 of 60) were judged by the patients to be the active substance, as were 24 percent of the control injections (44 of 180). Neutralizing doses given by some of the physicians to treat the symptoms after a response were equally efficacious whether the injection was of the suspected allergen or saline. The rate of judging injections as active remained relatively constant within the experimental sessions, with no major change in the response rate due to neutralization or habituation. CONCLUSIONS. When the provocation of symptoms to identify food sensitivities is evaluated under double-blind conditions, this type of testing, as well as the treatments based on "neutralizing" such reactions, appears to lack scientific validity. The frequency of positive responses to the injected extracts appears to be the result of suggestion and chance.

(1990) Purification and characterization of cytochrome P-450 isozymes from phenobarbital-induced adult hen liver.

1. Two cytochrome P-450 isozymes (P-450 PB-A, PB-B) and cytochrome b5 were purified from livers of phenobarbital-treated adult hens. 2. Both the enzymes exhibited the same apparent molecular weight (54,000). 3. They could be distinguished on the basis of immunochemical properties, spectral properties, peptide pattern after partial proteolysis, tryptic peptide pattern, and N-terminal sequence. 4. The antibodies raised against P-450 PB-A and PB-B did not cross-react with microsomal P-450s of rat, mice, cat, or catfish species by immunoblotting.

(1990) Purification and characterization of cytochrome P450 isozymes from beta-naphthoflavone-induced adult hen liver.

Cytochromes P450 beta NF-A, beta NF-B, and beta NF-C were purified from beta-naphthoflavone-treated adult hens. Cytochrome P450 beta NF-A, however, appeared at two places in the purification scheme. They were designated as cytochromes P450 beta NF-A1 and beta NF-A2 for property comparison. The cytochromes beta NF-A1 and beta NF-A2 were induced by both phenobarbital and beta-naphthoflavone treatment and were similar to P450 PB-A (previously purified from phenobarbital-induced hen livers) in molecular weights, isoelectric pH, spectral properties, behavior on chromatography columns, catalysis of substrates, immunological cross-reactivity on Ouchterlony plates and by immunoblotting, and NH2-terminal amino acid sequence. However, P450 PB-A differed from beta NF-A1
beta NF-A2 in peptide pattern after partial proteolysis by alpha-chymotrypsin and Staphylococcus aureus V8 protease, and complete digestion of 125I-labeled cytochromes by trypsin. The cytochrome P450 PB-A also differed from beta NF-A1 beta NF-A2, in that its antibodies cross-reacted with P-450 of normal, PB-, and beta-NF-induced rabbit liver microsomes. The cytochromes beta NF-B and beta NF-C, although immunochemically cross-reactive with each other, were distinct enzymes on the basis of molecular weights, spectral characteristics, isoelectric pH, peptide pattern on partial proteolysis, tryptic peptide pattern, cross-reactivity of their antibodies with other species, and NH2-terminal amino acid sequence. The most notable difference between beta NF-B and beta NF-C was that the anti-beta NF-C IgG completely inhibited O-dealkylation of 7-methoxyresorufin and 7-ethoxyresorufin by beta-NF-induced microsomes. These activities increased 40- to 50-fold in beta-NF-induced microsomes as compared to only 2- to 4-fold in PB-treated hens. The amino-terminal sequences of beta NF-B and beta NF-C were different from those of mammalian and other nonmammalian species.

(1990) Multiple sclerosis, solvents, and pets.


Seventy-two adult surgical patients were studied to compare neuromuscular and cardiovascular effects of mivacurium chloride during nitrous oxide-fentanyl-thiopentone (BAL group) or nitrous oxide-halothane (HAL group) anaesthesia. Eighteen patients in the BAL group received an initial bolus of mivacurium, either the ED25 (n = 9) or the ED50 (n = 9) (0.03 and 0.05 mg kg-1). These doses were based on the assumption that the slope of the dose-response curve during nitrous oxide-opioid anaesthesia would be approximately the same as the slope of the neuromuscular response from the first human studies with mivacurium. Twenty-seven additional patients were allocated to subgroups of nine patients to receive mivacurium 0.04, 0.08 or 0.15 mg kg-1. Twenty-seven patients in the HAL group were allocated also to subgroups of nine patients to receive mivacurium 0.03, 0.04 or 0.15 mg kg-1. During stable anaesthesia, mean endtidal halothane concentrations were maintained at 0.49 +/- 0.01%. The estimated ED50, ED75 and ED95 for BAL and HAL groups were 0.039, 0.05 and 0.073 mg kg-1 and 0.040, 0.053 and 0.081 mg kg-1, respectively. Halothane did not
potentiate maximum block or time to maximum block. Halothane did affect spontaneous recovery. With the 0.15-mg kg-1 dose, time to 95% recovery was prolonged significantly in the HAL group (30.0 (SEM 1.4) min) compared with the BAL group (24.1 (1.5) min). Recovery index from 25% to 75% recovery was also prolonged significantly in the HAL group (7.0 (0.4) min) compared with the BAL group (5.4 (0.4) min). There were no significant haemodynamic changes in groups given mivacurium doses up to and including 2 x ED95 by bolus i.v. administration.


A preliminary study of dermal and respiratory exposure to chlorpyrifos (Dursban TC) during structural treatments was conducted with eight workers from a commercial pest control company. The compound was applied by sub-slab and soil injection to four houses, with each application involving two workers. Crawl space applications were included in three of the jobs. Field sampling extended over the entire workday, and included personal air samples and dermal exposure evaluation with patches and handwashes. A fluorescent tracer was added to the formulation for qualitative determination of skin deposition patterns. Pre-exposure and complete 72 hour urine samples were also collected. Total dermal exposure averaged 5.94 mg/hr. The major contributors were the upper legs (38%) and the forearms (34%). Accidents occurred during two of the four applications observed, and the two workers involved in the accidents were the most highly exposed individuals. The mean estimated absorbed daily dose was 9.5 ug/kg/day, with approximately 73% contributed by the dermal route. Thus, under these work conditions the Threshold Limit Value is not an appropriate guide for worker safety. The principal urinary metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol, was found in measurable quantities in all urine samples. Urinary metabolite levels collected 24-48 hr postexposure were highly correlated (R2 = 0.86) with total absorbed dose estimates. The high variability among individual excretion patterns suggests against the use of urine spot sampling, but longer collections may prove useful in the development of a Biological Exposure Index for chlorpyrifos.


Long term occupational exposure to organic solvents may cause adverse effects to the central nervous system. This collaborative study between six Swedish departments of
occupational medicine examines the overall prognosis in terms of working capacity, symptoms, and psychometric test performance for individuals occupationally exposed to organic solvents. After re-analyses of the data from an initial clinical investigation of 111 men, the subjects were divided into two subgroups: one group of 65 with symptoms but no impairment on the tests and one group of 46 with toxic encephalopathy (symptoms and test impairment). At least five years after the initial examination the subjects were asked to attend a re-examination that included a structured medical interview and a psychometric investigation. The results indicate that effects on the central nervous system persist even when exposure has ceased. In the group of 46 more men had stopped working and were receiving sickness or early retirement pensions. This group also had reduced activity levels with regard to everyday life, leisure activities, and education or training and more neuropsychiatric symptoms. There was no support for the view that a solvent induced toxic encephalopathy is a progressive disease comparable with presenile dementia such as Alzheimer's disease or Pick's disease. If a worker was removed from exposure when he presented symptoms without signs of impairment in intellectual function recovery was seen in most cases.


Poisonings resulting from DEET are rarely encountered in companion animals. In human patients, DEET toxicosis has been associated with the development of a toxic encephalopathy characterized by tremors, seizures, behavioral changes, and abnormal movements. Generally, DEET toxicosis in companion animals is of short duration and is characterized by vomiting, tremors, ataxia, and excitation. Treatment for DEET toxicosis includes symptomatic therapy and decontamination.

(1990) Medical surveillance for neurologic endpoints.
Cone, JE, Bowler, R and So, Y Journal/Occup Med. 5: 547-62.

Except for screening for noise-induced hearing loss, medical surveillance for neurologic disease in the workplace has not been done on a routine basis in the past. In the future, however, as occupational medicine focuses increasingly on the detection of preclinical effects of exposure and strategies to prevent such exposures, medical surveillance for neurologic disease will become a necessity.


The mechanisms and sites of action of organochlorine (DDT-types and chlorinated alicyclics) and synthetic pyrethroid insecticides are presented with discussion of symptoms, physiological effects, and selectivity. The structural requirements for toxicity are assessed, and structure-activity relationships are considered for each subclass. Lipophilicity is important for all the groups because it facilitates delivery of these neurotoxicants to the site of action in the nerve. Steric factors including molecular volume, shape, and isomeric configuration greatly influence toxicity. Electronic parameters also have been demonstrated to affect biological activity in some of the groups of insecticides, e.g., Hammett's sigma and Taft's sigma as indicators of electronegativity. New synthetic pyrethroids continue to be developed, with varied structures and different physicochemical and biological properties.


There industrial organophosphorus compounds were tested for their ability to cause organophosphorus compound-induced delayed neurotoxicity (OPIDN) in the adult hen. The compounds tested were tributyl phosphate (TBP), tributoxyethyl phosphate (TBEP), and dibutylphenyl phosphate (DBPP). The acute oral LD50 of TBP and DBPP were estimated to be 1,863 and 1,500 mg/kg, respectively, and the dose equal to the LD50 was used as a test dose. The acute oral LD50 of TBEP was greater than 5,000 mg/kg and 5,000 mg/kg was used as a test dose. An oral dose of 750 mg tri-o-cresyl phosphate (TOCP) was used as a positive control. For the acute delayed neurotoxicity test, hens were given two test doses of the test materials 21 days apart and killed 21 days after the second dose. None of the hens given TBP, TBEP, or DBPP exhibited nerve damage or clinical signs which distinguished them from untreated control animals. A single dose of TOCP resulted in paralysis and a histopathological profile typical of a distal neuropathy. For the assay of the inhibition of esterases, hens were killed 24 hours after a single dose equal to the greater of either the LD50 or 5000 mg kg. TOCP administration resulted in over 90% inhibition of brain neurotoxic esterase (NTE), but none of the other three compounds inhibited NTE to an extent (greater than 70%) which would be expected to result in OPIDN. Administration of TOCP, TBEP, or DBPP resulted in approximately a 70% decrease in plasma butyrylcholinesterase (BuChE) activity. TBP caused a 2-3 fold increase in BuChE activity. TBEP administration resulted in about 45% inhibition of acetylcholinesterase (AChE) in brain.
These results indicate that TBP, TBEP, and DBPP are all unlikely to cause OPIDN with any single sublethal dose.

(1990) Environmental illness. A controlled study of 26 subjects with '20th century disease'.

Environmental illness is a polysymptomatic disorder believed by "clinical ecologists" to result from immune dysregulation brought on by common foods and chemicals. We systematically evaluated 26 subjects who had been assigned a diagnosis of environmental illness. The subjects indicated a strong interest in their diagnosis, were generally satisfied with their clinical ecologist, and were dissatisfied with traditional medical approaches. Subjects reported varying treatments, including dietary restrictions, avoidance of offending agents, and physical treatments. Using the Diagnostic Interview Schedule, we found that 15 (65%) of 23 subjects met criteria for a current or past mood, anxiety, or somatoform disorder compared with 13 (28%) of 46 age- and sex-matched community controls. We conclude that patients receiving this diagnosis may have one or more commonly recognized psychiatric disorders that could explain some or all of their symptoms.


Previous studies suggest that social anxiety, allergies and distressed affect may be interrelated in some persons. For example, extremely introverted patients experience a poorer course and outcome of allergies as well as greater degrees of distressed affect such as depression and anxiety than do extraverts. Patients with affective disorders have a higher prevalence of atopic allergy than the general population; families of patients with panic disorder and major depression have the highest frequency of shy children. Preliminary investigation also indicate that behaviorally inhibited Caucasian children (initially shy and cautious in unfamiliar situations) and their families have more allergies, especially hay fever, than do uninhibited, socially outgoing children. The present survey evaluated the frequency of self-reported shyness. The most introverted subjects had significantly higher scores on self reports of depression, fearfulness, and fatigue, as well as a higher prevalence of hay fever. The data support the possibility of a distinct subgroup of shy individuals with concomitant vulnerability to specific allergies and affective disorders.
(1990) **Relationship of normal serum vitamin B12 and folate levels to cognitive test performance in subtypes of geriatric major depression.**

This retrospective study evaluated the relationships between normal serum vitamin B12 and folate levels and neuropsychologic measures in a sample of 60 geriatric inpatients with psychotic depression, nonpsychotic depression, bipolar disorder, and dementia--all consecutively referred for cognitive testing. The psychotic depression subgroup demonstrated numerous significant positive correlations between B12 and cognitive subtests not seen in other diagnostic subgroups, especially those of IQ, and verbal and visual memory. Metabolic factors including vitamin B12 may play specific roles in the cognitive dysfunctions of different geropsychiatric disorders.

(1990) **Vitamin B12 and folate status in acute geropsychiatric inpatients: affective and cognitive characteristics of a vitamin nondeficient population.**

This chart review study examined the serum vitamin B12 and folate status of 102 geriatric patients newly admitted to a private psychiatric hospital. Only 3.7% were B12 deficient and 1.3% were folate deficient; 4% were anemic. Nevertheless, those with below-median values of both vitamins had significantly lower Mini-Mental State scores than patients higher in one or both vitamins. Patients with "organic psychosis" with a negative family history for psychiatric disorder had significantly lower B12 levels than those with a positive family history. In major depression, folate levels correlated negatively with age at onset of psychiatric illness and length of hospitalization. These data suggest that (1) biochemically interrelated vitamins such as B12 and folate may exert both a separate and a concomitant influence on affect and cognition; (2) poorer vitamin status may contribute to certain geropsychiatric disorders that begin at a later age and lack a familial predisposition.

(1990) **Cerebrospinal fluid proteins in men with chronic encephalopathy after exposure to organic solvents.**
Cerebrospinal fluid was examined for 23 patients with chronic toxic encephalopathy after heavy exposure to organic solvents and 23 healthy age-matched referents. No differences were found between the patients and referents with respect to the levels of albumin, immunoglobulin, prealbumin, alpha-1-antitrypsin, beta-2-microglobulin, haptoglobin, or the astroglial cell proteins S100 and glial fibrillary acidic protein in the cerebrospinal fluid. The albumin ratio was normal for both the patients and the referents. The patient group had had heavy exposure to organic solvents, but its members had not been exposed for at least one year before the study. It was concluded that, if exposure to organic solvents affects proteins in cerebrospinal fluid, such effects are probably reversible.


An intestinal permeability test analyzing the differential urinary elimination of lactulose and mannitol orally ingested at the same dosage was carried out first in fasting condition, then combined with specific food ingestion, in 17 children with clinical symptoms of irritable bowel syndrome (IBS). Foods were selected based on a suggestive clinical history or on a positive radioallergosorbent or prick test. Comparison of the results with those of a control population reported in a previous study showed that in nine IBS patients, specific food ingestion was associated with a modification of intestinal permeability. The nine children all had a personal and/or familial history of allergy and/or raised total IgE. The symptoms disappeared in the nine patients after food exclusion either alone (seven patients) or together with further treatment by cromolyn (two patients). We conclude that, at least in some children, symptoms of IBS may be related to food hypersensitivity.


Abou-Donia, MB, Suwita, E and Nomeir, AA Journal/Toxicology. 61: 13-25.

The absorption, distribution, elimination, and metabolism of a single oral dose of 50 mg (4.6 microCi)/kg of uniformly phenyl-labeled [14C]tri-o-cresyl phosphate (TOCP) was investigated in adult chickens. Three treated hens were killed at each time interval: 0.5, 1, 2, and 5 days. TOCP was absorbed from the gastrointestinal tract and subsequently distributed throughout the body. Generally, the highest concentrations of radioactivity were associated with gastrointestinal tract parts, bile, kidneys, liver, and lungs. Most of
the radioactivity (47%) was excreted in the combined fecal-urinary excreta during the first 12 h. Very small fractions of the dose were deposited in egg albumen and egg yolk, 0.12% and 0.24%, respectively during the 5-day study. After 5 days, 99% of the dose was eliminated in excreta. TOCP and its metabolites in bile and the combined fecal-urinary excreta were analyzed by high-performance liquid chromatography and liquid scintillation spectrometry. TOCP and nine of its metabolites were identified. In the bile a TOCP active metabolite, saligenin cyclic-o-cresyl phosphate, was the predominant compound found compared to the parent compound in the excreta. These results suggest that in the hen TOCP is excreted slower than the rat and also undergoes metabolic activation. The absorption, elimination, and metabolic profile of TOCP in the hen may contribute to its sensitivity to delayed neurotoxicity.

-----------------------------------------------------------------------------------------------


A single oral dose of 50 mg/kg of [14C]TOCP was administered in corn oil to male rats. Three animals were sacrificed at each of 2, 6 and 12 h and 1, 2 and 5 days following dosing, and tissues and excreta were analyzed for 14C. Within 5 days, 63 and 36% of the dose were recovered in the urine and feces, respectively. Initially, the highest concentrations of radioactivity were observed in the gastrointestinal tract, its contents, the urinary bladder, liver and kidneys. Appreciable concentrations of 14C were detected in plasma, red blood cells, lungs and adipose tissues, while neural tissues, muscle, spleen and testes contained lower concentrations of radioactivity. Among neural tissues, the sciatic nerve contained the highest concentrations of 14C at all time points studied. The concentration of TOCP in plasma was at maximum by 6 h then declined biexponentially with terminal half-life of 46 h. The predominant metabolites in plasma were o-cresyl dihydrogen phosphate, di-o-cresyl hydrogen phosphate and o-hydroxybenzoic acid (salicylic acid). Small concentrations of the neurotoxic metabolite of saligenin cyclic-o-tolyl phosphate, were detected in plasma at all but the last time point analyzed. Most of the radioactivity extracted from the livers of rats sacrificed at 2 and 4 h were metabolites. No TOCP was detected in the urine or feces collected within 3 days after dosing. The major metabolite in the urine and feces was o-cresyl dihydrogen phosphate followed by di-o-cresyl hydrogen phosphate, salicylic acid, o-hydroxybenzyl alcohol and o-cresol. This study supports the hypothesis that the insensitivity of the rat to TOCP-induced delayed neurotoxicity may be attributed, in part, to the disposition and metabolism of this chemical.

-----------------------------------------------------------------------------------------------
Some organophosphorus compounds produce neurologic dysfunctions, known as OPIDN, after a delay period that is accompanied by neuropathic damage in the central and peripheral nervous systems. This group of chemicals may be divided into two classes, Type I and II, based on chemical structure, species selectivity, age sensitivity, the length of latent period, clinical signs, morphology and distribution of neuropathologic lesions, protection with phenylmethyl sulfonyl fluoride, inhibition of neurotoxic esterase, and effect on catecholamine secretion from bovine adrenome-dullary chromaffin cells. The importance of this effect is underlined by the fact that incidents involving more than 40,000 cases of OPIDN in humans have been documented from 1899 to 1989. Most of these compounds are direct or indirect inhibitors of AChE, and produce acute cholinergic effects. Neurologic deficits are characterized by three phases: progressive, stationary, and improvement. Prognosis of OPIDN depends on the extent of damage of the nervous system. Improvement or even recovery of functions may follow mild cases, whereas severe toxicity results in long-lasting neurologic dysfunctions reflecting spinal cord damage. Recent studies have shown that delayed neurotoxic organophosphorus compounds interact with Ca2+ calmodulin kinase II (CaM kinase II), an enzyme responsible for the endogenous phosphorylation of cytoskeletal proteins, i.e. microtubules, neurofilaments, and MAP-2. This leads to an increased activity of CaM kinase II and enhanced phosphorylation of cytoskeletal elements, and eventually in the disassembly of cytoskeletal proteins. The dissociation of cytoskeletal proteins causes increased fast axonal transport in the treated animals resulting in the accumulation of altered cytoskeletal elements in the distal portions of the axon. Abnormal tubulin and neurofilaments are transformed into filamentous polymers and undergo condensation and dissolution. Concomitantly, proliferated endoplasmic reticulum and accumulated mitochondria degenerate and release Ca2+ ions. This leads to Ca2(+-)-activated proteolysis of the cytoskeleton and interruption of ionic balance across the axonal membrane resulting in the uptake of water and axonal swelling, which subsequently degenerates. A similar mechanism may cause secondary myelin degeneration.
flawed by lack of scientific rigor, inadequate medical input, and lack of attention to financial conflicts of interest. The adoption by the Occupational Safety and Health Administration of many poorly supported values as permissible exposure limits reflects also the underutilization of industrial medicine in identifying health effects of exposures below the TLVs. It is thus the responsibility of the medical profession to act on the presumption that the TLV permissible exposure limits are unsafe limits until a sound underlying body of medical and scientific literature exists for the substances on the list. It is industry's responsibility to commit itself seriously to medical and exposure monitoring and to begin to remedy the knowledge deficit that exists about the less immediate health effects of most industrial materials.


An experiment was conducted to determine, under different conditions, the capacity of young adult East African goats to eliminate intravenously inoculated [75Se]selenomethionine-labelled Trypanosoma brucei from the bloodstream. Over 80% of labelled trypanosomes, preincubated for 1 h in inactivated normal goat serum, were detectable in the circulation 1 h after inoculation into normal goats. By contrast, after incubation in serum from goats which had been immunised against the homologous trypanosome clone, parasites were largely removed from the bloodstream within 5 min after inoculation. When the goats were necropsied 1 h after the inoculation of radiolabelled trypanosomes, 50% of the injected activity was found in the liver and lungs, the contribution of each organ being dependent to some extent on whether the inoculum was via a mesenteric or the jugular vein. The same result was obtained when labelled parasites were incubated in normal goat serum, and then inoculated into immunised goats; thus, rapid blood clearance occurred, and high activity was detected in the lungs and liver. The results confirm those of previous studies in laboratory mice in which the removal of trypanosomes from the circulation of an immune animal was achieved primarily by uptake of opsonised trypanosomes by elements of the mononuclear phagocytic system.

Three patients exposed to hydrogen sulfide developed persistent cognitive impairment, as suggested by the P-300 event-related potential and measured by neuropsychological testing. Routine neurological and physical examinations were unremarkable, although the patients were sufficiently impaired so as to be unable to work. The P-300 event-related potential and neuropsychological testing proved to be important in the detection of cognitive dysfunction following acute hydrogen sulfide exposure. The three patients with neurocognitive dysfunction were acutely exposed to hydrogen sulfide. The incidents occurred independently and under different circumstances. Each patient was evaluated at the Northern California Occupational Health Clinic, San Francisco, examined neurologically and neuropsychologically, and evaluated with a P-300 event-related potential. Each patient had persistent neurological symptoms, neuropsychological deficit, and abnormally prolonged P-300 latencies.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2757531


The results of two field studies in painters and spray painters, the outcomes of examinations of workers with suspected work-related disease due to solvents, as well as data from an evaluation of an epidemiologic study in painters with confirmed occupational disease, are presented and discussed. The results of these studies and the experiences in occupational medicine in the Federal Republic of Germany do not support the assumption of high neurotoxic risks in solvent-exposed workers, which can be postulated from various epidemiologic studies from Scandinavian countries. Several factors may explain the different conclusions: 1) lower solvent exposures of German painters in the past decades; 2) false positive diagnosis of a toxic encephalopathy; 3) aetiological misclassification; 4) differences in legislation relevant for the acknowledgement of occupational diseases. In conclusion, there is a need for further well-designed epidemiologic studies in occupationally solvent-exposed workers. Suggestions regarding assessment of exposure and neurobehavioral tests are given.

The field of clinical ecology is based on a putative diagnosis of "environmental illness," applied to persons who have multiple symptoms and are believed to be sensitive to numerous items in the environment. Increasingly this diagnosis is being used by workers for an occupational disability claim. Medical records of 90 workers claiming work-related "environmental illness" were reviewed. The majority were women. They worked in a variety of occupations with no unifying feature of the type of work or the claimed causative exposure. Symptoms were multiple and unaccompanied by objective clinical findings. Careful review of medical records showed that most had their symptoms before the claimed occupational exposure. Examining physicians who were not clinical ecologists invariably arrived at other diagnoses, usually psychiatric. This retrospective review lends no support to the clinical ecology concept of "environmental illness."


The hemodynamic effects of mivacurium chloride were studied in 54 adult cardiac patients anesthetized with midazolam and sufentanil. After baseline data were collected, a placebo (N = 9) or mivacurium was administered over 60 seconds, the latter in doses of 0.15 (N = 18), 0.20 (N = 18), or 0.25 (N = 9) mg/kg. Measurements were repeated 2, 5, and 10 minutes later. Baseline measurements were similar. A slight decrease in heart rate over time reached statistical significance in several groups including the control group. Mean arterial, mean pulmonary arterial, pulmonary arterial occlusion, and right atrial pressures and cardiac output did not change, nor did systemic and pulmonary vascular resistances and cardiac index. Besides the decrease in heart rate, the only hemodynamic change to reach statistical significance was an increase in stroke volume in patients given mivacurium 0.25 mg/kg. Significant hypotension occurred in two patients; in one, a sudden decrease in mean arterial pressure of 24% occurred 1 minute after mivacurium 0.20 mg/kg. Blood pressure was restored by ephedrine 10 mg. In the other patient, given mivacurium 0.25 mg/kg, mean arterial pressure decreased 50% from 73 to 37 mm Hg. Recovery was rapid without treatment. It is concluded that mivacurium administered in doses of 0.15 to 0.25 mg/kg over 60 seconds to cardiac patients is associated with few significant hemodynamic effects. However, a small number of patients may experience significant transient hypotension when given doses greater than of 0.15 mg/kg, two times the ED95.

The biomedical model of disease, in which health is viewed as the absence of disease, is becoming obsolete. Burgeoning health care costs coupled with an increased focus on health promotion and illness prevention have created new demands on the health care delivery system. A biopsychosocial model of health care--in which disease is seen as an interplay between environmental, physical, behavioral, psychological, and social factors--can integrate mental health services into the primary care sector. Social workers, as primary providers of psychosocial care, can close the gap between physical health and mental health services. Strategies for implementing the biopsychosocial model, methods to evaluate its effectiveness, potential problems, and recommendations for future research are discussed.

(1989) Teratogenesis of polychlorocycloalkane insecticides in chicken embryos resulting from their interactions at the convulsant recognition sites of the GABA (pro)receptor complex.

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2545292


The dose-effect relationship of mivacurium chloride on arterial blood pressure, heart rate, and plasma histamine was determined in 97 consenting ASA physical status I-II patients receiving nitrous oxide-oxygen-opiate-barbiturate anesthesia. In the absence of surgical stimulation during steady state anesthetic conditions with controlled ventilation, average maximum change in tachograph-counted heart rate was 7% or less after 10-15-s injection of mivacurium at all doses from 0.03 to 0.30 mg/kg. Average peak change in mean arterial pressure measured via radial arterial catheter was 7% or less after all doses from 0.03 to 0.15 mg/kg. Transient (0.2-4.5 min) decreases in arterial blood pressure were noted after 10-15-s injection in some patients at 0.20, 0.25, and 0.30 mg/kg. When they occurred, these changes were usually accompanied by facial erythema lasting 2-5 min and were correlated with increases in plasma histamine level (P less than 0.001). Facial erythema, decrease in
blood pressure, and elevation of histamine level were all accentuated by increasing the
dose of mivacurium and by more rapid injection of the drug. For example, mean blood
pressure decreased an average of 13% after injection of mivacurium 0.25 mg/kg over
10-15 s. In contrast, during administration over 30 and 60 s of this dose, arterial
pressure decreased 7.6 and 1.5%, respectively (P less than 0.001, 10-15 s vs. 60-s
injection). Average peak histamine level, which increased to 132% of control after
administration of 0.25 mg/kg over 10-15 s, did not change after injection over 60
s.(ABSTRACT TRUNCATED AT 250 WORDS)


on cellular and humoral immune response systems.
Rodgers, KE, Stern, ML and Ware, CF Journal/Toxicology. 54: 183-196.

Biosis copyright: biol abs. rrm mouse malathion insecticide impurity interleukin-2
concanavalin a lipopolysaccharide phytohemagglutinin antibody response t-lymphocyte

(1989) Protection from O,O,S-Trimethyl Phosphorothioate-Induced Immune
Suppression.
Rodgers, KE, Haviland, DL and Ware, CF Journal/Immunopharmacology, Vol. 17, No.
Experiments were performed to determine the effects of various protective treatment
regimes on O,O,S-trimethyl-phosphorothioate (152205) (OOS-TMP) induced
immunosuppression in female C57B1/6-mice. The mice were divided into four
treatment schedule groups: group one received a single dose of OOS-TMP or
O,O,O-trimethyl-phosphorothioate (152181) (OOO-TMP); group two received
co-administration of OOS-TMP with OOO-TMP; group three received four daily doses
of OOS-TMP; and group four received four daily doses of OOS-TMP with a larger
challenge dose of OOS-TMP. Twenty four hours following the treatment schedule, the
animals were sacrificed. No change was noted in lymphoid organ size following any of
the treatments. However, splenocytes from animals that were exposed to treatment
regimes one, two, and four had significantly elevated proliferative responses to
mitogens concanavalin-A and lipopolysaccharide. The ability of splenocytes to
generate an antibody secreting cell response to sheep red blood cells was elevated
following treatment with group one and at the lower dose in treatment group four. No changes in this immune parameter were noted in the other treatments. No difference was observed in the ability of splenocytes to generate a cytotoxic T-lymphocyte response following these treatment regimes. The degree of protection from immune suppression by these treatments varied with the sensitivity of the immune parameters to suppression by acute administration of OOS-TMP.

(1989) Food and chemicals as environmental incitants.
Susceptibility to environmental incitants such as air, food and water components is becoming an increasingly recognized health problem. These sensitivities and reactions can induce a spectrum of symptoms affecting smooth muscle, mucous membranes and collagen in the respiratory, gastrointestinal, genitourinary and vascular systems. These reactions may be mistaken for hypochondriasis, but actually are due to reactions to foods and chemicals found in the patient's home and work environments. Careful clinical histories should alert the nurse and physician, who can confirm suspicions by eliminating and challenging the patient with potentially offending agents under controlled circumstances.

(1989) In vitro binding of \([14C]\)acrylamide to neurofilament and microtubule proteins of rats.
Acrylamide produces a dying back type of neuropathy in which there is an accumulation of neurofilaments in the axons. The in vitro binding of [14C]acrylamide to neurofilament and microtubule proteins obtained from rat spinal cord and brain was investigated. The relative binding to the high and middle molecular weight neurofilament was greater than to the low molecular weight neurofilament, while the rate of binding to MAP-1 (microtubule associated protein-1) and -2 was much greater than to tubulin. The binding rate to a 53 kDa protein which co-purified with the neurofilaments was between those of the middle and high molecular weight neurofilaments while the lowest rate of binding was to glial fibrillary acidic protein. These data indicate that there is a direct binding of acrylamide to cytoskeletal proteins.
(1989) Protection from o.o.s trimethylphosphorothioate-induced immune suppression au - Rodgers KE.
Haviland, DL and Ware, CF Journal/Immunopharmacology. 17: 131-140.

Biosis copyright: biol abs. rrm mouse malathion contaminant ectoparasiticide lung damage cytotoxic t lymphocyte generation blockade splenic proliferative response

(1989) Care for "environmental illness".


The neuromuscular and cardiovascular effects of mivacurium chloride were studied during nitrous oxide-oxygen narcotic (fentanyl) (n = 90) and nitrous oxide-isoflurane (ISO) anaesthesia (n = 45). In addition, a separate group (n = 9) received succinylcholine during fentanyl anaesthesia to compare its neuromuscular effects with mivacurium. Mivacurium was initially administered as a single bolus in doses from 0.03 mg.kg-1 to 0.25 mg.kg-1 to study the dose-response relationships, as well as the cardiovascular effects of mivacurium. Neuromuscular block (NMB) was measured by recording the twitch response of the adductor pollicis muscle following ulnar nerve stimulation (0.15 Hz, 0.2 ms supramaximal voltage). The ED95 values for mivacurium were estimated to be 0.073 mg.kg-1 and 0.053 mg.kg-1 in the fentanyl and ISO groups respectively. The duration of block (time from injection to 95 per cent recovery) for a dose of 0.05 mg.kg-1 mivacurium was 15.3 +/- 1.0 min and 21.5 +/- 1.3 min for fentanyl and ISO anaesthesia, respectively. The recovery index (25-75 per cent) between initial bolus dose (6.1 +/- 0.5 min), repeat bolus doses (7.6 +/- 0.6 min), mivacurium infusion (6.7 +/- 0.7 min) and succinylcholine infusion (6.8 +/- 1.8 min) were not significantly different. There was minimal change in mean arterial pressure (MAP) or heart rate (HR) following bolus doses of mivacurium up to 0.15 mg.kg-1. Bolus administration of 0.20 mg.kg-1 or 0.25 mg.kg-1 of mivacurium decreased MAP from 78.2 +/- 2.5 to 64.0 +/- 3.2 mmHg (range 12-59 per cent of control) (P less than 0.05). The same doses when administered slowly over 30 sec produced minimal change in MAP or HR.
Castleman, BI and Ziem, GE Journal/Arch Environ Health. 44: 68, 127.

Carrington, CD, Lapadula, DM and Abou-Donia, MB Journal/Brain Res. 476: 179-82.

The effect of a neurotoxic dose of 5.0 mg/kg, s.c. diisopropyl phosphorofluoridate (DFP) on anterograde transport of 35S-methionine labeled proteins in cat peripheral nerve was studied. Seven days after dosing, after 24 h of flow there was 48% less radioactivity in the distal portion of the nerve. A lesser effect was also found at 4 and 14 days after dosing. After 10 or 14 h of flow, the height of the crest was unchanged, but the distance of the crest from the ganglia was greater in the DFP-treated animals. These experiments indicate that DFP treatment accelerates fast anterograde transport.

(1989) *Consultation patterns in an urban hospital setting.*

(1989) *Outcome versus process in decision making.*


(1989) *Elevated antidepressant plasma levels after addition of fluoxetine.*
Aranow, AB, Hudson, JI, Pope, HG, Jr., Grady, TA, Laage, TA, Bell, IR and Cole, JO

Four patients treated with tricyclic antidepressants and one patient treated with trazodone all demonstrated marked increases in plasma levels of these drugs after the addition of fluoxetine. Such increases could increase adverse effects.

Abou-Donia, MB, Othman, MA and Obih, P
Journal/Toxicology. 55: 37-51.

Gossypol is a naturally occurring yellow substance in cotton plant that has male reproductive toxicity both in humans and some experimental animal species. Interspecies oral bioavailability and pharmacokinetic profile of (+/-)-gossypol were compared in male Fischer-344 rats and B6C3F mice after a 1) single intravenous dose, 2) single oral dose, and 3) 14 consecutive, daily, oral doses; all doses were 10 and 50 mg/kg rats and mice, respectively. In both species, the intravenous plasma (+/-)-gossypol concentrations showed a triexponential pattern, indicating a 3-compartment, open-model system. The apparent half-life of elimination of (+/-)-gossypol following intravenous injection was 9.1 h and 7.7 h in rats and mice, respectively. The total plasma clearance (Cl), volume of distribution (Vd), and AUC_plasma after a single intravenous injection were 1.84 and 1.23 l/h per kg, 0.20 and 1.74 l/kg, and 36.0 and 115.8 mg.h/l, in rats and mice, respectively. The bioavailability of a single, oral dose of (+/-)-gossypol was 86% and 14.3% in rats and mice, respectively. In rats the change in plasma (+/-)-gossypol concentration after a single dose was monophasic; multiple doses showed a biphasic pattern. In mice a single dose of (+/-)-gossypol showed a biexponential plasma concentration pattern; daily dosing was monoeponential and was eliminated twice as fast as the single dose. Also, multiple doses of (+/-)-gossypol in the mouse were eliminated 7 times faster than in the rat. These findings are consistent with previous results that daily, oral dosing of (+/-)-gossypol, but not a single dose, produces infertility in the male rat, while the mouse is insensitive to (+/-)-gossypol action. The results of this study indicate that differential sensitivity of rats and mice to the contraceptive action of (+/-)-gossypol may be related, at least in part, to its pharmacokinetic profiles in both species.


Clinical ecologists propose the existence of a unique illness in which multiple environmental chemicals, foods, drugs, and endogenous C. albicans have a toxic
effect on the immune system, thereby adversely affecting other bodily functions. The proposal uses some concepts that superficially resemble those that apply to clinical allergy and toxicology and others that are novel. Review of the clinical ecology literature provides inadequate support for the beliefs and practices of clinical ecology. The existence of an environmental illness as presented in clinical ecology theory must be questioned because of the lack of a clinical definition. Diagnoses and treatments involve procedures of no proven efficacy. Case reports by clinical ecologists and evaluation of these patients by other physicians indicate that this diagnosis is applied most frequently to persons with symptoms of physiologic (somatic) or psychologic dysfunction, or both. Proof of cause-effect relations between environmental factors and symptoms of "environmental illness" is particularly difficult because clinical ecologists implicate such a broad range of agents, including chemicals, foods, hormones, and microorganisms. Most patients are believed to react to multiple environmental substances by any route of exposure, and some are said to be intolerant to the entire environment, the so-called "total allergy syndrome." The principal method of proof cited by clinical ecologists for the existence of "environmental illness" is the symptom-provocation test used in diagnosis of individual cases after the condition is suspected because of a history of symptoms and suspected causes. Published studies on the provocation test employed widely different subject-selection methods and outcome-measurement criteria. All were seriously flawed by the absence of matched patient-control groups, absence or inadequacy of the placebo, and failure to achieve or document randomness of trials. Not surprisingly, therefore, the conclusions from these studies are conflicting. Those studies reporting results of immunologic tests are insufficient to address theories of environmental illness; the number of cases is small and selection criteria are not clear. Enumeration of lymphocyte subsets and quantitation of serum immunoglobulin and complement levels in patients with "environmental illness" have not yielded clear-cut evidence of immunologic abnormality. Clinical ecologists use a treatment program that includes avoidance of environmental chemicals, rotation of foods in the diet, and neutralization of symptoms with injected or sublingual extracts. Except for small-dose oral nystatin, which is used for treatment of patients with the candida hypersensitivity syndrome, drug therapy is intentionally avoided, although some clinical ecologists recommend mineral salts, oxygen, vitamins, minerals, and antioxidants for relief of symptoms.(ABSTRACT TRUNCATED AT 400 WORDS)

van Wijnen, JH and Stijkel, A Journal/Int Arch Occup Environ Health. 61: 77-87.

A modelled approach for the assessment of exposure and health risks in a case of soil pollution with an unknown but probably large number of potential contaminants is presented. In 1983 the Steendijkpolder, a housing estate of about 800 houses, an agglomeration of schools and a tennis hall was built directly on a 4-m-thick layer of harbour sludge. The sludge originated from around 20 harbour basins in Rotterdam
and the industrial area around the Nieuwe Waterweg. In the soil organic solvents, PAH's, aldrin, dieldrin, isodrin, telodrin and several heavy metals were found to be present as contaminants. Not all contaminants, including a number of halogenated compounds, were identified. The investigation of the other relevant environmental compartments in this situation, e.g. drinking-water, indoor-air and home grown vegetables showed that soil ingestion was the predominant route of intake of contaminants. Therefore the exposure of infants (age: 2-3 years) was calculated. The calculated intake of PAH by soil ingestion was around half the average intake of PAH in the daily diet. The extra exposure to drins (a group of cyclodiene insecticides) due to soil ingestion and inhaled contaminated indoor air was calculated to exceed twice the Acceptable Daily Intake (ADI) of dieldrin. The calculated maximal intake of Pb by soil ingestion exceeded the average intake of Pb in the daily diet by around 1.4 times. The maximal intake by soil ingestion of the other identified contaminants was relatively low. It was concluded that with the present knowledge the calculated exposure would not result in observable health damage.


In vitro measurement of IgE antibodies in serum has an established role in the study of allergic disease, but the place of in vitro tests in routine diagnosis is not well established. They are particularly helpful in confirming new allergens in the workplace and in situations where skin testing is potentially dangerous or technically not feasible. The basic procedure is the radioallergosorbent test (RAST). Each modification has its peculiar advantages and disadvantages. A clinician depending upon in vitro tests for diagnosis must be aware of the technical problems, the inherent limitation in sensitivity in comparison to skin testing, and above all, the fact that in vitro tests detect the presence of an IgE antibody in serum but give no direct information about its pathogenetic role in an individual patient.


Doxacurium chloride is an investigational long-acting neuromuscular blocking drug, which has been shown to be devoid of cardiovascular side effects when administered in modest doses to healthy patients. This is the first hemodynamic study of doxacurium in adult patients with cardiac disease. Forty-one patients scheduled to undergo cardiac
surgery were studied. Anesthesia consisted of induction with midazolam 0.2-0.3 mg/kg and sufentanil 0.01-0.03 mg followed by an infusion of sufentanil at 0.03-0.06 mg.min⁻¹. Baseline hemodynamic data were collected during a stable state of sufentanil anesthesia. Doxacurium was then administered in doses of 1, 2, or 3 times its ED95 of 0.025 mg/kg. Hemodynamic measurements were repeated at 2, 5, and 10 min after doxacurium injection in the absence of surgical stimulation. An additional group of control patients received saline instead of doxacurium. Baseline hemodynamic measurements were similar among groups. There was a slight decrease in heart rate in all groups over time. However, there was no significant difference between the groups of patients receiving doxacurium and the control group in which the heart rate decreased progressively from 52 beats/min at baseline to 49 beats/min 10 min after doxacurium administration. At no time was there any significant change in mean arterial pressure, right atrial pressure, or cardiac output. Likewise derived hemodynamic variables including cardiac index, stroke volume, and pulmonary vascular resistance were unchanged. In addition to the decrease in heart rate, the hemodynamic changes, which reached statistical significance, were clinically insignificant and occurred predominantly in the group of patients receiving doxacurium 0.08 mg/kg. (ABSTRACT TRUNCATED AT 250 WORDS)

Somkuti, SG, Tilson, HA, Brown, HR, Campbell, GA, Lapadula, DM and Abou-Donia, MB Journal/Fundam Appl Toxicol. 10: 199-205.

Tri-o-cresyl phosphate (TOCP), which produces a delayed neurotoxic syndrome in humans and some animal species, was given to Fischer 344 (F344) male (18 week old) rats to determine if it causes biochemical, sensorimotor, and neuropathological effects. Animals were given TOCP by gavage in doses ranging from 10 to 100 mg of TOCP/kg daily for a period of 63 days. The rats were subjected to a series of neurobehavioral tests including fore- and hindlimb grip strength, motor activity, tremor, and latency to respond to a thermal stimulus. Central and peripheral nervous tissues were examined for damage characteristic of organophosphorous compound-induced delayed neurotoxicity (OPIDN). Brain neurotoxic esterase and acetylcholinesterase activities were inhibited in a dose-dependent fashion. A group of three chickens treated with 100 mg of TOCP/kg/day for 18 days was included as the positive control for enzymatic and histopathological alterations associated with OPIDN. Rats showed no consistent neurobehavioral changes or evidence of neuropathological damage in nervous tissues associated with treatment. In contrast, chickens treated with TOCP developed delayed neurotoxicity characterized by ataxia, which progressed to paralysis. These neurological changes included swelling, fragmentation, and degeneration of the axon and myelin in both central and peripheral nervous tissues. This study concludes that the F344 rat is not sensitive to the delayed neurotoxic effects
of TOCP. When studying OPIDN in rats, care must be exercised in choosing the experimental animal since some strains, e.g., F344, are not sensitive.


Food components and ingested chemicals may be metabolized in the gut, not only by digestive and intestinal mucosal enzymes, but also by the resident bacteria, which are found in greatest numbers in the large intestine. The gut microflora is a large (about 10(11) organisms per g colon contents) and diverse (over 400 species) population of organisms and possesses a correspondingly diverse range of metabolic activities, including reductions, hydrolyses and degradations. In many cases, these reactions both complement and antagonize those of the liver, which are mainly oxidative and synthetic. The metabolism, by the gut flora, of chemicals ingested in food or secreted in bile can have numerous toxicological sequelae, including activation to more toxic, mutagenic or carcinogenic derivatives, detoxication and enterohepatic circulation. These toxicological consequences may be modified by changes in the flora due to diet, drugs and interindividual differences. Examples presented of the interaction between the gut flora and its host are the influence of intestinal bacteria on hepatic tumor incidence in mice, the effect of bacterial hydrolysis of rutin on the activity of hepatic enzymes which activate dietary carcinogens, and the role of the gut flora in demethylation and detoxication of methylmercury.


The dose dependency and kinetics of immunomodulatory effects of O,S,S-trimethyl-phosphorodithioate (22608533) (OSS-TMP) on the cell mediated and humoral immunity were investigated by measuring the generation of cytotoxic
T-lymphocytes (CTL) to alloantigen (H-2 incompatible) antibody forming cells of sheep red blood cells (SRBC), mitogenic responses and interleukin-2 (IL-2) production. Female C57BL/6-mice were treated with oral doses of OSS-TMP dissolved in corn-oil. Treatment with 20 or 40mg/kg doses increased the ability of splenocytes to generate a CTL response on day one or seven, respectively. At a 60mg/kg dose level, serum cholinesterase levels were suppressed and thymic size decreased causing a significant suppression of the ability of splenocytes to generate a CTL response. At 80mg/kg, the CTL response to alloantigen was significantly suppressed at all time points. Mitogenic responses to lipopolysaccharide and phytohemagglutinin were elevated at all doses of OSS-TMP administered by day seven following treatment. However, the proliferative response to concanavalin-A was elevated in a dose dependent manner. Acute administration of 60 or 80mg/kg doses suppressed IL-2 production at all time points and at all doses tested on day five following treatment. The authors conclude that OSS-TMP enhanced the generation of humoral and cell mediated immune responses of C56BL/6-mice following administration of nontoxic doses.


Strenuous exercise leading to heat stroke is known to cause rhabdomyolysis and acute renal failure in men, but there are no reports of this environmental illness in otherwise healthy women. We report the first case of heat and exercise induced acute renal failure in a young nonacclimatized adult female following intense exertion in the Grand Canyon. This individual displayed the typical clinical features of exertional heat stroke including hyperpyrexia, CNS disturbance, rhabdomyolysis, oligoanuric acute renal failure, and disseminated intravascular coagulopathy. The pathophysiology is discussed as well as sexual differences in response to heat and exercise. The specific factors that may have predisposed this young woman to heat stroke from exertion are identified.

(1988) Pharmacokinetic profile of (+/-)-gossypol in male Sprague-Dawley rats following single intravenous and oral and subchronic oral administration.
The pharmacokinetic profile of (+/-)-gossypol was determined in male Sprague-Dawley rats following a single intravenous or oral 10 mg/kg dose and after receiving a daily oral 10 mg/kg dose for 14 days. The intravenous plasma (+/-)-gossypol level data were fitted with a three-compartment, open-model system. The apparent half-life of elimination of (+/-)-gossypol following intravenous administration was 11.44 hr, corresponding to an elimination rate constant of 0.05 hr-1. The total plasma clearance (Cl), volume of distribution (Vd), and AUCplasma following a single intravenous administration were 0.16 liter/hr/kg, 0.05 liter/kg, and 63.09 mg.hr/liter, respectively. The bioavailability of a single oral dose of (+/-)-gossypol in rats was 60%. The change in plasma (+/-)-gossypol concentration after a single or after multiple doses showed a biphasic pattern. A single oral dose of (+/-)-gossypol, however, was eliminated five times faster than the daily administered chemical. Thus, a single oral dose of (+/-)-gossypol was eliminated at a rate constant of 0.01 hr-1, corresponding to half-life of 64.76 hr. Subchronic oral administration of (+/-)-gossypol showed an apparent half-life of 101.91 hr-1, corresponding to a rate constant of 0.007 hr-1. The results indicate that multiple oral dosing of (+/-)-gossypol resulted in its longer retention in body tissue than a single oral dose. This study suggests that pharmacokinetics of (+/-)-gossypol may play, at least in part, a role in the reproductive toxicity of subchronic but not single oral dosing.


The purpose of this study was to evaluate neuromuscular and cardiovascular effects of doxacurium chloride, a new long-acting neuromuscular blocking agent, during a stable state of nitrous oxide and narcotic anesthesia. Ninety-three ASA physical status I or II patients were studied after informed written consent had been obtained. Eighty-one patients (group A) received doxacurium. The 81 patients were divided into nine subgroups according to the dose of doxacurium administered (0.01-0.06 mg.kg-1). Patients in a control group (group B) (n = 12) received pancuronium. To assess neuromuscular responses, a force displacement transducer recorded the twitch response of the adductor pollicis muscle following ulnar nerve stimulation. The ED50 and ED95 for doxacurium were estimated to be 0.013 mg.kg-1 and 0.023 mg.kg-1, respectively. The time to maximum twitch suppression following a dose of 1.0 (ED95) and 1.7 (ED95) was 10.3 +/- 1.3 min and 7.6 +/- 0.8 min, respectively. After an ED95 dose of doxacurium the time to spontaneous recovery to 95% of control twitch height was 73.7 +/- 8.7 min. With larger doses of doxacurium, 0.04 mg.kg-1 (1.7 X ED95) and 0.05 mg.kg-1 (2.2 X ED95), the time to spontaneous recovery to 95% of control twitch height was 125.8 +/- 24.8 and 204.0 +/- 21.2 minutes, respectively. When 25% twitch
height recovery or more was present the reversal of doxacurium induced neuromuscular blockade was prompt. (ABSTRACT TRUNCATED AT 250 WORDS)


As no published data was available, dust was collected from 102 university student dormitory rooms and 33 were selected on a random basis for analysis. Mean dust per dormitory room was 4.47 g of coarse, 0.96 g of fine, and a 24-hour sedimented volume of fine dust of 6.90 mL. The mean number of mites was 63/g of coarse dust, and 240/g and 36/mL of fine dust. They were identified as D. pteronyssinus (D.p.), 81.9%; D. farinae, 11.2%; and Cheyletus, 4.7%. Fifteen samples from homes were controls. Mean values were 0.60 g of coarse dust, and 0.20 g and 2.3 mL of fine dust. Mites numbered 985/g of coarse, and 3409/g and 244/mL of fine dust. They were D.p., 87.2%; D. farinae, 3.0%; Cheyletus, 3.7%; and Euroglyphus, 1.6%. Differences between dormitories and homes in amount of dust and number of mites were significant at P less than .001. Dust and mites were significantly less in dormitories with linoleum than those with carpets (P less than .05 and .01, respectively). In conclusion, university dormitories have significantly less mites than homes despite a greater amount of dust harvested.


The present studies were carried out to investigate the comparative roles of protein cross-linking and alteration in protein phosphorylation in the accumulation of neurofilaments due to aliphatic hexacarbons. In these studies, rats were given 2,5-hexanedione (0, 0.1, 0.25 and 1.0%) for 70 days in their drinking water. In a separate study of in vitro protein phosphorylation rats were given 1% 2,5-hexanedione for 14 days in their drinking water. Spinal cord neurofilaments were isolated and
analyzed using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, immunoblotting using anti-neurofilament antibodies, radioimmunoassays (RIAs) of phosphorylated epitopes on neurofilament proteins and protein phosphorylation. Protein cross-linking of neurofilaments was found in all animals treated with 2,5-hexanedione including the lowest dose (0.1%) which did not produce clinical signs of intoxication. Protein phosphorylation of neurofilament proteins, as well as MAP-2 was significantly decreased upon treatment. Protein staining revealed a decreased amount of neurofilament protein and immunoblotting demonstrated neurofilament protein cross-linking in these animals. Protein staining of glial fibrillary acidic protein (GFAP) was unaltered by this treatment. RIAs of phosphorylated and non-phosphorylated epitopes of neurofilament proteins indicated that in vivo phosphorylation of these proteins was also decreased. Two-dimensional gel electrophoresis indicated a shift of the neurofilament proteins to a basic pI, indicating a dephosphorylation of neurofilament proteins. Cross-linked neurofilament proteins also exhibited a pI which was more basic than any of the individual neurofilament proteins. This report demonstrates differential effects of 2,5-hexanedione on neurofilament proteins and indicates that several mechanisms may be responsible for their accumulation.


This study investigated the clinical usefulness of the intracutaneous provocative-neutralization food test (IPFT). Thirty-seven patients were tested for five identical food allergies by eight physicians in different geographical locations. Throughout the study, comparison was made between the IPFT when interpreted by skin response (IPFT SK) and when interpreted by symptom provocation (IPFT PR). Double-blind IPFT results were compared with those of previously accomplished oral challenge food tests (OCFT). IPFT reliability was determined by a double-blind comparison of the initial IPFT, with two subsequent IPFTs performed 7 days apart. Correlation of the IPFT SK and IPFT PR with the OCFT provided validity coefficients of 0.78 and 0.61 respectively, both significant beyond the 0.01 level of confidence. Reliability of the IPFT SK and IPFT PR was shown to be 0.68 and 0.40, respectively. The IPFT SK was significant beyond the 0.01 level of confidence and the IPFT PR was significant beyond the 0.05 level of confidence.


Presented is a triple-blind crossover study that investigates the efficacy of subcutaneous neutralization food hypersensitivity therapy. Seven physicians and thirty-three patients from various parts of the country participated. Each patient underwent three 2-week treatment sessions, with 1 week off treatment between each session. During each treatment session, one injection a day was given. The injection consisted of a placebo for one 2-week session, and the active allergen during the other two sessions. The active dose was determined by earlier intracutaneous provocative food testing. The diet during the study period was not varied. Medication-symptom diaries were maintained and treatment result evaluations for both individual complaints and overall results were detailed on a standard form at the end of each treatment session. While the number of foods treated per patient varied from 1 to 13, the majority were treated with 3 to 5 foods. Treatment with the active medication was more efficacious than with placebo. A few patients' symptoms were aggravated with the active medication. This indicates a correct diagnosis, but incorrect treatment dose. In the clinical setting such adverse response should be reversed. Overall, neutralization subcutaneous treatment should be beneficial approximately 75% of the time, and further enhanced by supplemental diet manipulation.

(1988) Comparative properties of channel catfish (Ictalurus punctatus) and blue crab (Callinectes sapidus) acetylcholinesterases.

1. Acetylcholinesterases (AChEs) from channel catfish and blue crabs were examined for substrate preference, Kms, effects of inhibitors, and pH and osmotic activity profiles. 2. Similarities were noted for substrate preference along with pH and osmotic optima. 3. Crab AChE had a lower Km (9 x 10(-5) vs 2 x 10(-4) M) and was more sensitive in terms of KI50S than fish AChE to eserine (2.6 x 10(-7) vs 3 x 10(-7) M), malathion (4.5 x 10(-5) vs 1.6 x 10(-4) M) and parathion (6.9 x 10(-5) vs 7 x 10(-4) M). 4. Fish AChE appeared easier to solubilize using Triton X-100.


Investigations into the historical development of specific Threshold Limit Values (TLVs) for many substances have revealed serious shortcomings in the process followed by the American Conference of Governmental Industrial Hygienists. Unpublished
corporate communications were important in developing TLVs for 104 substances; for 15 of these, the TLV documentation was based solely on such information. Efforts to obtain written copies of this unpublished material were mostly unsuccessful. Case studies on the TLV Committee's handling of lead and seven carcinogens illustrate various aspects of corporate influence and interaction with the committee. Corporate representatives listed officially as "consultants" since 1970 were given primary responsibility for developing TLVs on proprietary chemicals of the companies that employed them (Dow, DuPont). It is concluded that an ongoing international effort is needed to develop scientifically based guidelines to replace the TLVs in a climate of openness and without manipulation by vested interests.

(1988) In vivo 31P nuclear magnetic resonance studies on the absorption of triphenyl phosphite and tri-o-cresyl phosphate following subcutaneous administration in hens.

Tri-o-cresyl phosphate (TOCP) and triphenyl phosphite (TPP) are known to be neurotoxic in several species. In a previous study, we found that the subcutaneous administration of the compounds may result in toxicological effects which are prolonged in comparison to administration by other routes. In order to test the hypothesis that slow absorption from the injection site could account for our results, we monitored the disappearance of either compound from the injection site using in vivo 31P nuclear magnetic resonance (NMR). In addition, the test samples and some potential metabolites were examined in vitro with NMR. The disappearance of equimolar doses of subcutaneously injected TOCP (1187 mg/kg) and TPP (1000 mg kg) from the injection site, with time, showed a biphasic pattern. The first phase took place within a few hours, while the second phase was very slow, with a half-life of about 2 weeks for both compounds. These results may account for the prolonged neuropathy target enzyme inhibition and explain the delayed neurotoxicity produced by subcutaneous injection of TOCP and TPP. Two animals given TPP exhibited an atypical pattern, in that the TPP apparently converted to diphenyl phosphonic acid within several hours of injection. In these hens, this phenomenon was accompanied by acute lethality. The conversion to diphenyl phosphonic acid also took place when the TPP was placed in an aqueous solution in vitro. Diphenyl phosphonic acid may play a role in the unique toxicity of TPP.

Carrington, CD, Brown, HR and Abou-Donia, MB Journal/Neurotoxicology. 9: 223-33.
The signs of neurotoxicity observed in the cat and the rat following single or multiple doses of the phosphorous acid ester triphenyl phosphite (TPP) have been reported to differ from the syndrome known as organophosphorous compound induced delayed neuropathy (OPIDN) caused by some phosphoric acid esters. Since the hen is the test animal traditionally used to test compounds for OPIDN, we chose to study the neurotoxicity of single, subcutaneous doses of TPP using the hen. TPP (1000 mg/kg) produced progressive ataxia and paralysis which developed 5-10 days after dosing. The clinical signs were accompanied by axonal damage in the lateral columns of the spinal cord and peripheral nerve. Similar signs were observed following neurotoxic doses of the OPIDN-causing agents tri-o-cresyl phosphate (TOCP) or diisopropyl phosphorofluoridate (DFP). In addition, TPP caused damage to axons in the brain and gray matter of the spinal cord, and chromatolysis and neuronal necrosis were frequently observed in the spinal cord. These latter areas were not affected by TOCP or DFP. The minimum neurotoxic dose of TPP was found to be 500 mg/kg. Prior administration of phenylmethylsulfonyl fluoride (PMSF) reduced the incidence of damage to the peripheral nerve of animals dosed with TPP, but did not prevent toxic effects on the cell bodies in the spinal cord or the clinical effects. The results of this study indicate that TPP causes neuronal damage in addition to the axonal damage observed with OPIDN. Therefore, we conclude that two distinct mechanisms underlie the neurotoxicity of TPP.


The present study is concerned with the involvement of strain differences in rodent sensitivity to organophosphorous compound-induced delayed neurotoxicity (OPIDN). The inhibitory effect of three doses of tri-o-cresyl phosphate (TOCP) on neurotoxic esterase (NTE) and acetylcholinesterase (AChE) in brain was compared in three strains of rat: Long-Evans (LE) animals, which have been reported to be sensitive to the neurotoxic effects of TOCP, and Sprague-Dawley (SD) or Fischer 344 (F344) strains, with which negative results have been obtained. Differences in basal levels were found for NTE (LE greater than F344) greater than SD, with a range of 4.87-7.47 nmol phenylvalerate hydrolyzed/mg protein), but not AChE. Strain differences in inhibition by TOCP were found with both assays, with Sprague-Dawley animals being much less sensitive to esterase inhibition than either Long-Evans or Fischer 344 rats. The ED50 values for NTE inhibition were estimated to be 458, 209, and 288 mg/kg for SD, F344, and LE rats, respectively. The ED50 values for AChE inhibition were estimated to be 1007, 408, and 420 mg/kg for SD, F344, and LE rats, respectively. Liver microsomes from the Fischer animals had less cytochrome P-450 than those from the other two strains. Differences in the ability of the strains to either form or inactivate the active metabolite of TOCP may account for the variation observed. While metabolism may play a role in the differences in the level of NTE inhibition in SD rats...
compared to the LE strain, it cannot account for the lack of sensitivity of the F344 animals to OPIDN. These results may be important in selecting a strain for the study of the toxic effects of organophosphorous compounds in rats.


The neuropathic syndrome resulting in the cat and the rat from single or multiple doses of the phosphorous acid ester tiphenyl phosphite (TPP) has been reported to differ from the syndrome caused by numerous phosphoric acid esters, which is known as organophosphorous compound-induced delayed neurotoxicity (OPIDN). Since the hen is used to test compounds for OPIDN, we chose to study the neurotoxicity of single subcutaneous doses of TPP using this animal model. TPP (1000 mg/kg) produced progressive ataxia and paralysis which began to develop 5-10 days after dosing. Similar signs were observed when subcutaneous doses of the OPIDN-causing agents tri-o-cresyl phosphate (TOCP) or diisopropyl phosphorofluoridate (DFP) were administered. The minimum neurotoxic dose of TPP was 500 mg/kg. Prior administration of phenylmethylsulfonyl fluoride (PMSF) prevented the development of a neuropathy induced by DFP, but did not fully protect the hens from TPP or TOCP. PMSF slowed, but did not prevent, the neuropathy caused by TOCP. PMSF reduced the neurotoxicity of 500 mg/kg TPP, but increased the neurotoxicity of 1000 mg/kg TPP. TPP was found to be a very potent inhibitor of neurotoxic esterase (NTE), the putative target site for OPIDN, in vitro, with a ki of about 2.1 x 10(5) M-1 min-1. Equimolar doses of either TPP (1000 mg/kg) and TOCP (1187 mg/kg) caused over 80% inhibition of neurotoxic esterase (NTE) in brain and sciatic nerve. This high level of NTE inhibition persisted for several weeks. This prolonged inhibition probably accounts for the inability of PMSF to block the neurotoxicity of TOCP.(ABSTRACT TRUNCATED AT 250 WORDS)


Several characteristics help distinguish MPI in the workplace from illness outbreaks due to physical causes: no laboratory or physical findings confirming an specific organic cause evidence of specific physical or psychological stressors victims are mostly women and those of lower socioeconomic status in the workplace hyperventilation-type symptoms are prominent apparent transmission by audiovisual cues rapid spread of the illness followed by rapid remission of symptoms, unless symptoms are fixed by physicians and litigation benign morbidity If a physical or
chemical cause of the illness is not obvious and if episodes recur, the illness remains a
mystery and the workplace becomes a breeding ground for anxiety, confusion, fear,
and rumor. Economic pressures to resume normal operations are counteracted by
fears that an environmental contaminant still exists. Once all physical explanations
have been ruled out, investigators may turn to psychological explanations and focus on
mass hysteria, but that explanation is primarily based on the absence of physical
evidence rather than the presence of agreed-upon psychosocial conditions. Some
reports suggest that the diagnosis of MPI is really an excuse for not conducting an
adequate evaluation of low-level environmental contaminants. The disability in some
workers is prolonged and points to non-work-related factors that may be contributing.
Were it not for the unverifiable physical complaints and the workers’ insistence that the
symptoms are the result of physical disease and their concern about the complaints
and their reactions to dismissal of their complaints, we would not consider these
patients to have a mental disorder. These individuals are reinforced in their beliefs by
some physicians and attorneys, and resultant litigation tends to fix their symptoms. In
fact, a "conspiracy theory" evolves when there are enough convinced people—and
enough people trying to dissuade them. Group phenomena reinforce their beliefs and
make renouncement tantamount to betrayal. The mass psychogenic illness or
psychiatric epidemic that occurs in the workplace offers an opportunity not only to
study the elements of a biopsychosocial system, but also offers opportunities for
medical anthropological studies that relate the causes and courses of specific episodes
of MPI to the cultures of the individuals who develop symptoms and the cultures of the
area in which the epidemic occurs.


Psychologic reactions to a neurotoxic exposure can produce prolonged physical
symptoms which are as debilitating as the direct effects of the neurotoxic substance. A
group of patients exist who experience reoccurrence of exposure-related symptoms
when exposed to a variety of common environmental substances, such as perfume,
gasoline, and cigarette smoke. We propose a classical conditioning model to explain
the development of this phenomenon. Identification and treatment of these individuals
are also discussed.

(1988) Fluoxetine induces elevation of desipramine level and exacerbation of
geriatric nonpsychotic depression.
Abou-Donia, MB, Lapadula, DM and Suwita, E Journal/Toxicology. 49: 469-77.

Concurrent exposures to organophosphorus insecticide leptophos and the industrial solvents n-hexane and toluene were implicated in causing an outbreak of neuropathy in workers. Although both leptophos and n-hexane produce central-peripheral distal axonopathy, the morphology and distribution of neuropathic lesions are distinct, reflecting different modes of action. The molecular mechanisms of organophosphorus compound-induced delayed neurotoxicity (OPIDN) and aliphatic hexacarbon-induced neurotoxicity have been investigated utilizing various biochemical techniques, (i.e. one- and two-dimensional gel electrophoresis, immunoblotting, peptide mapping). Oral administration of tri-o-cresyl phosphate (TOCP) produced delayed neurotoxicity and increased in vitro Ca2+ and calmodulin-dependent kinase protein phosphorylation of cytoskeletal proteins in brain, spinal cord, and sciatic nerve of chickens. This enhanced protein phosphorylation correlated well with the following characteristics of OPIDN: test chemical, whether an OPIDN-producing or not; dose-dependence and time course of the effect; and the animal sex sensitivity, age selectivity, and species susceptibility. The proteins that showed an increased phosphorylation were identified to be; alpha- and beta-tubulin, microtubule-associated protein-2 (MAP-2), and the 3 neurofilament proteins 70 kDa, 160 kDa, and 210 kDa. Further studies suggested that the increased protein phosphorylation is not related to an effect on protein phosphatase or ATPase activity, but rather to altered Ca2+-calmodulin kinase II activity. Aliphatic hexacarbon-induced neurotoxicity is characterized by an accumulation of 10 nm neurofilaments above the nodes of Ranvier in the spinal cord and peripheral nerve. Treatment of rats with 2,5-hexanedione, the active neurotoxic metabolite of n-hexane, produced protein crosslinking in a dose-dependent manner. This treatment also decreased protein phosphorylation of neurofilament proteins as well as MAP-2. These studies demonstrate the involvement of cytoskeletal proteins in the molecular pathogenesis of chemical-induced neurotoxicity.


The science of allergy and immunology has advanced to the point where effective procedures for diagnosis and treatment of food allergy can be proven to be effective. Currently available procedures of proven effectiveness are sufficiently satisfactory for diagnosis and treatment of food allergy so that ones of unproven effectiveness should not be employed in routine fashion, but rather should be considered experimental and reserved for use with informed consent in controlled trials which have been approved.
for safety and scientific merit by competent institutional review boards. Leucocytoxic testing, intracutaneous and subcutaneous provocation and neutralization, and sublingual provocation and neutralization are unproven procedures and should be reserved for experimental use only.


Eight symptomatic individuals chronically exposed to indoor formaldehyde (HCHO) at low concentrations (0.07-0.55 ppm) were compared to 8 nonexposed subjects with respect to: (1) presence of IgG and IgE antibodies to HCHO conjugated to human serum albumin (F-HSA); (2) the percentage of venous blood T and B cells by E and EAC-rosetting; and (3) the ability of T and B cells to undergo mitogen (PHA, PWM) stimulated blastogenesis as measured by the incorporation of tritiated thymidine. Anti-F-HSA IgG, but no IgE, antibodies were detected in the sera of the 8 exposed subjects; none were found in 7 of the unexposed controls. T lymphocytes were decreased in the exposed (48 +/- 11.5%) compared to the control (65.9 +/- 4.97%) subjects (p greater than .001 less than .01). B cells were 12.6 +/- 1.6% (HCHO group) and 14.75 +/- 2.1% (controls) (p greater than .02 less than .05). The incorporation of labeled thymidine by T cells (PHA) was decreased: 17,882 +/- 2,293 cpm (HCHO group) and 28,576 +/- 3,807 cpm (p greater than .001 less than .01). T and B cell blastogenesis (PWM) was 9,698 +/- 1,441 cpm (HCHO group) and 11,279 +/- 1,711 (controls) (p greater than .05 less than .1). Exposure to HCHO appears to stimulate IgG antibodies to F-HSA and decrease the proportion of peripheral T cells.


(1987) "Multiple chemical sensitivities:" immunologic critique of clinical ecology theories and practice.

The concept of multiple chemical hypersensitivities as a disease entity in which the patient experiences numerous symptoms from numerous chemicals and foods caused
by a disturbance of the immune systems lacks a scientific foundation. Published reports of such cases are anecdotal and without proper controls. There is no convincing evidence for any immunologic abnormality in these cases. Diagnostic methods have been shown to be unreliable. Diagnosis, treatment, and theoretical concepts underlying the purported disease are not consistent with current immunologic knowledge and theory. As defined and presented by its proponents, multiple chemical hypersensitivities constitutes a belief and not a disease.


A dermal dose of 50 mg/kg (7.5 microCi/kg) of [14C]2,5-hexanedione (2,5-HD) was applied on a protected area on the backs of hens. Five groups of three hens were killed after 4, 8, 24, 36, and 48 hr. 2,5-HD disappeared monoexponentially from the application site with a half-life of 6 hr. After 48 hr, 35% of the radioactivity was expired as volatile material, largely as 2,5-HD. The combined urinary fecal excreta accounted for 15% of the eliminated radioactivity, while the 14CO2 accounted for 11.9% of the radioactive dose. The highest concentration of 14C was detected in the bile. Among tissues analyzed, liver and kidney contained the highest concentrations of radioactivity, whereas the brain, spinal cord, and peripheral nerves showed smaller concentrations. The half-lives for the elimination of 14C were longest for muscle (71 hr) and shortest for adipose tissue (12 hr), while the remaining tissues showed half-lives ranging from 20 to 30 hr. Radioactivity in the plasma reached a peak at 4 hr. Most of this radioactivity was identified as 5-hydroxy-2-hexanone followed by 2,5-HD and 2,5-dimethylfuran; these chemicals then disappeared biexponentially with terminal half-lives of 7.6 hr, 12.6 hr, and 28.6 hr, respectively. 2,5-HD was the most accounted chemical found in the liver, lung, and kidney, while 5-hydroxy-2-hexanone was found to be most abundant in the combined urinary-fecal excreta.


(1987) Reproductive tract lesions resulting from subchronic administration (63 days) of tri-o-cresyl phosphate in male rats.

An initial dose-range pilot study where animals were gavaged with between 100 and 1600 mg tri-o-cresyl phosphate (TOCP)/kg/day for 14 days resulted in decreased epididymal sperm density and disruption of the seminiferous epithelium in 100% of treated animals. A subchronic 63-day study (reflecting the 49-day length of the rat seminiferous epithelium cycle plus the 14-day transit time of spermatids through the epididymis was initiated. Dose-dependent (10 to 100 mg TOCP/kg/day) decreases in cauda epididymal sperm motility and density, testicular enzyme activities, and alterations in sperm morphology were observed. Concurrent pair-fed controls (matched to the highest dose group, 100 mg TOCP/kg/day) indicated that weight loss resulting from TOCP administration had minimal contributory effects to the testicular toxicity seen. Plasma alpha-tocopherol acetate (vitamin E) and testosterone concentrations were unaffected. Tri-p-cresyl phosphate (TPCP), the nonneurotoxic structural analog of TOCP, produced no toxic effects, demonstrating the necessity of the ortho-cresol moiety for induction of damage. A minimum effective (threshold) dose for observable testicular toxicity was determined to be 10-25 mg TOCP/kg in this study. These data suggest that TOCP interferes with spermatogenic processes and sperm motility directly and not via an androgenic mechanism or decreased vitamin E availability.


Tri-o-cresyl phosphate (TOCP), a known neurotoxic compound, causes testicular toxicity in both leghorn roosters and Fischer 344 rats. The present study was initiated to follow the onset of the testicular lesion through possible changes in sperm numbers and production, serum hormones, and various enzyme activities. Rats were administered TOCP daily (150 mg/kg) for periods of 3, 7, 10, 14, or 21 days. Vehicle-treated animals served as controls. Sperm motility and sperm number per milligram cauda epididymis were both lower in treated animals by Day 10. Testicular weight to body weight ratio was significantly decreased only in the longest treatment duration animals (21 days). Testicular neurotoxic esterase and nonspecific esterase activities were also inhibited, while beta-glucuronidase activity was not affected. Luteinizing and follicle-stimulating hormone levels were normal, as were both serum and interstitial fluid testosterone concentrations. Sertoli cell fluid secretion, as measured by testis weight increase after efferent duct ligation, showed no significant changes. Other organs (spleen, liver, kidney, pancreas, small intestine, adrenal and pituitary glands) had no overt signs of pathology as observed by light microscopy in animals treated for 21 days. A separate group of animals was treated for 21 days and subsequently examined after 98 days of observation (two cycles of the rat seminiferous
epithelium). No recovery of spermatogenesis was seen, indicating that the toxicity was irreversible at the dose used. The effects noted in these studies further define the testicular lesion produced by TOCP and show that 150 mg/kg/day for 21 days produced irreversible testicular toxicity.

(1987) Testicular toxicity following oral administration of tri-o-cresyl phosphate (TOCP) in roosters.

Tri-o-cresyl phosphate (TOCP) is a neurotoxic organophosphorus compound that induces a characteristic central-peripheral distal axonopathy and Wallerian-type degeneration, 6-14 days after exposure. This organophosphorus compound-induced delayed neurotoxicity (OPIDN) has been extensively studied in the chicken, the standard test model. Reports of neurotoxic agents causing adverse effects on the male reproductive system initiated the present study which was designed to examine the effects of TOCP on the rooster. Previous work from this laboratory has demonstrated 100 mg TOCP/kg/day to be an OPIDN-inducing dose with minimal mortality in roosters. This dose level was administered to adult leghorn roosters (p.o., n = 10) for 18 consecutive days. By days 7-10 of the study, TOCP-treated birds exhibited limb paralysis characteristic of OPIDN. Analysis at termination revealed significant inhibition of neurotoxic esterase activity (NTE) in both brain and testis. There was also a slight decrease in brain acetylcholinesterase (AChE) activity. Sperm motility was shown to be greatly decreased. In addition, sections of formalin-fixed, methacrylate-embedded testes from TOCP-treated birds showed vacuolation of, and disorganization in the seminiferous epithelium. The marginal body weight decreases (17%) in treated animals were not considered to contribute to the testicular toxicity induced by TOCP. Parathion (O,O-diethyl-O-4-nitrophenyl phosphorothioate, 0.1 mg/kg/day, p.o., n = 3) was used as a positive control for AChE inhibition and a negative control for inducing OPIDN. Roosters treated continuously with parathion showed a decrease in brain AChE activity, but no changes in NTE, testicular histology, or limb function. These studies demonstrate the testicular toxicity of TOCP in roosters and suggest that this effect is not related to the chemical's anticholinergic action.

(1987) Vocal cord dysfunction: the importance of psychologic factors and provocation challenge testing.
We present three case reports involving patients with vocal cord dysfunction. The onset of symptoms in one case was coincident with a generalized cutaneous reaction to penicillin with laryngeal involvement. The other cases had been misdiagnosed as food allergy and chemical sensitivity. We describe the psychologic factors in these cases in terms of the primary and secondary gain operative in the somatoform disorder of conversion reaction and emphasize the importance of belief and learned sensitivity in the induction of symptoms. The necessity of considering psychologic factors and the use of blinded, controlled, provocation challenges to evaluate subjective symptomatology is underscored. This study emphasizes the heterogeneity of clinical presentations involving vocal cord dysfunction and illustrates the value of fiberoptic-assisted examination of laryngeal function in conjunction with provocation challenge testing in establishing causal relationships for specific clinical symptoms.


Changes in the auditory nerve action potential (AP), evoked responses from the inferior colliculus (IC-ER) and auditory cortex (AC-ER) were assessed after exposure to white noise of 120 dB SPL for 1 h in awake guinea pigs. Auditory thresholds were estimated with the aid of averaged AP, IC-ER and AC-ER, besides the threshold shifts also the changes in amplitude-intensity functions were evaluated. Auditory thresholds for tone pips and clicks increased by 20-30 dB 1 h after exposure and were similar in all the three investigated structures. The maximum threshold shifts for tone pips were observed at 8 kHz and were 33.2 +/- 12.9 dB for AP, 30.4 +/- 12.7 dB for IC-ER and 30.8 +/- 13.0 dB for AC-ER (n = 20). The thresholds recovered to preexposure levels within one week. Reduction in AP and IC-ER amplitudes 1 h after exposure was similar, the amplitude-intensity functions were shifted by 20-40 dB. In contrast, the amplitude-intensity functions in the auditory cortex 1 h after exposure were steeper than before exposure and this amplitude enhancement was present for 24 h after exposure. The enhancement of the AC-ER which resembles recruitment and which may be a sign of hypersensitivity of the animal to auditory stimuli was present only when the animals exposed to noise were awake. The noise exposure in animals anaesthetized with urethane reduced the amplitude-intensity functions of all three recorded potentials.

In the coterminous United States, MS mortality rates demonstrate a north-south gradient, which is confirmed by more sophisticated--and more expensive--prevalence studies. Mortality rates from idiopathic Parkinson's disease show a similar north-south gradient, and they correlate significantly with the MS mortality and prevalence data. This demonstration that Parkinson's disease may be place-related provides support for the hypothesis that Parkinson's disease, like MS, is an acquired, environmental illness.


Treatment of MCS, an illness characterized by reaction to a multiplicity of factors coming from within the patient and from the social and physical environment, must incorporate multiple types of help, all directed toward supplying what these patients require. Medical, psychiatric, and social work treatment are all significant and all different, with overlap in several areas. As in all practice in the medical setting, the overall function of the social worker is to enable the MCS patient to make use of what the physician has to offer by supporting the patient's capacity to cope with the social and emotional impact of his/her illness.


Triethyllead chloride and 2,5-hexanediol are known neurotoxicants that apparently work through separate mechanisms. The effect of combined treatment of triethyllead
chloride and 2,5-hexanedione for 6 weeks on Fischer 344 rats was investigated. Ten rats were given 0.7 mg/kg triethyllead chloride in a volume of 2 ml/kg by gavage while another group was given 0.5% 2,5-hexanedione in drinking water and vehicle by gavage (2 ml/kg). A third group was given a combination of the two treatments. A fourth group served as controls and was given vehicle by gavage. 2,5-Hexanediode produced a reversible loss of body weight, decreased grip strength, and decreased horizontal motor activity. Triethyllead chloride alone increased hot-plate latencies. Triethyllead chloride and 2,5-hexanedione treated animals recovered 4 weeks after cessation of treatment. Neither treatment alone produced fatalities. In combination (2,5-hexanedione + triethyllead chloride) decreases in body weight appeared additive and there was a 40% mortality by 6 weeks of dosing. Rats given the combined treatment had significant loss of both grip strength and increased hot-plate latencies. Neurobehavioral deficits and neuropathological changes were greater in the combined treatment with 2,5-HD and TEL than when either chemical was used alone; there was little indication of a synergistic interaction between these two types of neurotoxicants.


The difficult task of managing patients with MCS requires a multidisciplinary effort involving the occupational medicine physician, social worker, occupational therapist, physical therapist, psychologist, vocational rehabilitation specialist, industrial hygienist, and other involved professionals. Important objectives of management include complete review of the history and clinical findings, appropriate choice of diagnostic tests, search for additional exposure information, emphasis of "well" behavior, health education of the patient and prevention of further illness. Because of the chronic nature of MCS and the difficulty many patients have in coping with MCS, pharmacologic and psychologic interventions should be considered. Interaction of the clinic with the patients employer, insurance carrier, or attorney must be carefully planned and communicated only after receiving the patient's informed consent. Patient education should include general principles of toxicology, industrial hygiene measures to reduce hazardous exposures, factors which may aggravate the illness, and resources available to obtain further information and assistance.

A simple, low-cost, fast method for the extraction and cleanup of DEF (S,S,S-tri-n-butyl phosphorotrithioate) from fish tissues and water samples was developed. The method combines extraction and cleanup in one step. The basis of the method is passing water samples or aqueous tissue homogenates containing DEF through a C-18 disposable cartridge. DEF is eluted from the cartridge by acetone or ethyl acetate. The eluates are analyzed by gas chromatography using a thermionic-specific detector. The method detects levels as low as 100 parts per trillion (ppt) in water samples; recovery efficiency from spiked fish tissues was greater than 95%. In addition, detectable levels of DEF were recovered from liver, brain, and muscle tissue of fish exposed to this compound. The method has a potential for use with other pesticides.


Patients with MCS show numerous physiological and biochemical abnormalities and are generally sicker than a control group of allergic patients. Associated with MCS are mitral valve prolapse, hypothyroidism, autoimmune thyroiditis, specific abnormalities of amino acid and essential fatty acid metabolism, and diminished activity of ESOD and EGPx. Equally prevalent among MCS patients and controls are deficiencies of magnesium and Vitamin B6. Since patients with MCS feel sick almost all of the time, it is likely that some of these abnormalities contribute to their general level of ill health, if not to their sensitivities. It is also possible that these various abnormalities are caused by some unidentified fundamental metabolic or neuroendocrine disturbance that is common to states of hypersensitivity. A provocative finding is the high frequency with which impaired anti-oxidant levels were detected. Erythrocyte activity of SOD was low in 89% and EGPx was low in 48% of MCS patients. Furthermore, 41% showed impaired excretion of essential amino acids, despite a high protein diet, and leucocyte vitamin C was low in the 5 patients not taking vitamin C supplements. Anti-oxidant deficiencies may certainly contribute to hypersensitivity to environmental pollutants and toxic chemicals. In fact, treatment with anti-oxidants, including selenium, vitamin C, copper, zinc, and sulfur-containing amino acids was associated with major clinical improvement in 14 (25%) of the patients in the MCS group and with limited relief of symptoms in another 10 (18%). In all patients in whom ESOD or EGPx were repeated, improvement in levels was observed following treatment. (ABSTRACT TRUNCATED AT 250 WORDS)


query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3313768

(1987) Multiple chemical sensitivities and other "environmental illness": a psychiatrist's view.

The clinical ecology subculture, like earlier medical subcultures, is the product of patient concerns that the medical establishment cannot allay by treatment or by reassurance. For social and behavioral scientists, it represents a "natural" experiment that can be studied. For those physicians who believe that clinical ecology is without scientific basis generally and/or that its practitioners interpret laboratory results incorrectly, it is a challenge and an irritant. The clinical ecologist-physician feels rejected and the victim of bias and unfair attack. The patient in this subculture feels that finally he has found someone who understands him and is trying to help him, but that he must pay the price of being disapproved or rejected by his former physicians.


The first article in this series discussed the importance of properly designed clinical trials to validate various diagnostic and therapeutic procedures and also described clinically accepted and proved tests. This article discusses other challenge tests and unproved procedures. The value of provocation-neutralization procedures has been controversial; two promising clinical models have been developed that may allow
definitive trials of efficacy. Immunotherapy with allergenic extracts has been shown to be a safe and effective procedure in carefully selected patients treated with potent, well-standardized antigens administered in adequate dosage. It has been proposed that many nonspecific signs or symptoms could be caused by exposure to Candida albicans or low-dose environmental substances. The cause-and-effect relationships between exposure to C albicans or other environmental substances and the disorders that are alleged to be associated with them are, for the most part, unproved.


Twenty-four Boran cattle were injected with isometamidium chloride (1 mg/kg bodyweight) to investigate the duration of drug-induced prophylaxis against infection by metacyclic forms of Trypanosoma congoense and to determine if specific antibody responses to the organism were mounted by animals under chemoprophylactic cover. Complete protection against either single challenge by five tsetse flies infected with T congoense, or repeated challenge at monthly intervals by five tsetse flies, lasted for five months. Six months after treatment, two-thirds of the cattle were resistant to challenge, irrespective of whether subjected to single or multiple challenge with trypanosome-infected tsetse flies, or titrated doses of in vitro-cultured metacyclic forms of T congoense (5 x 10^2 to 5 x 10^5 organisms), inoculated intradermally. No animal which resisted infection developed detectable skin reactions at the site of deposition of metacyclic trypanosomes or produced trypanosome-specific antibodies. It was concluded that drug residues effectively limited trypanosome multiplication at the site of deposition in the skin, thus preventing subsequent parasitaemia or priming of the host's immune response.


A review of 50 patients with a clinical ecology diagnosis of environmentally induced illness is reported. Histories were extremely heterogeneous. Eight patients had no symptoms or disease, 11 had symptoms caused by preexisting nonenvironmental disease, and 31 had multiple subjective symptoms. No consistent physical findings or laboratory abnormalities were found. Serum levels of immunoglobulins and complement, and circulating lymphocyte, B-cell, T-cell, and T-cell subset counts were not significantly abnormal. The diagnostic provocation-neutralization procedure, environmental restrictions, and dietary advice of clinical ecology produced further symptoms and fear of environmental and food contaminants. The patients with chronic multisystem complaints had characteristic symptoms of psychosomatic illness, but this study does not support the clinical ecology theory that psychosomatic illness may be an expression of food and chemical sensitivities induced by the toxic effect of environmental chemicals on the immune system.


The effect of a single oral administration of 750 mg/kg tri-o-cresyl phosphate (TOCP) on endogenous phosphorylation of specific brain cytosolic proteins has been studied in roosters following the development of delayed neurotoxicity. In vitro phosphorylation assay using [gamma-32P]ATP was carried out. Proteins were then resolved on one dimensional 8% SDS-PAGE and two-dimensional gel electrophoresis, stained with Coomassie blue and autoradiographed. The amount of proteins, as well as the amount of 32P incorporation, were quantified by microdensitometry. TOCP-administration enhanced the phosphorylation of cytosolic proteins of M, 52-59 kDa, 70 kDa, and 300 kDa by as much as 155%, 199% and 166%, respectively. Two-dimensional gel electrophoresis confirmed the 52-59 kDa proteins as alpha and beta tubulin and the 300 kDa protein as microtubule-associated protein-2.


The effect of a single 750-mg/kg oral dose of tri-o-cresyl phosphate (TOCP) on the endogenous phosphorylation of brain microtubule preparations and spinal cord neurofilaments was assessed in hens after the development of delayed neurotoxicity. Protein phosphorylation with [gamma-32P]ATP was analyzed by one-dimensional and
two-dimensional gel electrophoresis, autoradiography, and microdensitometry. TOCP treatment enhanced the Ca\(^{2+}\)- and calmodulin-dependent phosphorylation of tubulin in crude chicken brain cytosol (160\% for alpha-tubulin and 140\% for beta-tubulin) and cold-stable microtubules (165\% and 155\% for alpha- and beta-tubulin, respectively). Microtubule-associated protein 2 (MAP-2) phosphorylation was also increased in brain fractions studied--i.e., brain cytosol (145\%), cold-stable microtubules (133\%), and cold-labile microtubules (328\%). There was significant increase in phosphorylation of a 70-kDa protein in the brain cytosol and in the cold-stable microtubule fractions. TOCP also stimulated the phosphorylation of spinal cord proteins of 70 kDa (119\%) and 160 kDa (129\%) in a Mg\(^{2+}\)-dependent manner. Addition of Ca\(^{2+}\) and calmodulin further enhanced the phosphorylation of these 70-kDa (563\%) and 160-kDa (221\%) proteins as well as of 52-, 59-, and 210-kDa proteins by as much as 126\%, 160\%, and 196\%, respectively. Two-dimensional electrophoresis was carried out to identify these proteins. They were confirmed as alpha- and beta-tubulin (52 and 59 kDa) in brain and spinal cord preparations and the neurofilament triplet proteins (70, 160, and 210 kDa) in the spinal cord preparation. The 70-kDa protein in brain was not neurofilament in origin. Peptide mapping using Staphylococcus aureus V8 protease showed the brain and spinal cord cytoskeletal proteins have identical phosphopeptide patterns in control and TOCP-treated hens, indicating that it was unlikely that the phosphorylation sites were altered by TOCP treatment.


Few biological theories of manic-depressive illness have focused on the longitudinal course of affective dysfunction and the mechanisms underlying its often recurrent and progressive course. The authors discuss two models for the development of progressive behavioural dysfunction--behavioural sensitisation and electrophysiological kindling--as they provide clues to important clinical and biological variables relevant to sensitisation in affective illness. The role of environmental context and conditioning in mediating behavioural and biochemical aspects of this sensitisation is emphasised. The sensitisation models provide a conceptual approach to previously inexplicable clinical phenomena in the longitudinal course of affective illness and may provide a bridge between psychoanalytic/psychosocial and neurobiological formulations of manic-depressive illness.

Enhancement of endogenous kinase-dependent in vitro protein phosphorylation of subcellular fractions from brains and spinal cords of hens paralyzed 3 weeks after intoxication with tri-o-cresyl phosphate was correlated with the development of organophosphorus compound-induced delayed neurotoxicity (OPIDN). This was documented by showing: parallel dose-dependence curves for both responses, phosphorylation enhancement in proteins from hens treated with OPIDN-producing O-4-bromo-2,5-dichlorophenyl-O-methyl phenylphosphonothioates, but not in those treated with non-OPIDN-producing O,O-diethyl-O-4-nitrophenyl phosphorothioate or tri-p-cresyl phosphate, and shared age and species selectivities for both effects. These results strengthen our earlier observation of a close temporal relationship between protein phosphorylation enhancement and OPIDN. Further studies suggest that the proximate cause of the enhanced phosphorylation is not related to an alteration in protein phosphatase activity or to the preservation of a rate-limiting pool of [gamma-32P]ATP by adenosine triphosphatase inhibition. Therefore, it is most likely related either to altered protein kinase activity or amount (due to chemically originated physical disruption of the neuron). These data support the hypothesis that increased protein phosphorylation may be involved in the development of OPIDN.


Five metabolites of the industrial neurotoxic chemical tri-o-cresyl phosphate (TOCP) were synthesized and their structures were verified by infrared, IR; proton nuclear magnetic resonance, 1H-NMR; and mass spectrometry. The 2 acids, o-cresyl dihydrogen phosphate and di-o-cresyl hydrogen phosphate were prepared in 2 steps. Step 1, POCI3 was reacted with o-cresol, using 1:1 and 1:2 molar ratios, in the presence of anhydrous AlCl3 as a catalyst, to form the 2 intermediates o-cresyl phosphorodichloridate and di-o-cresyl phosphorochloridate, respectively. Step 2, the chloridate intermediates were hydrolyzed under the appropriate condition to the corresponding acids. These acids were further derivatized to the corresponding methyl ester and the products were analyzed by the spectroscopic techniques. Saligenin cyclic-o-tolyl phosphate [2-(o-cresyl)-4H-1:3:2-benzodioxaphosphoran-2-one] was synthesized by reacting the potassium salt of o-hydroxybenzyl alcohol with o-cresyl phosphorodichloridate. Hydroxymethyl TOCP [di-o-cresyl o-hydroxymethylphenyl phosphate] and dihydroxymethyl TOCP [o-cresyl di-o-hydroxymethylphenyl phosphate] were synthesized by reacting di-o-cresyl phosphorochloridate with the potassium salt of o-hydroxybenzyl alcohol. The products were separated and purified by repeated preparative thin-layer chromatography (TLC) using 3 different solvent systems. The
purity of the 5 metabolites, which was determined by high performance liquid chromatography (HPLC), ranged from 92% to 99%.


The metabolism of a single, dermal dose of 50 mg/kg of [14C]tri-o-cresyl phosphate (TOCP) was studied in male cats. TOCP was applied to an unprotected, preclipped area on the back of the neck. Three animals were sacrificed on each of 0.5, 1, 2, 5, and 10 days following application. Radioactivity disappeared biexponentially from the dosing site with a faster initial rate; 73% of the dose disappeared in the first 12 h followed by a slower phase with a half-life of 2.03 days. No radioactivity was detected in the expired air. TOCP was absorbed from the skin and subsequently distributed throughout the body. Generally, the highest concentrations of radioactivity were associated with bile, gall bladder, urinary bladder, kidneys, and liver; the lowest were found in the neural tissues, muscle, and spleen. Within the 10-day experimental period, approximately 28% and 20% of the applied dose were recovered in the urine and feces, respectively. TOCP and its metabolites in the urine, feces, bile, and plasma were analyzed by high performance liquid chromatography and liquid scintillation counting. TOCP was the predominant compound in the feces (26.3% of total fecal radioactivity); it was detected in a smaller percentage in the urine (2.3% of total urinary radioactivity). The major metabolite in the urine was o-cresol followed by di-o-cresyl hydrogen phosphate and o-cresyl dihydrogen phosphate; in the feces di-o-cresyl hydrogen phosphate was the predominant metabolite followed by o-cresyl dihydrogen phosphate. Trace amounts of saligenin cyclic-o-tolyl phosphate, hydroxymethyl, and di(hydroxymethyl) TOCP were also detected in the urine and feces. Other metabolites identified in the urine and feces were the stepwise oxidation products of the methyl group of o-cresol. Unlike the feces, the bile contained mostly metabolites with only trace amounts of TOCP detected at 12 h and 24 h following application. o-Cresyl dihydrogen phosphate and di-o-cresyl hydrogen phosphate were the prevalent metabolites in the bile and plasma. While di(hydroxymethyl) TOCP was present in trace amounts in plasma, an appreciable amount of saligenin cyclic-o-tolyl phosphate, believed to be the active neurotoxic metabolite, was detected. This study shows that skin is an important port of entry for TOCP. Since TOCP represents organophosphorous chemicals capable of producing delayed neurotoxicity in test animals and in humans, it is essential that industrial hygiene control prevents skin contamination of workers handling these chemicals.
(1986) Environmental illness.
Markovitz, A Journal/Arch Intern Med. 146: 1244.

---------------------------------------------------------------


Although organic solvents are essential components of an industrial economy, they are not used without risk. The relationship between excessive exposure to organic solvents and subsequent development of chronic encephalopathy has been recognized for nearly 100 years. Fifteen industrial painters who underwent evaluation in an occupational health clinic for symptoms that they related to their work were found to have a high prevalence of neurasthenic symptoms, most frequently, memory loss and personality change. Although neurologic and screening laboratory examinations showed no consistent abnormalities, psychological tests documented poor short-term memory and an array of neuropsychologic deficits. Personality profiles revealed depression, anxiety, and preoccupation with somatic concerns. These findings agree well with previous reports of "chronic painter's syndrome." Heightened awareness among industrial physicians and prospective studies to evaluate existing threshold limit values and personal protective equipment requirements are indicated.

---------------------------------------------------------------

(1986) Psychosocial precursors and correlates of migraine headache.

---------------------------------------------------------------


The aliphatic hexacarbons n-hexane, methyl-n-butyl ketone, and 2,5-hexanedione are known to produce a peripheral neuropathy that involves an accumulation of 10-nm neurofilaments above the nodes of Ranvier in the spinal cord and peripheral nerve. In this study, rats were treated with 0.5% 2,5-hexanedione in drinking water for 180 days, and their spinal cord neurofilaments were isolated after development of the
neuropathy. Visualization by sodium dodecyl sulfate-polyacrylamide gel electrophoresis revealed a significant reduction in content of the neurofilament triplet proteins in treated animals and the presence of bands migrating at 138K and 260K that were not present in control animals. Analysis of the lanes using immunoblotting procedures and anti-70K, anti-160K, and anti-210K neurofilament antibodies revealed many cross-linked peptides. The 138K band cross-reacted with the anti-160K neurofilament antibody. This suggests that the 138K band is an intramolecular cross-link of the 160K neurofilament subunit. In addition to this peptide, there were numerous high-molecular-weight peptides immunoreactive with all three neurofilament protein antibodies. In addition to cross-linking, there was also a diminished amount of immunoreactive breakdown product of all three neurofilament proteins. This report demonstrates direct evidence of 2,5-hexanedione-induced cross-linking of neurofilament proteins in vivo, which maybe responsible for the accumulation of neurofilament proteins pathognomonic of this neuropathy.

(1986) Regulation of tetrahydrobiopterin biosynthesis in cultured adrenal cortical tumor cells by adrenocorticotropin and adenosine 3',5'-cyclic monophosphat.
Duch, DS, Woolf, JH, Edelstein, MP, Viveros, OH, Abou-Donia, MA and Nichol, CA

Y-1 adrenal cortical tumor cells in culture, which contain substantial amounts of tetrahydrobiopterin [6R-(L-erythro-1',2'-dihydroxypropyl)5,6,7,8-tetrahydropterin] (BH4) and GTP cyclohydrolase (GTP-CH), were used to study the regulation of BH4 biosynthesis by ACTH and cAMP. ACTH produced a dose-dependent increase in steroidogenesis, BH4 levels and GTP-CH activity. Maximal stimulation of BH4 biosynthesis occurred at the same concentration of ACTH that caused maximal stimulation of steroidogenesis. ACTH-(1-24) was more potent than ACTH-(1-39). The stimulation of BH4 biosynthesis by ACTH was dependent on cell density, being greater at lower cell densities, but was independent of time in culture. The lack of stimulation by ACTH at higher cell densities was due to an increase in the specific activity of GTP-CH in the control cells as density increased. This increase may be due in part to the increased release of steroids, since exogenous steroids added to low density cultures also resulted in an increase in the specific activity of the enzyme. Addition of steroids had no effect on ACTH-dependent stimulation of BH4 biosynthesis at low cell densities. (Bu)2cAMP, 8-bromo-cAMP, and forskolin all produced time- and dose-dependent increases in BH4 levels, GTP-CH activity, and steroidogenesis. Maximum increases in GTP-CH and BH4 occurred at concentrations similar to those required for maximal stimulation of steroidogenesis. In the Kin-8 mutant of Y-1 cells, which has a type 1 cAMP-dependent protein kinase with an altered regulatory subunit, ACTH was unable to increase BH4 levels or GTP-CH activity at a concentration that produced maximal stimulation of BH4 and steroid biosynthesis in the parent Y-1 line.
These studies indicate that Y-1 cells in culture are useful for studying the regulation of BH4 biosynthesis in the adrenal cortex.


The toxicity to mice of intraperitoneally-administered polychlorocycloalkane (PCCA) insecticides is generally correlated with their potency as in vitro inhibitors of the brain specific [35S]t-butylbicyclophosphorothionate [(35S)TBPS] binding site with correction for metabolic activation and detoxification. These findings from our earlier studies are extended here to in vivo investigations relating convulsant action to inhibition of the TBPS binding site in poisoned mice. Radioligand binding assays involved brain P2 membranes washed three times with 1 mM EDTA to remove endogenous gamma-aminobutyric acid (GABA) or other modulator(s) which otherwise serves as a noncompetitive inhibitor of [35S]TBPS binding at the GABA-regulated chloride ionophore. Examination of lindane, technical toxaphene, toxaphene toxicant A, and 10 polychlorocyclodiene insecticides revealed 62 +/- 4% binding site inhibition 30 min after their LD50 doses with 32 +/- 3% inhibition at one-half and 6 +/- 3% inhibition at one-quarter of their LD50 doses. This correlation between binding site inhibition and convulsant action is also evident in dose- and time-dependency studies with endosulfan sulfate. The brain P2 membranes of treated mice contain the parent compound with each of the PCCAs plus activation products of some of the cyclodiienes, i.e. endosulfan sulfate from alpha- and beta-endosulfan and 12-ketoendrin from isodrin and endrin. The finding that the brains of treated mice contain sufficient PCCA or its activation products to achieve a magnitude of [35S]TBPS binding site inhibition correlated with the severity of the poisoning signs supports the hypothesis that the acute toxicity of PCCA insecticides to mammals is due to disruption of the GABA-regulated chloride ionophore.


For the purpose of assessing the neurotoxic potential of organophosphorus compounds, it has been determined that paraoxon-preinhibited hen brain has both neurotoxicant (mipafox)-sensitive (neurotoxic esterase; NTE) and -insensitive esterase components. Several experiments designed to investigate the kinetic parameters
governing the reaction of these esterases with two substrates and one organophosphorus inhibitor are presented. First, kinetic parameters for the hydrolysis of phenyl valerate and phenyl phenylacetate were measured. At 37 degrees C, the Km values of NTE for phenyl valerate and phenyl phenylacetate were found to be about $1.4 \times 10^{-3}$ and $1.6 \times 10^{-4}$ M respectively. At 25 degrees C, the Km of NTE for phenyl valerate was determined to be about $2.4 \times 10^{-3}$ M. Secondly, the kinetic constants of NTE for mipafox were measured at both 25 degrees C and 37 degrees C. With either phenyl valerate or phenyl phenylacetate as substrate, the Km at 37 degrees C was determined to be about $1.8 \times 10^{-4}$ M, and the phosphorylation constant ($k_2$) was about $1.1 \text{ min}^{-1}$. For phenyl valerate only, the Km at 25 degrees C was found to be about $6 \times 10^{-4}$ M, and the $k_2$ was about $0.7 \text{ min}^{-1}$. The data obtained at 25 degrees C were analysed by using a two-component model without formation of Michaelis complex, a two-component model with formation of Michaelis complex on the second component (NTE), or a three-component model without formation of Michaelis complex. The fact that the Michaelis model fit the data significantly better than either of the other two models indicates that the higher apparent Ki values that occur with low concentrations of mipafox are due to formation of Michaelis complex at high concentrations, rather than because of the presence of two NTE isoenzymes, as has been suggested by other investigators.

(1986) And it wasn't her fault anyway.


Human monitoring for toxic substances exposure in the workplace raises opportunities for occupational disease prevention but can also lead to possible undesirable and discriminatory consequences for workers. The scientific requisites for sound monitoring practices are discussed, and caution is urged against unjustified and unfair use of screening results.

(1986) Regulation of guanosine triphosphate cyclohydrolase and tetrahydrobiopterin levels and the role of the cofactor in tyrosine hydroxylation in primary cultures of adrenomedullary chromaffin cells.
Selective modification of the tetrahydrobiopterin levels in cultured chromaffin cells were followed by changes in the rate of tyrosine hydroxylation. Addition of sepiapterin, an intermediate on the salvage pathway for tetrahydrobiopterin synthesis, rapidly increased intracellular levels of tetrahydrobiopterin and elevated the rate of tyrosine hydroxylation in the intact cell. Tyrosine hydroxylation was also enhanced when tetrahydrobiopterin was directly added to the incubation medium of intact cells. When the cultured chromaffin cells were treated for 72 h with N-acetylserotonin, an inhibitor of sepiapterin reductase, tetrahydrobiopterin content and the rate of tyrosine hydroxylation were decreased. Addition of sepiapterin or N-acetylserotonin had no consistent effect on total extractable tyrosine hydroxylase activity or on catecholamine content in the cultured chromaffin cells. Three-day treatment of chromaffin cell cultures with compounds that increase levels of cyclic AMP (forskolin, cholera toxin, theophylline, dibutyryl- and 8-bromo cyclic AMP) increased total extractable tyrosine hydroxylase activity and GTP-cyclohydrolase, the rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin. Tetrahydrobiopterin levels and intact cell tyrosine hydroxylation were markedly increased after 8-bromo cyclic AMP. The increase in GTP-cyclohydrolase and tetrahydrobiopterin induced by 8-bromo cyclic AMP was blocked by the protein synthesis inhibitor cycloheximide. Agents that deplete cellular catecholamines (reserpine, tetrabenazine, and brocresine) increased both total tyrosine hydroxylase and GTP-cyclohydrolase activities, although treating the cultures with reserpine or tetrabenazine resulted in no change in cellular levels of cyclic AMP. Brocresine and tetrabenazine increased tetrahydrobiopterin levels, but the addition of reserpine to the cultures decreased catecholamine and tetrahydrobiopterin content and resulted in a decreased rate of intact cell tyrosine hydroxylation in spite of the increased activity of the total extractable enzyme. These data indicate that in cultured chromaffin cells GTP-cyclohydrolase activity like tyrosine hydroxylase activity is regulated by both cyclic AMP-dependent and cyclic AMP-independent mechanisms and that the intracellular level of tetrahydrobiopterin is one of the many factors that control the rate of tyrosine hydroxylation.


To investigate the cat as a test animal for organophosphorous compound-induced delayed neurotoxicity, tri-o-cresyl phosphate (TOCP) was applied directly on the unprotected back of the neck of young adult cats. Single dermal doses, ranging from 250 to 2000 mg/kg TOCP, or subchronic daily administration of 1 to 100 mg/kg produced delayed neurotoxic effects in the cat. Severity of delayed neurotoxicity
depended on the dose and duration. Clinical signs were characterized by hindlimb weakness, ataxia, and paresis. Electromyographic abnormalities resulting from acute denervation were observed in most cats that developed a neurologic deficit. No changes were seen in the motor nerve conduction, thus suggesting that the deficits were in the terminal branch rather than being diffuse lesions in the peripheral nerves. These results correlated well with histopathologic results showing lesions in the most distal portion of the longest tracts in both central and peripheral nervous systems. In the spinal cord, histopathologic studies showed that the ascending tracts of the upper cervical levels and descending tracts of the lumbosacral regions were affected most frequently. Although this study shows that the cat, like the chicken, is susceptible to TOCP-induced delayed neurotoxicity, it demonstrates two differences between the cat and the chicken: greater sensitivity of the cat to the acute effect of TOCP, and greater extent of recovery or improvement of the cat from delayed neurotoxicity. This recovery was demonstrated by: improvement of clinical signs, gain in body weight, disappearance of electromyographic abnormalities, and regeneration of peripheral nerves. Dermal administration of a single 100-mg/kg dose or subchronic 0.5-mg/kg doses of TOCP did not produce delayed neurotoxicity.

Abou-Donia, MB and Nomeir, AA Journal/Fundam Appl Toxicol. 6: 190-207.

Attempts have been made to review the role of pharmacokinetics and metabolism in species and age sensitivity as well as the development of various toxic conditions of some neurotoxic chemicals. The route of administration may play a prominent role in the development of various toxic effects of some organophosphorus compounds such as DEF. Such variation was attributed to the differential metabolism which was found to be highly dependent on the route of administration. It is obvious from the data presented here that animals that are sensitive to OPIDN are less active in the metabolism and elimination of the neurotoxic chemical and/or its metabolite(s). So, a compound may stay for a longer period in the body of the sensitive animals resulting in greater accessibility of target tissues to the deleterious effects of the neurotoxic compounds. However, many of these neurotoxic chemicals require metabolic activation to exert their effect. While the insensitive species may convert the compound to its active metabolite faster than that of the insensitive species, this is circumvented by the far greater capability of the insensitive animals to metabolize the active metabolite and or the parent compound to less toxic, more polar, excretable metabolites. However, it must be stressed that these studies are far from complete, and caution should be exercised in interpreting and correlating many of these results. It is difficult, and sometimes misleading to compare data from various studies due to differences in dosage, the number of animals used, route of administration, experimental protocols, etc. With respect to hexacarbons, species sensitivity is obvious, but not as extensively investigated as OPIDN. To our knowledge, no studies are available addressing species
difference in pharmacokinetics and metabolism of these chemicals. The data presented in this review suggest that metabolism and pharmacokinetics may play an important role in the development of OPIDN. However, this does not rule out the influence of other factors such as target sensitivity. This necessitates further qualitative and quantitative metabolic studies which are carefully planned to address these issues.

(1986) Brain acetylcholinesterase, acid phosphatase, and 2',3'-cyclic nucleotide-3'-phosphohydrolase and plasma butyrylcholinesterase activities in hens treated with a single dermal neurotoxic dose of S,S,S-tri-n-butyl phosphorothioate.

The changes in brain acetylcholinesterase (AChE), acid phosphatase (APase), and 2',3'-cyclic nucleotide-3'-phosphohydrolase (CNP), and plasma butyrylcholinesterase (BuChE) activities were investigated in hens treated with a single, dermal dose (100-1000 mg/kg) of S,S,S-tri-n-butyl phosphorothioate (DEF). Three control groups consisted of hens left untreated, given a single, dermal dose of 500 mg/kg tri-o-cresyl phosphate (TOCP, positive control for organophosphorous compound-induced delayed neurotoxicity), or 10 mg/kg O,O-diethyl O-4-nitrophenyl phosphorothioate (parathion, negative control). Brain AChE activity, determined 28 days after application, was significantly inhibited in hens given 500-1,000 mg/kg DEF and in TOCP- and parathion-treated hens. In contrast, brain APase and CNP activities were significantly higher in all treatments as compared with those of the untreated hens. Parathion, however, caused the least increase in these enzymatic activities as compared to DEF or TOCP. A single, dermal dose of DEF or TOCP also caused an initial decrease in plasma BuChE activity with maximum depression of enzymatic activity observed 1 to 7 days after administration. This decrease was dose dependent and the enzymatic activity showed partial recovery with time. Hens treated with single, dermal doses of DEF, ranging from 250 to 1000 mg/kg, developed ataxia which progressed to paralysis in some hens. Histopathologic examination revealed axon and myelin degeneration of the spinal cord and peripheral nerves of some hens. The severity and frequency of the neuropathologic lesions were dose dependent. Neurologic dysfunctions and neuropathologic lesions seen in DEF-treated hens were similar to those exhibited in TOCP-treated hens. While parathion produced acute cholinergic effects, it did not cause delayed neurotoxicity. The changes in brain and plasma enzymes are discussed in relation to their role in the pathogenesis of DEF-induced delayed neurotoxicity.

(1986) Environmental illness and patients with multiple unexplained symptoms.
Journal/Arch Intern Med. 146: 1447-8, 1450.
(1985) Allergy practice in California. Diagnostic and therapeutic methods used by allergists and otolaryngologists.

Terr, AI. Journal/Clin Rev Allergy. 3: 3-23.


The purpose of this article is to encourage allergists to expand their interest in environmental intolerance to include chemicals found in everyday exposure. By incorporating controlled challenge procedures into outpatient practice capabilities, the practicing allergist can expand both clinical interest and practice potential. By merging scientific principles of toxicology and psychology with the traditional investigative skills of the well-trained clinical allergist, we believe that discipline of allergy/immunology can realize a rather remarkable new dimension.


Natural killer (NK) activity of human mononuclear cells is sensitive to inhibition by radiation, under the control of polymorphic X linked genes. In order to define the mechanism of this inhibition, we have evaluated the ability of treatments known to damage DNA to inhibit NK activity. The alkylating agents streptozotocin (SZ) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were potent inhibitors of NK activity. Further, a specific competitive inhibitor of adenosine diphosphoribosyl polymerase (ADPRP), 3-aminobenzamide, was able to prevent inhibition by gamma-radiation, UV
radiation, and the two alkylating drugs, SZ and MNNG, suggesting the ADPRP, known to be activated by DNA strand breakage, mediates the inhibition by these treatments. NK activity of radioresistant subjects was somewhat more resistant to inhibition by SZ or UVR when compared to radiosensitive NK activity but neither of these treatments gave the clear phenotypic distinction of gamma-radiation, suggesting that chemical strand breakage does not precisely model gamma-radiation and also that the mechanism of UVR inhibition may differ from that of gamma-radiation. These results indicate a role for activation of ADPRP in the inhibitory effect of UV and gamma-radiation on human NK activity and suggest that the biochemical basis for polymorphism in the sensitivity of NK activity to gamma-radiation will be found in the sensitivity to ADPRP activation or the level of activation of this enzyme, known to be the key to DNA repair.


The effect of a single oral 750 mg/kg dose of tri-o-cresyl phosphate (TOCP) on the endogenous phosphorylation of brain and spinal cord proteins was assessed in hens during the development of and recovery from delayed neurotoxicity. Crude membrane and cytosolic fractions were prepared from the brains and spinal cords of control and TOCP-treated hens at 1, 7, 14, 21, 35, and 55 days after treatment. Brain and spinal cord protein phosphorylation with [gamma-32P]ATP was analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), autoradiography, and microdensitometry. TOCP administration conferred calcium and calmodulin dependence on the phosphorylation of a few brain cytosolic proteins and caused an increase in the phosphorylation of a number of other cytosolic and membrane proteins. This effect of TOCP was large in magnitude, and its time course reflected the onset of and recovery from the signs of ataxia and paralysis associated with delayed neurotoxicity in the hen. The molecular weights (Mr) and maximal phosphorylation (percent of control) for the most prominently affected bands were as follows: brain cytosol--50K (183%), 55K (575%), 60K (529%), 65K (273%), and 70K (548%); brain membranes--50K (622%) and 60K (697%); and spinal cord cytosol--20K (182%). The role of endogenous phosphorylation reactions in and their potential usefulness as biochemical indicators of delayed neurotoxicity are being explored further.

The optimal conditions for endogenous protein phosphorylation with 5 microM [gamma-32P]ATP, 10 mM MgCl2 in preparations containing synaptosomal cytosol or membranes (shocked crude mitochondrial fraction P2) from adult hen brains were determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, autoradiography and microdensitometry. Phosphate incorporation increased linearly with protein concentration from 75-125 micrograms/200 microliters in brain cytosol and was maximal at 75 micrograms/200 microliters in brain membranes. Optimal incubation times were 60-90 s for brain cytosol and 10-15 s for brain membranes. With the exception of the 20 kilodalton myelin basic protein in the membrane fraction, pH 6.5 is generally optimal. While temperature optima varied considerably with different bands, most of them were found between 35 and 45 degrees C. When identical preparations from hen and rat brain were co-electrophoresed, one of the most striking differences was that the enhancement of phosphorylation of a 55 kilodalton doublet, which may be tubulin, by addition of 50 microM Ca2+ was at least 3 times greater in rat than in hen brain cytosol. Another species difference was apparent in the membrane fractions in which the 20 kilodalton hen brain presumptive myelin basic protein (MBP) was phosphorylated to approximately the same extent as that of the 16 and 20 kilodalton rat brain MBPs combined.


Analytical methods, using capillary gas chromatography and normal-phase high-performance liquid chromatography, were developed for the analysis of the neurotoxic chemicals n-hexane, 2-hexanone, and 2,5-hexanedione and their suspected metabolites. Two gas chromatographic methods, using a 50-m glass capillary OV 101 column and cyclohexane as an internal standard, were employed. In both methods, the injector and detector temperatures were 220 and 280 degrees C, respectively. In method I the following temperature program was used: isothermic at 50 degrees C for 30 min, followed by a temperature increase of 10 degrees C/min to a final temperature of 180 degrees C, which was then maintained for 7 min. This method was used to analyze the following compounds: n-hexane, 2,5-dimethylfuran, 2-hexanone, 3-hexanone, hexanal, 1-hexanol, 2-hexanol, 3-hexanol, 5-hydroxy-2-hexanone, gamma-valerolactone, 2,5-hexanedione, and 2,5-hexanediol. Method II, which was developed for n-hexane and eight of its more common metabolites, used the following temperature program: isothermic at 70 degrees C for 15 min, followed by a temperature increase of 40 degrees C/min to a final temperature of 220 degrees C, which was maintained for 5 min. A linear relationship between peak area and amount injected was observed over a 100-fold range. The minimum detectable amounts ranged from 0.05 to 1 microgram, depending on the compound.
Normal-phase HPLC, using a 5-micron silica cartridge fitted into an RCM-100 radial-compression separation system, was utilized to analyze 2-hexanone and its metabolites 2,5-dimethylfuran, gamma-valerolactone, 5-hydroxy-2-hexanone, and 2,5-hexanedione. (ABSTRACT TRUNCATED AT 250 WORDS)


The sensitivity of the mouse to organophosphorus-induced delayed neurotoxicity (OPIDN) has been investigated. One group of five mice received two single 1000-mg kg po doses of tri-o-cresyl phosphate (TOCP) at a 21-day interval (on Days 1 and 21 of the study); a second group of five mice was given 225 mg/kg of TOCP daily for 270 days. A third group of five animals served as an untreated control. All animals were killed 270 days after the start of the experiment. Daily po dosing of 225 mg/kg TOCP caused a decrease in body weight gain, muscle wasting, weakness, and ataxia which progressed to severe hindlimb paralysis at termination. On the other hand, po administration of two single 1000-mg/kg doses of TOCP at a 21-day interval produced no observable adverse effects. Brain acetylcholinesterase (AChE) and neurotoxic esterase (NTE) activity were 35 and 10% of the control, respectively, in daily dosed animals while AChE and NTE in mice receiving two single 1000-mg/kg doses of TOCP were not significantly altered from the control group. Plasma butyrylcholinesterase activity was 12% of the control group in daily dosed animals. Hepatic microsomal enzyme activities of aniline hydroxylase and p-chloro-N-methylaniline demethylase and NADPH-cytochrome P-450 content in daily dosed animals were increased (141 to 161% of the control group) when compared to controls and mice receiving two single 1000-mg/kg doses of TOCP; the latter being not significantly different from each other. Degeneration of the axon and myelin of the spinal cord and sciatic fascicle were observed and were consistent with OPIDN. This study demonstrates that chronic dosing of TOCP produces OPIDN and induces hepatic microsomal enzyme activity in mice. It is concluded that while the mouse is susceptible to OPIDN, it is a less sensitive and a less appropriate test animal for studying this effect when compared to the adult hen.

(1985) Stimulation of retinal dopamine biosynthesis in vivo by exogenous tetrahydrobiopterin: relationship to tyrosine hydroxylase activation.
Intravitreal injection of tetrahydrobiopterin (BH4), the cofactor for tyrosine hydroxylase (TH), increases 3,4-dihydroxyphenylalanine (DOPA) accumulation in retinas of dark-adapted rats, as does exposure to light. In contrast, BH4 had no significant effect on DOPA accumulation in retinas of light-exposed rats. The levels of endogenous retinal BH4 and the uptake of injected BH4 into the retinal tissue were not affected by light exposure. These data indicate that TH is not saturated with endogenous BH4 in the retinas of dark-adapted rats. In addition, the observations support the interpretation that the decrease in apparent Km of TH for the cofactor in response to light exposure is of sufficient magnitude to allow near saturation of TH by endogenous BH4 and, thus, is causally related to the increase of dopamine biosynthesis in response to short-term photic stimulation.


Each of three young-adult female cats with normal hearing received a total of eight permanent electrodes which were implanted bilaterally in cochlear nucleus (CN) and inferior colliculus (IC). Three experiments were performed using behaviorally measured thresholds for electrical stimulation of CN and IC. In Expt. 1, electrical stimulation thresholds (in dB re 1.0 microA) were obtained in the presence of a continuous tone of moderate intensity and in quiet. In comparison with quiet, electrical stimulation thresholds measured during tone were lower by as much as 15 dB (stimulation hypersensitivity). In Expt. 2, a brief exposure to an intense sound produced a temporary threshold shift (TTS) for acoustic stimuli but only produced small changes in electrical stimulation threshold. The acoustic stimuli used in Expts. 1 and 2 were termed noninjurious since no permanent hearing loss was produced. Expt. 3 employed an exposure to a white noise that resulted in a mean permanent threshold shift (PTS) of 34.1 dB for acoustic stimulation. The PTS was accompanied by a mean stimulation hypersensitivity of 9.6 dB. Comparing Expts. 1 and 3, it was shown that the transient hypersensitivity produced by the noninjurious continuous tone correlated strongly with the permanent hypersensitivity that was produced by the PTS. In regard to the origin of stimulation hypersensitivity, the suggestion is made that it is an indication of a physiological change localizable perhaps in the auditory nuclei of the upper brainstem.

The target size of neurotoxic esterase (NTE), the putative target site for the initiation of organophosphorus-compound-induced delayed neurotoxicity, and acetylcholinesterase (AChE) from hen brain were examined by determining the rate at which the activities of the esterases were destroyed by ionizing irradiation. Samples of hen brain were prepared by slowly drying a microsomal preparation under vacuum. The dried samples were then irradiated with electrons from a 1 MeV Van de Graaff generator. The doses ranged from 0 to 28 Mrad. The radiation doses were calibrated by the rate of inactivation of T1-bacteriophage plaque induction. Following the irradiation procedure, the samples were resuspended in buffer and enzymic activity was measured. The target size of NTE from hen brain was determined to be about 105 kDa, whereas hen brain AChE was found to have a target size of about 53 kDa. The target size of NTE was found to be similar in experiments with rat brain and cat brain. In addition, commercial preparations of electric-eel electric-organ AChE and horse serum butyrylcholinesterase were found to have target sizes that were identical with each other, and also were very similar to that of AChE from hen brain.


We have recently found that there is a proximo-distal delay in the recovery of neurotoxic esterase (NTE) following inhibition along the sciatic nerve of the hen. To determine whether this delay could be due to a requirement for the transport of newly synthesized NTE from the cell body, we investigated the transport of NTE by measuring the rate of accumulation of activity at either one or two ligations. Although rapid turnaround of accumulated protein confounds calculation of the transport rate, it appeared that NTE is transported down the hen sciatic nerve at a rate close to 300 mm day. Acetylcholinesterase (AChE) was found to be transported at a rate of about 500 mm/day, which is close to the expected rate of fast axoplasmic transport in the chicken. The relatively rapid turnaround of NTE compared with the retrograde transport rate precluded the estimation of a retrograde transport rate. A model is presented that accounts for turnaround as a result of exchange between mobile and stationary transport pools. Exchange of NTE between pools may account for the rapid turnaround described in this paper and for the proximo-distal delay in recovery as a dilution of newly synthesized NTE in the anterograde fast transport pool by inhibited protein as it travels down the nerve.

The experiments described in this paper were designed to isolate [3H]di-isopropyl phosphorofluoridate-binding proteins by sodium dodecyl sulphate/polyacrylamide-gel electrophoresis for the purpose of characterizing and identifying potential initiation sites for organophosphorus-compound-induced delayed neurotoxicity. The major Paraoxon-insensitive Mipafox-sensitive binding protein (Mr 160 000) was found to be identical with one previously identified as neurotoxic esterase, an enzyme that has been proposed to be the target site for organophosphorus-compound-induced delayed neurotoxicity. However, two other binding proteins with suitable binding characteristics were also found in smaller amounts, one of which has not been detected previously. Di-isopropyl phosphorofluoridate was found to phosphorylate all three of these proteins at rates similar to the rate at which neurotoxic esterase is inhibited by di-isopropyl phosphorofluoridate. Varying the concentration of di-isopropyl phosphorofluoridate or the time of incubation produced similar increases in binding to each of the labelled proteins. This suggests that the reaction rates of di-isopropyl phosphorofluoridate with proteins may be described by first-order kinetics, and the concentration of the Michael is complex formed during binding is minimal for all the phosphorylated proteins. The recovery of the binding activity in the 160 000-Mr band was found to be similar to the recovery of neurotoxic esterase activity, lending further support to the contention that this band is identical with neurotoxic esterase.


It has recently been reported that two paraoxon-insensitive carboxylesterases may be distinguished by their sensitivity to mipafox. However, we have not been able to reliably detect two components under the conditions of the widely used assay for neurotoxic esterase (NTE). We have determined that this discrepancy is a result of differences in the technique of preinhibition by paraoxon and mipafox. We report here that paraoxon is apparently able to reduce the rate of inhibition of both neurotoxic esterase isozymes by mipafox in a concentration-dependent manner. As a result, the rate of inhibition of NTE by mipafox is greater when sequential, rather than concurrent, preinhibition is utilized. An apparently greater reduction in the inhibition rate of the more sensitive minor component may make the two isozyme species indistinguishable in the presence of paraoxon at concentrations at or above 40 microM.

(1985) Pattern of neurotoxicity of n-hexane, methyl n-butyl ketone, 2,5-hexanediol, and 2,5-hexanedione alone and in combination with O-ethyl O-4-nitrophenyl phenylphosphonothioate in hens.
This investigation was designed to study the neurotoxicity produced in hens by the aliphatic hexacarbons n-hexane, methyl n-butyl ketone (MnBK), 2,5-hexanediol (2,5-HDOH), and 2,5-hexanedione (2,5-HD) following daily dermal application of each chemical alone and in combination with O-ethyl O-4-nitrophenyl phenylphosphonothioate (EPN). Dermal application was carried out on the unprotected back of the neck. To assess whether the joint neurotoxic action of various chemicals is caused by the enhancement of absorption through the skin or by interaction at the molecular level, two additional experiments were performed. In the first experiment, EPN was dissolved in each of the aliphatic hydrocarbons prior to their topical application. In the second experiment, EPN was dissolved in acetone and applied at a different location from that of the aliphatic hexacarbons. Dermal application was carried out for 90 d followed by a 30-d observation period. The results show that hens treated with EPN developed severe ataxia followed by improvement during the observation period; n-hexane produced leg weakness with subsequent recovery, whereas the same dose of MnBK, 2,5-HDOH, or 2,5-HD produced clinical signs of neurotoxicity characterized by gross ataxia; concurrent dermal application of EPN with n-hexane or 2,5-HDOH at the same site or at different sites produced an additive neurotoxic action; simultaneous dermal application of EPN and MnBK at different sites resulted in an additive effect, whereas it caused potentiation when applied at the same site; and concurrent topical application of EPN and 2,5-HD produced a potentiating neurotoxic effect. While no histopathologic lesion was produced at the end of the observation period when any test chemical was applied alone, binary treatments of EPN and aliphatic hexacarbons resulted in histopathologic changes in some hens, with morphology and distribution characteristic of EPN neurotoxicity. The joint potentiating or additive action of aliphatic hexacarbons on EPN neurotoxicity was: 2,5-HD greater than MnBK greater than 2,5-HDOH greater than n-hexane. The mechanism of this joint action seems to be related both to enhancing skin absorption of EPN and/or its metabolic activation by n-hexane and its related chemicals.

(1985) The synergism of n-hexane-induced neurotoxicity by methyl isobutyl ketone following subchronic (90 days) inhalation in hens: induction of hepatic microsomal cytochrome P-450.

The effect of methyl isobutyl ketone (MiBK) on n-hexane-induced neurotoxicity was investigated via inhalation in seven groups of five hens each for 90 days followed by a 30-day observation period. One group was exposed to vapors containing 1000 ppm n-hexane and another group to vapors having 1000 ppm MiBK. Four groups were exposed simultaneously to 1000 ppm of n-hexane and 100, 250, 500, or 1000 ppm
MCS Scientific Studies Library.enl Page 1049

MiBK. Another group was exposed similarly to ambient air in an exposure chamber and used as a control. Hens continuously exposed to 1000 ppm MiBK developed leg weakness with subsequent recovery, while inhalation of the same concentration of n-hexane produced mild ataxia. Hens exposed to mixtures of n-hexane and MiBK developed clinical signs of neurotoxicity, the severity of which depended on the MiBK concentration. Thus, all hens exposed to 1000 ppm n-hexane in combination with 250, 500, or 1000 ppm MiBK progressed to paralysis. Hens continuously exposed to 1000 ppm n-hexane/MiBK showed severe ataxia which did not change during the observation period. The neurologic dysfunction in hens exposed simultaneously to n-hexane and MiBK was accompanied by large swollen axons and degeneration of the axon and myelin of the spinal cord and peripheral nerves. The results indicate that the nonneurotoxic chemical MiBK synergized the neurotoxic action of the weak neurotoxicant n-hexane since the coneurotoxicity coefficient for joint exposure was more than two times the additive effect of each treatment alone. In another experiment, to investigate the mechanism of MiBK synergism of n-hexane neurotoxicity, continuous inhalation for 50 days of 1000 ppm n-hexane had no effect on hen hepatic microsomal enzymes, whereas inhalation of 1000 ppm MiBK for 50 days or a mixture of 1000 ppm of each of n-hexane and MiBK for 30 days significantly induced aniline hydroxylase activity and cytochrome P-450 contents in hen liver microsomes. Liver microsomal proteins from these hens and from hens treated with beta-naphthoflavone (beta-NF) and phenobarbital (PB) were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. While beta-NF increased the 55-kDa band (1408%), PB, MiBK, and MiBK/n-hexane increased the protein band (49 kDa) (258, 335, and 253%, respectively), indicating that MiBK induces chicken hepatic cytochrome P-450. The results suggest that the synergistic action of MiBK on n-hexane neurotoxicity may be related to its ability to induce liver microsomal cytochrome P-450, resulting in increased metabolic activation of n-hexane to more potent neurotoxic metabolites.


The neurotoxic action of inhaled technical grade methyl butyl ketone and dermally applied (O-ethyl O-4-nitrophenyl phenylphosphonothioate (EPN) was studied. Three groups of five hens each were treated 5 days/week for 90 days with a dermal dose of 1.0 mg/kg of EPN (85%) on the unprotected back of the neck. These groups were exposed simultaneously to 10, 50, or 100 ppm of technical methyl butyl ketone (MBK; methyl n-butyl ketone:methyl isobutyl ketone, 7:3) in inhalation chambers. A fourth group was treated only with the dose of EPN and a fifth group with only 100 ppm MBK. The control consisted of a group of five hens treated with a dose of 0.1 ml acetone. Treatment was followed by a 30-day observation period. Simultaneous exposure to
EPN and MBK greatly enhanced the neurotoxicity produced when compared to the neurotoxicity produced by either chemical when applied alone. Continued exposure to EPN and MBK resulted in earlier onset and more severe signs of neurotoxicity than exposure to either individual compound. The severity and characteristics of histopathologic lesions in hens given the same daily dermal dose of EPN in combination with inhaled MBK depended on the MBK concentration. Histopathologic changes were more severe and prevalent in the 100 ppm MBK:1 mg/kg EPN group than in the others. In this group, Wallerian-type degeneration was seen along with paranodal axonal swellings. The morphology and distribution of these lesions were characteristic of those induced by MBK. In the 50 ppm MBK:1 mg/kg EPN group axonal swelling was evident but not clearly identifiable as paranodal. Hens treated with 10 ppm MBK:1 mg/kg EPN had minimal lesions with low incidence of axonal swellings. These were not as large as those seen in MBK neurotoxicity, but instead resembled the histopathologic lesions caused by EPN. The results indicate that the combined treatment gave a value for neurotoxicity coefficient which was two times the additive neurotoxic effect of each treatment alone. Pretreatment with three daily ip doses of 5 mmol/kg technical grade MBK or methyl n-butyl ketone (MnBK), equally increased chicken hepatic microsomal cytochrome P-450 content. Also, hepatic microsomes from MBK-treated hens metabolized [14C]EPN in vitro to [14C]EPN oxon to a much greater extent than those from control hens. These results suggest that MBK potentiates the neurotoxic effect of EPN, at least in part, by increasing the metabolic activation of EPN to the more neurotoxic metabolite EPN oxon. (ABSTRACT TRUNCATED AT 400 WORDS)


The authors report three cases in which clonazepam controlled the acute symptoms in one manic and two schizoaffective patients. Clonazepam treatment led to a decrease in agitation and logorrhea, without the side effects associated with neuroleptics.


Twenty subjects underwent a double-blind evaluation by analyzing six variables to determine if subcutaneous injection of the food extract neutralizing dose would protect subjects from reactions. Twelve subjects had four of the six variables neutralized 60% of the time following the food antigen neutralizing dose. The placebo trials neutralized
four of six variables 15% of the time. The sign/symptom results show statistical significance favoring food extract neutralization over placebo. The remaining eight subjects had at least two of the six variables neutralized by the food extract up to 85% of the time. It appears that the phenomenon of subcutaneous food neutralization can be scientifically endorsed for clinical use in the treatment of food reactions.


The disposition and metabolism of a single dermal dose of 50 mg (5.8 muCi)/kg of tri-o-cresyl [phenyl-U-14C]phosphate (TOCP) were investigated in adult male cats. TOCP was applied on a preclipped area on the back of the animals neck. Three treated cats were sacrificed at each time interval 0.5, 1, 2, 5, and 10 days following application. Plasma, brain, spinal cord, sciatic nerve, liver, kidneys, and lungs were extracted and analyzed for TOCP and its various metabolites by high performance liquid chromatography and liquid scintillation counting. TOCP reached its highest concentration in plasma at 12 hr, while its metabolites attained their maximum concentration levels between 24 and 48 hr after dosing. The disappearance of TOCP from the plasma followed a monoexponential kinetics with a half-life of 1.2 days. Di-o-cresyl hydrogen phosphate and o-cresyl dihydrogen phosphate were the major metabolites in the plasma while dihydroxymethyl TOCP was present in trace amounts. Appreciable concentrations of saligenin cyclic-o-tolyl phosphate, which is believed to be the active neurotoxic metabolite, were detected in the plasma at all time points. TOCP was the predominant compound in the brain, spinal cord, and sciatic nerve, while the liver, kidneys, and lungs contained mostly metabolites. The major metabolite identified in the liver, kidneys, and lungs was o-hydroxybenzoic acid (salicylic acid) followed by di-o-cresyl hydrogen phosphate whereas di-o-cresyl hydrogen phosphate and o-cresyl dihydrogen phosphate were the most abundant metabolites in the brain, spinal cord, and sciatic nerve. (ABSTRACT TRUNCATED AT 250 WORDS)

Liberman, MC and Dodds, LW Journal/Hear Res. 16: 55-74.

Tuning curves were obtained from 100 to 150 auditory-nerve fibers spanning the range of characteristic frequencies (CFs) in each of eight cases of permanent noise-induced and three cases of permanent kanamycin-induced threshold shift. In each ear, from one to six neurons were intracellularly labeled with horseradish peroxidase. Locating the labeled terminals in plastic-embedded surface preparations of the cochlea enabled
us to accurately correlate particular tuning-curve abnormalities with the condition of the sensory cells generating them. The correlations between structural and functional changes suggest that a normal tuning-curve tip requires that the stereocilia on both the IHCs and OHCs (especially those from the first row) be normal. Selective damage to the OHCs is associated with elevation of the tips and hypersensitivity of the tuning-curve tails. This tuning-curve pattern also originates from cochlear regions at the basal border of hair cell lesions where the local hair cells (and their stereocilia) appear completely normal at the light-microscopic level. Total destruction of the OHCs in a region in which the IHCs appear normal (as can happen in cases of kanamycin poisoning) is associated with bowl-shaped tuning curves which appear to lack a tip. Combined damage to the IHCs and OHCs (as typically happens in cases of acoustic trauma) is invariably associated with elevation of both tips and tails on the tuning curve. A framework for the interpretation of the results is suggested in which the activity of the OHCs is transmitted via the tectorial membrane to the tall row of stereocilia on the IHCs.


The differential effects of oral and dermal administration of single doses of 100 to 1000 mg/kg S,S,S-tri-n-butyl phosphorotrithioate (DEF) on nonspecific esterases and liver metabolism enzymes were investigated one day following administration. O,O-Diethyl O-(4-nitrophenyl) phosphorothioate (parathion) and tri-o-cresyl phosphate (TOCP) were used as negative and positive controls for organophosphorus-induced delayed neurotoxicity (OPIDN). Brain acetylcholinesterase was significantly inhibited with topical doses of 500 and 1,000 mg/kg of DEF and with orally and dermally applied parathion. Plasma cholinesterase and liver microsomal carboxylesterase activities were significantly reduced from control in all treatment groups. Neurotoxic esterase (NTE) was significantly decreased from control with topical dosing of 200, 500, and 1000 mg kg DEF and with TOCP treatments. Oral doses of DEF increased cytochrome P-450 content by 70 to 200% while dermal application caused a 200 to 325% increase over control. p-Chloro-N-methylaniline demethylase was also increased by DEF treatments but to a lesser extent than that of aniline hydroxylase or cytochrome P-450 content. TOCP and parathion had no significant effect on liver microsomal oxidative enzymes. Liver microsomal proteins from hens treated with phenobarbital (PB), 3-methylcholanthrene (3MC), or DEF were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. A striking increase in a 49K protein band in microsomes from PB and DEF (616 and 338%, respectively) treated hens was seen, while the 55K protein band showed an 861% increase in microsomes from 3MC-treated hens. In conclusion, dermally applied DEF was more effective in inhibiting
esterases and inducing cytochrome P-450 than orally administered DEF; toxicity was directly related to the dose and route of administration.

----------------------------------------------------------------------


----------------------------------------------------------------------


The purpose of the study was to determine if permanent, sound-induced hearing loss altered behaviorally measured thresholds for the detection of electrical stimulation applied to auditory nuclei. Electrodes were placed in cochlear nucleus and inferior colliculus in four cats. Behaviorally measured thresholds for the detection of brief trains of electrical pulses were determined before and after a 48 h exposure to a 1 kHz tone of approximately 110 dB SPL. The mean decrease in electrical stimulation threshold as a result of the sound exposure was 10.4 dB. The ongoing electrical activity (in microV, rms) recorded from the electrodes showed a mean 2.2 dB decrease after the sound exposure. In some electrodes, there was partial recovery towards pre-exposure levels for stimulation threshold and for ongoing activity, but typically, the changes persisted until the animals were terminated 30 days later. The magnitudes of the decreases in stimulation threshold and background activity proved not to be highly correlated. The permanent auditory threshold shift across all cats and all frequencies was 19 dB. This mild hearing loss produced a marked alteration in certain characteristics of the central auditory mechanisms.

----------------------------------------------------------------------


Neurotoxic esterase (NTE) has been proposed to be the initiation site of organophosphorus compound-induced delayed neurotoxicity (OPIDN). There are two apparent problems associated with this hypothesis: NTE activity in the brain returns to
nearly normal levels before the onset of the neuropathy, and NTE is present in and inhibited by organophosphorus compounds in young animals and other species which are relatively insensitive to the neurotoxic effects of these compounds. This paper presents data suggesting that differences in the recovery rates of NTE activity may account for some of these discrepancies. First, the onset of recovery of NTE activity following sc administration of 1.7 mg/kg of O,O-diisopropylphosphorofluoridate (DFP) in the hen sciatic nerve occurred several days later than in the brain. Furthermore, recovery was slower in distal than proximal parts of the nerve. This information indicates that NTE activity is depressed for a longer period at the site of the neuropathy than it would appear from the measurement of NTE activity in brain. Second, the rate of recovery of NTE activity was faster in the brains of chicks, of rats, and of hens treated with a daily po dose of 15 mg/kg cortisone acetate than it was in untreated hens. However, there was no significant increase in the NTE recovery rate in the peripheral nerves of the chicks or the cortisone-treated hens. Thus, it appears that although slower distal recovery could account for the greater sensitivity of longer axons to OPIDN, other factors are operating in chicks and cortisone-treated hens.

Ali, SF, Abou-Donia, MB and Bondy, SC Journal/Neurochem Pathol.  2:  267-75.

A systematic survey of a series of high affinity binding sites in the forebrain of hens treated with a neurotoxic organophosphate has been carried out. Fourteen month old laying hens were treated with 750 mg/kg body weight triorthocresyl phosphate (TOCP) orally in gelatin capsules. Control birds received empty capsules. After 21 d, hens were killed and forebrain membrane fractions prepared for binding studies using the nitrocellulose filtration method. Incubations were carried out in the presence of low concentrations of pharmacological agents selective for certain classes of receptor sites. Nonspecific binding was characterized by simultaneous incubations in the presence of excess competing unlabeled ligands. Binding criteria that were satisfied in a prior study included specificity, saturability, and attainment of equilibrium during incubation. No significant change was found in treated hens assayed for dopaminergic, GABA, glycineric, beta-adrenergic, and benzodiazepine receptors. However, a 30% reduction in binding of 3H-quinuclidinyl benzilate was apparent in TOCP-treated hens. These data implied a selective reduction of muscarinic receptors, suggesting a down-regulation in response to cholinergic hyperactivity. This dose of TOCP also caused paralysis and ataxia in all treated hens 21 d after exposure to the toxicant. These data demonstrate that a selective lesion in cholinergic neurotransmitter circuitry can be caused by a single administration of TOCP.
(1983) **The cytotoxic test.**

---------------------------------------------------------------------

(1983) **Similar repair of O6-methylguanine in normal and ataxia-telangiectasia fibroblast strains. Deficient repair capacity of lymphoblastoid cell lines does not reflect a genetic polymorphism.**
Shiloh, Y, Tabor, E and Becker, Y Journal/Mutat Res. 112: 47-58.

The ability of human fibroblast strains to repair the mutagenic DNA adduct O6-methylguanine (O6-MeG) induced by brief exposure to N-methyl-N'-nitroso-N-nitrosoguanidine (MNNG) was investigated. The repair reaction proceeded rapidly during the first hour after alkylation, followed by a slow, continuous phase of repair, and both processes were saturated by low doses of carcinogen. This was similar to what had previously been found in human lymphoblastoid lines. Three fibroblast strains from healthy donors and six strains from patients with ataxia telangiectasia were all proficient in their capacity to repair O6-MeG and had the same sensitivity to the cytotoxicity of MNNG and methyl methanesulphonate as normal cells. Three of these cell strains were derived from individuals whose lymphoblastoid lines were deficient in their ability to repair O6-MeG. These lymphoblastoid lines were also extremely hypersensitive to killing by methylating carcinogens. Because non-transformed cells from the same donors behaved normally with regard to both parameters, we concluded that the repair deficiency accompanied by carcinogen hypersensitivity of the lymphoblastoid lines does not indicate a genetic deficiency in the donor. These findings imply that lymphoblastoid lines may not always be the appropriate cell type for investigating genetic susceptibility to chemical mutagens.

---------------------------------------------------------------------

(1983) **Effect of oral administration of tri-o-cresyl phosphate on in vitro phosphorylation of membrane and cytosolic proteins from chicken brain.**
Patton, SE, O'Callaghan, JP, Miller, DB and Abou-Donia, MB Journal/J Neurochem. 41: 897-901.

The effects of a single oral dose of 750 mg/kg tri-o-cresyl phosphate (TOCP) on the endogenous phosphorylation of specific brain proteins were assessed in male adult chickens following the development of delayed neurotoxicity. Phosphorylation of crude synaptosomal (P2) membrane and synaptosomal cytosolic proteins was assayed in vitro by using [gamma-32P]ATP as phosphate donor. Following resolution of brain proteins by sodium dodecyl sulfate polyacrylamide gel electrophoresis, specific protein phosphorylation was detected by autoradiography and quantified by microdensitometry. TOCP administration enhanced the phosphorylation of both...
cytosolic (Mr 65,000 and 55,000) and membrane (20,000) proteins by as much as 146% and 200%, respectively.


A method utilizing high-performance liquid chromatography (HPLC) has been developed for the analysis of tri-o-cresyl phosphate (TOCP) and its possible metabolites, o-cresyl dihydrogen phosphate, di-o-cresyl hydrogen phosphate, o-hydroxybenzyl alcohol, o-cresol, saligenin cyclic-o-tolyl phosphate [2-(o-cresyl)-4H-1:3:2:benzodioxaphosphoran-2-one], salicylic acid, salicylaldehyde, hydroxymethyl TOCP (di-o-cresyl o-hydroxymethylphenyl phosphate), and dihydroxymethyl TOCP (o-cresyl di-o-hydroxymethylphenyl phosphate). TOCP and its possible metabolites were analyzed on a reverse-phase C18 cartridge fitted into RCM-100 radial-compression separation system. Compounds were separated using a linear gradient of 25 to 80% acetonitrile in 2% aqueous acetic acid at a flow rate of 1.3 ml/min in a period of 22 min. Quantification was achieved by monitoring the ultraviolet absorbance of the column eluates at 254 nm and measuring peak areas. Retention times and peak areas were highly reproducible for all compounds analyzed. The relationship between peak area and amount injected was linear over a 100-fold range for all compounds analyzed. The minimum detectable level was 3 ng for salicylaldehyde, 25 ng for o-hydroxybenzyl alcohol and salicylic acid, and 50 ng for the remaining compounds. A mixture of TOCP and its possible metabolites was added to samples of cat liver, kidney, and plasma and then extracted and analyzed. High recovery and reproducibility for most compounds was observed in tissues analyzed.

(1983) Psychosomatic education: the University of Chicago’s program in liaison psychiatry.
Kimball, CP Journal/J Psychosom Res. 27: 5-8.

Psychiatric education for the medical student addresses itself to students’ and potential non-psychiatric physicians’ needs in identifying and addressing the biopsychosocial aspects of patient care. The education is best based on the clinical method, using the extended interview to identify the relationship of environmental and social circumstances to the anlage, onset and reaction to illness in the patient. Within this pattern, genetic, epigenetic developmental patterns, earlier illness, behavioral and personality patterns are identified. In addition, family and social variables, including the effects of treatment procedures, hospitalization and interaction with the health team are reviewed. To whatever extent possible, the student is sensitized to this approach at the
earliest phase of his/her education, preferably in the preclinical years. The approach is reinforced during the introduction to clinical medicine and physical diagnosis. In the clinical years, individual patient consultations are arranged for students working with medical, surgical, pediatric and obstetrical patients on these services in which they review with patients their illness experiences. This is viewed as both an analytic and synthetic experience having an educational value for the student and a therapeutic one for the patient. Preceptors of such programs need thorough grounding in general and sometimes specialty medical disciplines as well as considerable exposure to psychological, behavioral and psychiatric medicine. Evaluation and support of these programs remain in question and should be addressed in discussion.

Hansen, LG, Abou-Donia, MB, Francis, BM, Hollingshaus, JG and Johnson, MK
Journal/Neurotoxicology. 4: 147-55.

(1983) The time course of protection from delayed neurotoxicity induced by tri-o-cresyl phosphate and O,O-diisopropyl phosphorofluoridate by phenyl methyl sulfonyl fluoride in chickens.

The time dependence of the ability of phenyl methyl sulfonyl fluoride (PMSF) to protect adult hens from developing signs of paralysis following the administration of 750 mg/kg tri-ortho-cresyl phosphate (TOCP), p.o., of 1.7 mg/kg O,O-diisopropyl phosphorofluoridate (DFP), s.c., was investigated. PMSF was able to protect the hens from organophosphorus-induced delayed neurotoxicity (OPIDN) when given between 1 and 24 h before the administration of TOCP, or when given 4 h before DFP. However, PMSF was ineffective at preventing paralysis when given 24 h following dosing with TOCP or when given later than 4 h before DFP administration. These results support the notion that PMSF acts at the same site as the organophosphorus esters.

The regulation of GTP-cyclohydrolase (GTP-CH) activity and tetrahydrobiopterin (BH4) levels in the adrenal cortex were studied in intact and hypophysectomized rats. Treatment with a single dose of reserpine (5 mg/kg) or insulin-induced hypoglycemia (4 h) elevated adrenocortical BH4 3-fold by 10 h; BH4 levels remained elevated after 24 h and returned to control levels by 48-72 h. GTP-CH was significantly increased 24 h after hypoglycemic shock, and the increased enzyme activity preceded the changes in BH4 levels after reserpine treatment. Two and a half hours of stress by immobilization also increased GTP-CH activity and BH4 levels in the adrenal cortex. The activities of sepiapterin reductase and dihydrofolate reductase, putative enzymes in the biosynthetic pathway from GTP to BH4, were not increased by reserpine. Both reserpine and insulin increased the apparent maximum velocity for GTP, with no increase in the affinity of the enzyme for its substrate, further suggesting that the experimental treatments induce the synthesis of GTP-CH. Hypophysectomy completely blocked the reserpine-dependent increase in both cortical GTP-CH activity and BH4 content. The administration of purified porcine ACTH to intact and hypophysectomized rats elevated adrenocortical GTP-CH activity and cofactor levels. Synthetic ACTH-(1-24) also enhanced the enzyme activity and BH4 levels in the adrenal cortex. Thus, pituitary control of adrenal cortical GTP-CH synthesis and biopterin levels appears to be mediated through the secretion of ACTH. The changes in enzyme activity and cofactor levels after activation of the hypothalamo-hypophyseal axis or ACTH administration suggest that BH4, a cofactor for certain monooxygenases, has some function, as yet unknown, in the adaptive changes of the adrenal cortex in response to stress.


The metabolism, distribution, and excretion of the insecticide O-ethyl O-4-nitrophenyl phenylphosphonothioate (EPN) were studied in the male cat. Each cat was given a daily dermal dose of 0.5 mg/kg [14C]EPN for 10 consecutive days. Fifteen days after the last dose, the cats had excreted 62% of the cumulative dose in the urine and 10% in the feces. No 14CO2 was detected in the expired air. O-Ethyl phenylphosphonic acid (EPPA) was identified as the major urinary and fecal metabolite. Phenylphosphonic acid (PPA) was the second highest metabolite. Only traces of the intact EPN were recovered in the urine and feces. The disposition studies performed 1, 5, 10 and 15 days after the administration of the last dose showed that EPN was the major compound identified in the brain, spinal cord, sciatic nerve, adipose tissue, plasma and kidney. Most of the radioactivity in the liver was identified as EPPA followed by PPA. The time course of plasma EPN, determined after the 10th daily dose was biphasic. The slower process had a half-life of 17.0 days. After tissue distribution was completed, tissue elimination was adequately represented as a single first-order process.
(1983) The absorption, distribution, excretion, and metabolism of a single oral
dose of O-ethyl O-4-nitrophenyl phenylphosphonothioate in hens.
Abou-Donia, MB, Reichert, BL and Ashry, MA Journal/Toxicol Appl Pharmacol. 70:
18-28.

The disposition and metabolism of a single oral 10 mg/kg (LD50) of uniformly
phenyl-labeled [14C]EPN (O-ethyl O-4-nitrophenyl [14C]phenylphosphonothioate) were
studied in adult hens. The birds were protected from acute toxicity with atropine
sulfate. Three treated hens were killed at each time interval (days): 0.5, 2, 4, 8, 12.
Radioactivity was adsorbed from the gastrointestinal tract and distributed in all tissues.
Most of the dose was excreted in the combined urinary-fecal excreta (74%). Only
traces of the radioactivity (0.2%) were detected in expired CO2. Most of the excreted
radioactive materials were identified as phenylphosphonic acid (PPA), O-ethyl
phenylphosphonic acid (EPPA), and O-ethyl phenylphosphonothioic acid (EPPTA).
Radioactivity in tissues reached a peak of 11.8% in 12 days. The highest concentration
of radioactivity was present in the liver followed by bile, kidney, adipose tissue, and
muscle. EPN was the major compound identified in brain, spinal cord, sciatic nerve,
kidney, and plasma. Most of the radioactivity in the liver was identified as EPPA
followed by EPPTA and PPA. Kinetic studies showed that EPN disappeared
exponentially from tissues. The half-life of the elimination of EPN from plasma was
16.5 days corresponding to a constant rate value of 0.04 day-1. Relative residence
(RR) of EPN relative to plasma was shortest in liver and longest in adipose tissue
followed by sciatic nerve and spinal cord.

(1983) Physiological disposition and metabolism of O-ethyl-O-4-nitrophenyl
phenylphosphonothioate in male cats following a single dermal administration.
Abou-Donia, MB, Kinnes, CG, Abdo, KM and Bjornsson, TD Journal/Drug Metab Dispos. 11:
31-6.

The pharmacokinetics and metabolism of a single dermal 20.0 mg/kg of uniformly
phenyl-labeled [14C]EPN (O-ethyl O-4-nitrophenyl [14C]phenylphosphonothioate) were
investigated in adult male cats. Three treated cats were killed at each time interval: 0.5,
2, 4, 8, and 12. Radioactivity disappeared exponentially from administration site at a
rate constant of 0.46 day-1, corresponding to a half-life of 1.5 days. Most of the
absorbed radioactivity was excreted in the urine (29.9%). Only 3.2% of the 14C was
recovered in the feces. No radioactivity was detected in expired CO2. Only traces of
EPN were detected in the urine and feces. Most of the excreted 14C materials were
identified as O-ethyl phenylphosphonothioic acid (EPPTA), O-ethyl phenylphosphonic
acid (EPPA), and phenylphosphonic acid (PPA). The disposition studies showed that
EPN was the major compound identified 0.5 day after administration in the brain, spinal cord, sciatic nerve, adipose tissue, plasma, muscle, liver, and kidney. Most of the radioactivity in the liver and kidney was identified after 4 days as EPPTA, EPPA, and PPA. Kinetic and distribution studies showed that EPN was eliminated from the tissues and plasma according to exponential kinetics. The half-life of the elimination of EPN from plasma was 9.1 days corresponding to a constant rate value of 0.076 day⁻¹. Relative residence (RR) of EPN relative to plasma was longest in the sciatic nerve and shortest in the kidney.

Abou-Donia, MB, Jensen, DN and Lapadula, DM Journal/Neurobehav Toxicol Teratol. 5: 431-42.

The neurotoxic effects of tri-o-cresyl phosphate (TOCP) were studied in the cat to define the elements of neurologic testing and to correlate dysfunction with the results of histopathologic studies. Neurologic examination of treated cats categorized clinical signs of TOCP-induced delayed neurotoxicity in the cat into four stages: leg weakness, mild ataxia, severe ataxia, and paresis. These deficits correlated well with histopathological lesions found in the central and peripheral systems. The improvement seen, is attributed to regeneration and/or collateral sprouting of remaining axons of peripheral nerves that would not be expected in tracts of the central nervous system.

Abou-Donia, MB, Hernandez, YM, Ahmed, NS and Abou-Donia, SA Journal/Arch Toxicol. 54: 83-96.

The toxicokinetics and metabolism of a single 1 mg (2.7 μCi/kg) oral dose of uniformly phenyl-labeled [14C]EPN (O-ethyl O-4-nitrophenyl [14C]phenylphosphonothioate) have been studied in 1-week old chicks. One control and three treated chicks were killed at each of the following time intervals: 0.5, 2, 4, 8, and 12 days. Radioactivity was rapidly absorbed from the gastrointestinal tract and distributed in all tissues. 14C in tissues reached a peak of 16.9% of the dose after 0.5 day and decreased to 0.6% at 4 days. The tissues of the gastrointestinal tract had the highest concentration of radioactivity, followed by bile and liver. Among nervous tissues, concentration of the 14C was highest in the peripheral nerves. The spinal cord had the next highest concentration, while the brain had the least. After 4 days 91.3% of the 14C had been eliminated in the combined urinary-fecal excreta. By the end of the
12-day experiment this percentage reached 93.1%. No 14C was detected in the expired CO2. Following the oral administration of [14C]EPN, a monophasic body level curve was observed. The half-life for the elimination of 14C from chick body was 16 h, corresponding to a rate constant of 0.04 h⁻¹. Most of the excreted 14C materials were identified as O-ethyl phenylphosphonic acid, phenylphosphonic acid, and O-ethyl phenylphosphonothioic acid.


Daily dermal administration for 90 days of 0.01 to 10 mg/kg of O-ethyl O-4-nitrophenyl phenylphosphonothioate (EPN) technical grade (85%) in acetone (0.1 ml) on the unprotected back of the neck produced delayed neurotoxicity. Hens given 2.5 to 10 mg kg daily doses also received daily doses of atropine sulfate for 5 or 6 days to protect against cholinergic acute toxicity. Severity of the clinical condition depended on the concentration of the daily dermal dose of EPN; i.e., while hens given small doses showed only ataxia, those treated with large doses progressed to paralysis and died. The most consistent histopathologic alteration was the degeneration of axons and myelin in the spinal cord which was identical to that found in positive control hens that received daily dermal doses of 5 or 10 mg/kg tri-o-cresyl phosphate (TOCP). Some of the hens treated daily with the smallest tested dose of EPN (0.001 mg/kg) which did not show clinical signs of delayed neurotoxicity showed equivocal histological changes in the spinal cord. EPN and TOCP treatments had a more profound effect on the activity of plasma butyrylcholinesterase than that of brain acetylcholinesterase (AchE). by contrast O,O₂-diethyl O-4-nitrophenyl phosphorothioate (parathion) was more inhibitory to brain AChE. Negative control hens that were treated with 90 daily dermal doses of 1 mg/kg of parathion initially showed leg weakness followed by recovery. A group of hens that received the same volume of acetone (0.1 ml) daily remained normal.


Delayed neurotoxicity was produced in cats following the administration of either a single dermal dose of 22.5 to 225 mg/kg (0.2 to 5.0 times the LD50) or subchronic (90 days) administration of 0.5 to 2.0 mg/kg of technical grade O-ethyl O-4-nitrophenyl
phenylphosphonothioate (EPN). The study showed three differences from the condition produced in the chicken: difficulty to protect from acute poisoning, slower progression of delayed neurotoxicity, and propensity for improvement. These animals received atropine sulfate and pyridine-2-aldoxime methyl chloride (PAM) to protect them against acute poisoning, but most developed signs of acute cholinergic neurotoxicity, the degree of severity being dose dependent. Also cats given small single doses of EPN showed only leg weakness, while those treated with large doses progressed to severe ataxia and death. In cats treated with subchronic dermal daily doses of EPN, the extent and permanence of injury and progression or improvement of neurologic deficit also depended on the dose size and duration of exposure. Histopathologic changes were present in the most distal portion of the longest tracts in both the central and peripheral nervous system. Ascending tracts were most affected in the cervical spinal cord, while change in the descending tracts was concentrated in the lumbosacral spinal cord. Recovery to a varying degree from delayed neurotoxicity was seen in all surviving cats. The recovery was demonstrated as improvement in clinical signs, increase in body weight, and regeneration of peripheral nerves.

Abou-Donia, MB Journal/Neurotoxicology. 4: 113-29.

The data presented here indicate that rodents metabolize and excrete delayed neurotoxic organophosphorus esters with great efficiency. By contrast, the adult chicken seems to have difficulty carrying out these processes. The cat is intermediate between rodents and chickens. Although further studies are needed, these results suggest that the hen model may exaggerate the effect of neurotoxic organophosphorus esters. Extrapolation of findings from the chicken may thus overestimate the risk or hazard of organophosphorus esters to humans. This may explain why no human case of EPN-induced delayed neurotoxicity has been reported despite the fact that it has been in use for over a quarter of a century. Other neurotoxicity data from our laboratory seem to support the suggestion that the cat may be a better model to extrapolate neurotoxicity results to humans. The data presented in this review suggest that the pharmacokinetics and metabolism of organophosphorus esters may play a prominent role in species and age sensitivities for OPIDN. Animals that are sensitive to delayed neurotoxicity have a higher accumulation rate, coupled with slower elimination of the neurotoxic agent. These studies, however, do not rule out the possibility that the target tissue of organophosphorus delayed neurotoxicity itself is species or age specific.

(1983) Interaction between neurotoxicities induced by organophosphorus and long-chain hexacarbon compounds.
n-Butyl mercaptan (nBM) is a breakdown product of S,S,S-tri-n-butyl phosphorotrithioate (DEF) and S,S,S-tri-n-butyl phosphorotrithioite (merphos) in hens and in the environment. n-Butyl disulfide (nBD) is an oxidation product of nBM. A single 500 mg/kg dose of nBM and nBD was administered in gelatin capsules to groups of five 12-month old laying hens. A third group (five hens) was given gelatin capsules. One day after administration, the hens exhibited weakness which progressed to unsteadiness and inability to stand by the third day. These signs were accompanied by a pale comb 18--24 hr after dosing, which changed to dark color at 48 hr. Treated hens improved with time. Heinz bodies and extensive erythrocyte deformation and lysis were observed in blood smears taken from hens 24 and 48 hr after treatment. Hemoglobin concentration, packed cell volume, erythrocytes, and glucose-6-phosphate dehydrogenase activity were significantly lower than controls, while methemoglobin was significantly higher. As the clinical condition of these hens improved, these hematologic changes disappeared. nBM caused an initial increase in plasma butyrylcholinesterase activity which was dose-dependent and returned to normal by the end of the 28-day experiment. Also, brain acetylcholinesterase activity was not different from that of the control at termination.


(1982) **Characterization of the translation products of the major mRNA species from rabbit lactating mammary glands and construction of bacterial recombinants containing casein and alpha-lactalbumin complementary DNA.**

Total cytoplasmic polyadenylated RNA from lactating rabbit mammary glands was analysed on methylmercury hydroxide-agarose gels. The size of the most abundant mRNA species ranged between 0.5 and 5.0 kb (kilobases), with major bands at 0.55, 0.84, 0.92, 1.18 and 2.4 kb and discrete minor bands of 1.5, 1.7, 3.0 and 3.9 kb. Translation in vitro of total mRNA with [3H]leucine or [35S]methionine as precursor yielded four major bands with apparent Mr values of 16 000, 25 000, 26 000 and 29 000. The four protein bands were identified by immunoprecipitation by using specific antisera as alpha-lactalbumin and x-, kappa- and alpha-caseins, respectively. Labelling with [35S]cysteine followed by immunoprecipitation with anti-transferrin or anti-alpha-lactalbumin sera allowed the identification of two whey proteins. Translated transferrin was resolved as an 80 000-dalton band and alpha-lactalbumin appeared as a 16 000-dalton protein. A library of recombinant plasmids containing cDNA (complementary DNA) sequences representing cytoplasmic polyadenylated RNA was used to isolate clones for the major rabbit caseins and alpha-lactalbumin. A preliminary characterization of these cDNA clones was achieved by colony hybridization with enriched RNA fractions as probes. Positive clones were identified by use of hybrid-promoted translation in vitro and immunoprecipitation of the translation products. The corresponding mRNA species were further identified by hybridizing RNA blots with radioactively labelled cDNA clones. We present the restriction map of alpha-casein and kappa-casein cDNA clones.

(1982) **Medical manageability and psychosocial factors in childhood asthma.**
Staudenmayer, H Journal/J Chronic Dis. 35: 183-98.

Five psychosocial factors were empirically derived from a questionnaire administered to 175 asthmatic children who were taken from three subsamples representing hospitalized inpatients, outpatients and private practice patients. The scales included three measures of anxiety labeled Despair Over Social Debilitation, Quality of Life, and Dread of Illness, one attitude scale labeled Orientation Towards Compliance, and one scale labeled Family Communication. These scales correlated with measures of debilitation during the 6 month period prior to treatment, which included the number of asthma attacks, emergency room visits, days hospitalized, days of school missed and parental ratings of interference in physically strenuous activities. Two groups of children were defined for each psychosocial factor by a mean split of the scores. The incidence of children with relatively much anxiety as defined by three of these scales
and a poor attitude about compliance was greatest in the inpatient subsample and least in the private practice subsample. Inpatients also experienced the most debilitation during the 6 month period before testing. Follow-up measures of debilitation were recorded for the 6 month period post discharge. The relationship between the debilitation experienced by the children and their anxiety was evaluated. Patient groups with much and little anxiety both showed comparable and significant reductions in debilitation post hospital treatment. The results were interpreted to indicate that the anxiety assessed upon admission was the consequence of a history of poor medical manageability. The anxiety assessed did not appear to contribute to poor control of this illness.


Three hundred seventy workers in three tire-manufacturing plants were studied to determine the presence of respiratory morbidity among workers with relatively low current exposure to respirable dust (range, 0.04 to 0.70 mg/m3). Workers in the processing, milling, and less dusty areas of the plants were divided into three groups on the basis of their current and past exposure to respirable dust. Significantly more eye irritation (p less than .01) was found among workers in the milling areas. Workers in the milling areas who were current cigarette smokers had significantly (p less than .05) more chronic bronchitis and loose or productive objective cough than all other current cigarette smokers. The mean forced expiratory volume in 1 s (FEV1), when corrected for age and height, decreased significantly (p less than .01) with increasing duration of cigarette smoking. The mean FEV1 and the forced vital capacity (FVC), when corrected for age, height and cigarette smoking, were the lowest in the group with the lowest dust exposure and highest in the group with moderate dust exposure (the milling areas). The measurement of the difference in flow at 50% of FVC on air and on a helium-oxygen mixture is a sensitive test for small-airway obstruction in the laboratory. In the field, however, the helium-oxygen flow difference did not vary with duration of cigarette smoking as expected, and there was no significant variation by exposure category.

(1982) Metabolism of N-alkyl compounds during the biosynthesis of prostaglandins. N-Dealkylation during prostaglandin biosynthesis.
The microsomal fraction of ram seminal vesicles (RSV), when fortified with arachidonic acid, catalyzed the dealkylation of various N-methyl compounds. These included an analogous series of monomethyl- and dimethyl-substituted anilines as well as the drugs aminopyrine and benzphetamine. In contrast, S-alkyl and O-alkyl compounds were poor substrates for dealkylation by RSV microsomes fortified with fatty acid. RSV microsomal N-dealkylation was completely dependent on enzyme and arachidonic acid and could be inhibited by the prostaglandin synthetase inhibitors indomethacin, phenylbutazone, and flufenamic acid as well as by anaerobic conditions. Butylated hydroxyanisole also inhibited the reaction, whereas SKF-525A and metyrapone, which are inhibitors of cytochrome P-450-dependent N-dealkylation, did not. In addition to arachidonic acid, N-dealkylation was elicited by 15-hydroperoxyarachidonic acid, tert-butyl-hydroperoxide, and hydrogen peroxide; these latter reactions were not inhibited by either prostaglandin synthetase inhibitors or anaerobic conditions but did require the presence of microsomal protein. The time course of RSV N-dealkylation, which paralleled O2 consumption by this tissue (an indicator of prostaglandin biosynthesis) implied arachidonic acid-dependent irreversible self-inactivation of catalytic activity. Apparently, oxidizing agents are formed during the interaction of hydroperoxide intermediates of prostaglandin biosynthesis with prostaglandin synthetase, with the oxidizing agents then causing both substrate N-dealkylation and destruction of the enzyme. The metabolism of N-alkyl compounds during the biosynthesis of prostaglandins may provide an additional xenobiotic oxidation pathway to cytochrome P-450-dependent monooxygenases.

---

**1982** A laboratory technique for the assessment of pain behavior.
Philips, HC and Hunter, M Journal/J Behav Med. 5: 283-94.

The understanding and assessment of headache has been handicapped by inadequate assessment of pain behavior. The current study aimed to develop a simple laboratory technique to evaluate a headache sufferer's apparent oversensitivity to, and avoidance of, stimuli such as noise and bright lights. The results revealed that subjects could reliably calibrate the stimuli on a scale from "comfortable" to "definitely unpleasant." Significant group differentiation (controls/headache prone) was possible on the basis of auditory stimulus sensitivity, irrespective of current pain state. On the other hand, endurance time at an intense level differentiated subjects in pain from those pain-free, irrespective of group (headache/nonheadache). The advantages and potential of such an objective assessment of pain are discussed.

---

**1982** Differential metabolism of O-ethyl O-4-nitrophenyl phenylphosphonothioate by rat and chicken hepatic microsomes.

The electrophysiology of organophosphorus induced delayed neurotoxicity was studied to determine the extent peripheral nerve changes affect monosynaptic reflex responses of the spinal cord. Cats were given a single dermal dose of 1500 mg/kg or two dermal doses of 500 mg/kg of tri-o-cresyl phosphate. Animals were observed for 60 days after which monosynaptic reflex (MSR) responses were recorded from L7 and S1 ventral roots after stimulation of the tibial or common peroneal nerves. Post-tetanic potentiated responses as well as ventral and dorsal root compound action potentials were also recorded. There was a significant decrease from control in the unconditioned MSR. The post-tetanic potentiated response was significantly decreased in the S1 ventral root, however, when expressed as a factor of potentiation of the unconditioned MSR, it was found to be increased, although not significantly. The dorsal and ventral root compound action potentials were also significantly decreased from control with their conduction velocities being no different from control. The decrease in the unconditioned MSR as well as the dorsal and ventral root compound action potentials were attributed to peripheral nerve damage. The absence of any significant change in the post-tetanic potentiated response expressed as a factor of potentiation of the unconditioned MSR was attributed to a decrease in both the discharge zone as well as the subliminal fringe. The absence of any change in the conduction velocity indicates at least some of the large myelinated peripheral fibers were spared from significant damage.

(1982) The relative neurotoxicities of n-hexane, methyl n-butyl ketone, 2,5-hexanediol, and 2,5-hexanedione following oral or intraperitoneal administration in hens.
This study reports the differential neurotoxic effects of coumaphos [O,O-diethyl O-(3-chloro-4-methyl-7-coumarinyl) phosphorothioate] when applied orally or dermally in the adult hen. Dermal administration of single (50-500 mg/kg) or daily (100 mg/kg) doses resulted in delayed neurotoxicity in hens, similar to that caused by other delayed neurotoxic organophosphorus compounds. Coumaphos caused loss of weight and produced ataxia, which progressed to paralysis and death. Degeneration of axons and myelin in the spinal cord was the most consistent histopathologic alteration and was identical to that reported for other delayed neurotoxic organophosphorus esters. Only one hen showed peripheral nerve degeneration. Oral administration of a single 100 mg kg dose or daily doses of 10 mg coumaphos caused severe acute toxicity and killed all treated hens 1-8 d. These hens did not develop delayed neurotoxicity. Some hens given a single oral 50-mg/kg dose or daily 5-mg/kg doses of coumaphos recovered from the initial cholinergic effect and developed clinical signs of delayed neurotoxicity. These hens, however, improved with time and did not show unequivocal nervous-tissue damage at termination.

---------------------------------------------------------------
(1982) Neurotoxicity of continuous (90 days) inhalation of technical grade methyl butyl ketone in hens.
Neurotoxicity was produced in 1-yr-old hens (five hens per treatment) by continual 90-d exposure in inhalation chambers to atmospheres containing 50, 100, 200, or 400 ppm technical grade methyl butyl ketone (MBK) containing 70% methyl n-butyl ketone (MnBK) and 30% methyl isobutyl ketone (MiBK). A 30-d observation period followed. Severity of clinical condition and progression or improvement of neurological deficit signs were dependent on the concentration of MBK and duration of exposure. Hens exposed to the two highest levels developed ataxia and paralysis; they died or were sacrificed before the designated exposure period ended. The intermediate level of MBK (100 ppm) caused severe ataxia; most treated hens showed no change in clinical condition during the observation period. Hens exposed to 50 ppm exhibited gross ataxia, with most demonstrating partial regression of neurological deficit after the exposure ceased. Hens exposed to the lowest tested level (10 ppm) remained normal. Only hens exposed to 400 or 200 ppm showed significant weight loss. Some hens from the 50-400 ppm treatment groups showed unequivocal histopathologic changes in the spinal cord and peripheral nerves. Severity of histopathologic changes depended on the level and duration of MBK exposure. These changes were characterized by excessive swelling, phagocytosis, degeneration, and demyelination of the axons.


Guanosine triphosphate cyclohydrolase, the enzyme that is apparently rate-limiting in biopterin biosynthesis, is increased in adrenal cortex and medulla of rats treated with insulin or reserpine. Denervation and hypophysectomy block the increase in medullary and cortical enzyme activity, respectively, whereas cycloheximide presents the increase in both tissues. These results provide evidence for induction and regulation of guanosine triphosphate cyclohydrolase.


Twenty disabled patients with recurrent intractable nontraumatic phlebitis were studied. The patients were divided into two groups and matched for age and severity. The control group was continued on their standard anticoagulant regime, bed rest and support hose. The other group was placed in an especially designed Environmental Control Unit (ECU) where all air, food and water could be controlled. These patients were taken off all medication and not fed until the leg pain and swelling disappeared, which was four to seven days. The patients then showed specific sensitivities to foods and ambient subthreshold doses of inhaled chemicals such as formaldehyde less than 0.2 ppm, phenol less than 0.0024 ppm, chlorine less than 0.33 ppm, petroleum alcohol less than 0.5 ppm and pesticide (2,4 DNP) less than 0.0134 ppm under controlled double-blind challenges. Eight out of 10 patients had their phlebitis reproduced in this manner. When in the symptom-free state, these patients were required to ride an exercycle at 150 kpm for one mile daily to demonstrate absence of phlebitis (none
could walk across the room prior to examination). The five-year follow-up in the group showed two 48-hour episodes of phlebitis cleared by home bed rest and food abstinence. In contrast, the control group had more than 60 episodes of phlebitis at home and 41 episodes in the hospital. Medical costs in these comparable groups showed a differential of $20 per patient in the Environmental Control Unit treatment versus more than $20,000 per patient in the control group over the five-year follow-up.


The negotiation of the illness experience by ayurvedic vaidya and South Kanarese patients suffering from specific sources of psychosocial distress is examined in light of the cultural patterning of illness and communication within the clinical context. The negotiation process is initiated by the posing of rhetorical questions about somatic and affective states and structured by a conceptual framework which relegates such states to humoral interrelationships. By establishing a humoral explanatory model for an illness episode or affective state which takes into account environmental and constitutional factors over which one has little control, responsibility is mollified and dialogue about personal problems eased. A comparison of the interaction between ayurvedic practitioners and patients and astrologers and clients is made in this regard. The socially integrative and adaptive consequences of ayurvedic therapy is considered vis a vis a portrayal of a popular vaidya therapy for a number of illnesses associated with the somatization of psychosocial stress.


The mechanism of prostaglandin synthase-dependent N-dealkylation has been investigated using an enzyme preparation derived from ram seminal vesicles. Incubation of an N-alkyl substrate, aminopyrine, with enzyme and arachidonic acid, 15-hydroperoxyarachidonic acid, or tert-butyl hydroperoxide resulted in the formation of the transient aminopyrine free radical species. Formation of this radical species, which was detected by electron paramagnetic resonance spectroscopy and/or absorbance at 580 nm, was maximal approximately 30 s following initiation of the reaction and declined thereafter. Free radical formation corresponded closely with formaldehyde formation in this system, in terms of dependence upon substrate and cofactor concentration, as well as in terms of time course. Both aminopyrine free radical and
formaldehyde formation were inhibited by indomethacin and flufenamic acid, inhibitors of prostaglandin synthase. The results suggest that the aminopyrine free radical is an intermediate in the prostaglandin synthase-dependent aminopyrine N-demethylase pathway. The aminopyrine free radical electron paramagnetic resonance spectrum revealed that this species is a one-electron oxidized cation radical of the parent compound. A reaction mechanism has been proposed in which aminopyrine undergoes two sequential one-electron oxidations to an iminium cation, which is then hydrolyzed to the demethylated amine and formaldehyde. Accordingly, the oxygen atom of the aldehyde product is derived from neither molecular nor hydroperoxide oxygen, but from water.


Tetrahydrobiopterin, the cofactor for tyrosine hydroxylase and other monooxygenases, is present in tissues at apparent concentrations much less than those necessary to saturate the corresponding enzymes. Reserpine treatment or insulin-induced hypoglycemia in rats produces a statistically significant increase in the tetrahydrobiopterin content of both the adrenal medulla and the cortex. Adrenal denervation and hypophysectomy selectively block the increases in cofactor level in medulla and cortex, respectively, while cycloheximide prevents the increase in both tissues. Reserpine did not increase cofactor levels in liver, kidney, or corpus striatum but decreased that of the pineal gland. These results suggest that tetrahydrobiopterin is under neural control in the medulla and hormonal control in the cortex and that increases in cofactor may result from induction of enzyme(s) in the biosynthetic pathway. These results demonstrate regulation of tissue tetrahydrobiopterin and are consistent with the suggestion that cofactor levels participate in the regulation of tyrosine hydroxylase in the adrenal medulla and may have a function, as yet undetermined, in the adrenal cortex.


In certain animals, including humans, exposure to some organophosphorus esters causes delayed neurotoxicity (OPIDN). The clinical condition becomes manifest after a delay period, first as ataxia, followed by paralysis. Lesions are characterized by degeneration of axons with subsequent secondary degeneration of myelin in the peripheral and central nervous systems. Recovery is only likely in mild cases, whereas more severe cases show symptoms of an upper motor neuron lesion in the lower
limbs. The risk of use of these chemicals is related not only to human sensitivity to this syndrome, but also to the fact that in most disasters involving OPIDN, humans were the prime victims. Therefore, the neurotoxic action of a chemical is of great significance, since pesticides with this property are not recommended for use. Although OPIDN has been recognized for over a half a century, its mechanism of action is still unknown. It is believed, however, that the initial target in OPIDN is the phosphorylation of a neurotoxicity target protein in the nervous system. Study of the relationship between the chemical structure of organophosphorus esters and their neurotoxic potencies suggests that two hydrophobic areas may be present in the vicinity of the active site of the neurotoxicity protein. This article attempts to present an up-to-date overview of OPIDN. Despite the difficulties attributed to experimental variations of the reported studies, I feel that several significant points have come forth from the data.

(1980) [Electromagnetic flow probes for the measurement of mitral flow (author's transl)].

query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6452549

(1980) Procainamide delivery to ischemic canine myocardium following rapid intravenous administration.


A proportional mortality analysis of jewelry workers as identified on death certificates is presented. The study group consisted of 931 males who died in Attleboro, Mass., between 1956 and 1975. An excess proportion of pancreas cancer was found in the entire group (16/9; p < 0.05) and was not explained by ethnic or other non-occupational factors. Job titles were specific enough to identify a subset of polishers and findings for this job category were compared to those for all other categories. Excesses of stomach cancer (odds ratio 4.4; p < 0.01) and stomach ulcer (odds ratio 5.0, p < 0.01) were
found, but for each the observed number of deaths is small. Possible important exposures in the jewelry industry are reviewed.

(1980) Respiratory morbidity in workers exposed to dust containing phenolic resin.

Reichert, BL and Abou-Donia, MB Journal/Mol Pharmacol. 17: 56-60.

(1980) High-pressure liquid chromatography of neurotoxic phenylphosphonothioate esters and related compounds.


Inhibition of the sulfhydryl enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) by 2,5-hexanedione (2,5-HD) was found to be irreversible, proceeding via a reversible enzyme-inhibitor intermediate, while acetone was a weak reversible inhibitor. Comparison of 2,5-HD and acetone with p-chloromercuribenzoate (PCMB) and N-ethylmaleimide (NEM) demonstrated that the former are not significant sulfhydryl reagents, since they must be present at more than 10(4) times higher concentrations than PCMB or NEM to effect measurable inhibition of this enzyme. Thus it is unlikely that inhibition of GAPDH by 2,5-HD has any significance in the molecular pathogenesis of hexane neuropathy. The irreversibility of 2,5-HD inhibition, on the other hand,
suggests that 2,5-HD reacts with amino groups rather than sulphydryl groups on proteins. This reaction is proposed as the molecular lesion in hexane neuropathy.

(1980) Sequential thin-layer chromatography of phosfolan, mephospholan and related compounds.
Bakry, NM and Abou-Donia, MB Journal/J Anal Toxicol. 4: 212-4.

A sequential thin-layer chromatographic method (STLC) has been developed to analyze the two organophosphorus insecticides phosfolan (O,O-diethyl 1,3-dithiolan-2-ylidene phosphoramidate) and mephospholan (O,O-diethyl 4-methyl-1,3-dithiolan-2-ylidene phosphoramidate) and some of their possible degradation products. Gelman type SA, Instant Thin Layer Chromatography (ITLC) silicic acid-impregnated glass fiber sheets were first developed up to 6 cm with the primary solvent 2-butanone-1-butanol-water (9:3:1), then after drying, to 16 cm with the secondary solvent acetonitrile-n-hexane-benzene-acetic acid (80:40:40:1). This two-solvent sequential system separated each insecticide from its corresponding metabolites. The Rf values were: phosfolan, 0.69; ethylene dithioimido-carbonate hydrochloride, 0.08; ethylene dithiocarbonate, 0.90; potassium thiocyanate, 0.40; mephospholan, 0.76; O,O-diethyl 4-hydroxymethyl-1,3-dithiolan-2-amidate, 0.83; propylene dithioimidocarbonate hydrochloride; 0.15 and propylene dithiocarbonate, 0.87.

(1980) Late acute, delayed neurotoxic and cholinergic effects of S,S,S-tributyl phosphorotrithioite (Merphos) in hens.

(1980) Metabolism and pharmacokinetics of a single oral dose of O-4-bromo-2,5-dichlorophenyl O-methyl phenylphosphonothioate (Leptophos) in hens.

(1979) Myocardial procainamide concentration in canine atria and ventricles.

The aim of this investigation was to examine the distribution of procainamide in the canine heart. Eight anesthetized open-chest dogs received intravenous infusions of 14C-labeled procainamide at 40 micrograms/kg/min for 4 hr. Just prior to the end of the infusion period, 51Cr-labeled microspheres were injected into the left atrium to measure regional myocardial blood flow. The heart was then excised and dissected into regional myocardial sections from each cardiac chamber. Samples from each section were combusted, and the liberated 14CO2 was trapped and counted to determine regional myocardial procainamide concentration. The remainder of each section was analyzed for 51Cr to determine regional myocardial blood flow. Plasma procainamide concentration (mean +/- SE) at the termination of the infusion was 2.68 +/- 0.14 micrograms/ml. Left ventricular procainamide concentration was 6.09 +/- 0.46 micrograms/g. The right ventricular drug concentration was 94% (NS), the left atrial concentration was 85% (p less than 0.005), and the right atrial concentration was 79% (p less than 0.005) of the left ventricular concentration. Within the myocardium of each cardiac chamber there was no correlation between drug concentration and blood flow. We conclude that these concentration differences are insufficient to explain differences in procainamide efficacy between ventricular and atrial arrhythmias.

(1979) Sorption-desorption characteristics of methyl parathion by clays.
Kishk, FM, Abu-Sharar, TM, Bakry, NM and Abou-Donia, MB Journal/Arch Environ Contam Toxicol. 8: 637-45.

Methyl parathion (O,O-dimethyl O-(4-nitrophenyl) phosphorothioate) adsorption was studied on montmorillonite, kaolinite, halloysite, natural zeolite, ion exchange resins and calcium carbonate. Methyl parathion was highly adsorbed by montmorillonite, followed by zeolite, and very little adsorption was obtained on kaolinite and halloysite. Calcium carbonate did not exhibit any adsorption. The values of the partial molar free energy "delta G" were calculated for all systems. For the montmorillonite-methyl parathion system, the calculated partial molar heat of adsorption "delta H", and the
conformity of the data to Freundlich equation indicated a possible physical mechanism of adsorption. Increasing acetone concentration decreases methyl parathion adsorption and dehydration increased adsorption in the nonaqueous system. Moreover, the increased adsorption on the swollen clay indicated that methyl parathion was adsorbed on the interlamellar surfaces of the clay. This was also in agreement with the results of the desorption studies, since the insecticide was not desorbed using the same aqueous acetone solution. This indicated that methyl parathion was adsorbed as a water-insoluble organic compound.

---

(1979) **Adsorption of methyl parathion by soils.**

---

(1979) **Air pollution analysis used in operating an environmental control unit.**

A simple, fast and reliable method was developed to measure the origin and daily and seasonal variations of selected air pollutants in the Brookhaven Environmental Unit. None of the pollutants that were measured surpassed its threshold limit value. The average concentrations of the pollutants that were measured could be considered as preliminary standard for environmental units in hospitals as long as material analysis for outgassing is used simultaneously.

---

(1979) **Delayed neurotoxicity of O-ethyl O-2,4-dichlorophenyl phenylphosphonothioate: effects of a single oral dose on hens.**

---

(1979) **Delayed neurotoxic, late acute and cholinergic effects of S,S,S-tributyl phosphorotrithioate (DEF): subchronic (90 days) administration in hens.**
Subchronic administration of S,S,S-tributyl phosphorotrithioate (DEF) caused 3 toxicologic effects in hens, depending upon route of administration. Small delay oral doses (0.5–20 mg/kg) of DEF produced ataxia, which progressed to paralysis and death in some birds. Large daily oral doses (40 and 80 mg/kg) caused a 'late acute' effect 4 days after administration. The clinical signs of the late acute effect were identical to those produced by n-butyl mercaptan (nBM), a hydrolytic product of DEF, and were not relieved by atropine sulfate. The late acute effect of DEF overlapped with the clinical signs of delayed neurotoxicity. These hens died early, and while one hen showed histopathological lesions in peripheral nerves, another showed unequivocal lesions in the central nervous system. Topical application of daily doses of DEF consistently produced delayed neurotoxicity in the absence of late acute poisoning and was characterized by degeneration of the central and peripheral nerve tissues. Orally administered DEF was rapidly metabolized in the gastrointestinal tract to nBM, which apparently caused the late acute toxic effect. Topically administered DEF, which was not subjected to gastrointestinal tract hydrolysis, caused delayed neurotoxicity but did not produce a late acute effect.


(1979) Delayed neurotoxicity of subchronic oral administration of leptophos to hens: recovery during four months after exposure.

Daily oral administration of small doses of technical grade O-methyl O-4-bromo-2,5-dichlorophenyl phenylphosphonothioate (leptophos, 0.5-20.0 mg/kg) caused delayed neurotoxicity in hens. Severity of clinical condition and progression or improvement of signs of delayed neurotoxicity depended on the dose and duration of administration. Hens given 20.0 mg/kg suffered ataxia, paralysis, and death. Intermediate doses (5 and 10 mg/kg) caused ataxia, with most treated hens showing no change in clinical condition during the 4-mo observation period. Hens given small doses (2.5 and 1.0 mg/kg) demonstrated regression of neurological deficits after administration of leptophos was stopped. Hens given the smallest tested dose (.5 mg kg) developed mild ataxia and showed total recovery during the observation period. Days of administration and total administered dose before onset of ataxia depended on the daily dose. Degeneration of axons and myelin i, the spinal cord was the most
consistent histopathologic change and was identical to that observed in tri-o-cresyl phosphate (TOCP) control hens. Only one hen, which died early in the treatment period, showed peripheral nerve degeneration. Controls consisted of 3 groups of hens given a daily oral dose of 10.0 mg/kg TOCP, 1.0 mg/kg O,O-diethyl O-4-nitrophenyl phosphorothioate (parathion), or an empty gelatin capsule. TOCP-treated hens developed delayed neurotoxicity, whereas those given parathion showed initial leg weakness but subsequently recovery without developing delayed neurotoxicity. Controls given gelatin capsules remained normal.

(1979) Delayed neurotoxicity of phenylphosphonothioate esters.

Administration of a single oral dose of five phenylphosphonothioate esters produced delayed neurotoxicity in hens; their potency was, in descending order, cyanofenphos, EPN, desbromoleptophos, leptophos, and EPBP (Seven). Histological examination showed that in some hens there was marked axonal and myelin degeneration in the spinal cord and peripheral nerves. The results suggest that delayed neurotoxicity may be a general feature of phenylphosphonothioate insecticides.

(1979) Pharmacokinetics and metabolism of a topically applied dose of O-4-bromo-2,5-dichlorophenyl O-methyl phenylphosphonothioate in hens.

(1978) Relationship between regional myocardial procainamide concentration and regional myocardial blood flow during ischemia in the dog.

(1978) Food and chemical susceptibility after environmental chemical overexposure: case histories.

(1978) Environmentally triggered cardiac disease.

Twelve highly selected patients with non-arteriosclerotic cardiac arrhythmias and/or chest pain refractory to medication and having symptoms related to smooth muscle sensitization were studied in a rigidly controlled, relatively fume- and particle-free environment. The majority of signs and symptoms cleared in 10 patients without medication while under environmental control, and in 10 of the 12 patients all arrhythmias were reproduced with controlled, repeated individual-blind and double-blind incitant challenges. Blood abnormalities occurred in the complement and T-lymphocyte systems.


Recent investigation into a possible association between exposure to Leptophos and neurological symptoms in insecticide factory workers makes study of the neurological effects of Leptophos in the experimental situation particularly important. The present study utilizes a single oral dose of 200 mg/kg of Leptophos in 20 chickens which are sacrificed in pairs to define the temporal sequence of changes in the sciatic nerve, its major branches, and the spinal cord and to correlate these findings with the clinical symptoms of the animals. At this dose Leptophos produces degeneration of the spinal cord in a pattern similar to that seen with tri-o-cresyl phosphate (TOCP). The ataxia seen in these birds is probably due to the posterior and lateral column involvement. At this dose onset of paralysis correlates roughly with both the degeneration of the anterior descending tract of the spinal cord and degeneration of the peripheral nerve. The minimal degree of nerve involvement suggests that the cord lesion is more significant at this dose in the hen. Using TOCP, spinal cord lesions predominate in the hen while the peripheral nervous system appears more sensitive in the human and non-human primate. Assuming that Leptophos resembles TOCP in this regard,
peripheral nerve damage would be the expected earliest change, especially in the low-dose situation in the human.

(1978) Twenty-four-hour recording in REM-narcoleptics with special reference to nocturnal sleep disruption.
Montplaisir, J, Billiard, M, Takahashi, S, Bell, IR, Guilleminault, C and Dement, WC

Twenty narcoleptic patients and ten age-matched normals were polygraphically monitored for 58 consecutive hours. All subjects were on regimented sleep (hours between 2230 and 0700). Group A (11 patients and 10 normals) had enforced wakefulness during the day whereas Group B (9 patients) were permitted to sleep (mean = 2 1/2 hr.). On day 2, all subjects were permitted to sleep for 15-min periods every 2 hr. In narcoleptics, sleep recordings demonstrated a reduction of sleep latency, an increase of stage 1, and a decrease in stages 3 and 4 compared to normals, but total REM time and percentage of REM sleep were similar. Groups A and B showed no difference in the incidence of nocturnal awakenings. REM cyclic periodicity was larger in narcoleptics who also demonstrated a REM-sleep fragmentation. This fragmentation became more pronounced as time passed, with several shifts from REM to wakefulness and stage 1. Narcoleptics present REM onset sleep period but also show an inability to remain in REM sleep.

(1978) Delayed neurotoxicity induced by organophosphorus compounds in the wild mallard duckling: effect of leptophos.
Herin, RA, Komeil, AA, Graham, DG, Curley, A and Abou-Donia, MB

Feeding of 260 ppm of leptophos to mallard ducklings caused delayed neurotoxicity similar to that reported for hens. Thus leptophos caused ataxia, with subsequent paralysis, loss of appetite, and slow-down in the growth rate of the treated birds. Spinal lesions were identical in morphology and distribution to those seen in hens following leptophos administration. The severity of histologic changes correlated both with the clinical condition and the duration of intoxication.

(1978) Hormonal and cardiac response of autistic children to changes in environmental stimulation.
Graveling, RA and Brooke, JD
Journal/J Autism Child Schizophr. 8: 441-55.
A study was made of physiological responses of autistic children to variations in environmental load in order to examine the under-versus over-arousal dichotomy. More specifically, measures of urinary mucoprotein excretion and mean heart rate and three measures of heart rate variability were compared with matched controls in conditions of normal, high, and low total environmental load. The results suggest that, although behaviorally unresponsive, the autistic children responded physiologically, were generally in a lower state of arousal than the control group, and were labile in response to changes in stimulation.

(1978) Absorption of paraquat and diquat from the airways of the perfused rat lung.
Charles, JM, Abou-Donia, MB and Menzel, DB Journal/Toxicology. 9: 59-67.

The uptake of paraquat dichloride (bis-N-[14C]methyl-4,4'-bipyridinium chloride) and diquat dibromide (N,N-ethylene-[U-14C]2,2'-bipyridilium dibromide monohydrate) from the airways and by the vasculature of the isolated and perfused rat lung (IPL) were studied. A semilogarithmic plot of the percent unabsorbed with time revealed a bi-exponential decay, suggesting at least two phases of removal of paraquat and diquat from the airways. The rapid initial process was similar for both herbicides. The slow component had at t1/2 of 355.98 min for paraquat and 75.03 min for diquat. This second process may represent the storage pool associated with the pulmonary toxicity of paraquat. When paraquat or diquat was presented to the capillary side of the lung, long-term storage was not evident. Uptake by the lung occurred from the pulmonary circulation with similar velocity. These data suggest that the energy-dependent uptake observed with lung slices probably represents airway transport and may be associated with cell membranes lining the alveolus.

(1978) Hypersomnia, multiple-system symptomatology, and selective IgA deficiency.

(1978) Delayed neurotoxicity of O-ethyl O-4-nitrophenyl phenylphosphonothioate: subchronic (90 days) oral administration in hens.


Ten randomly selected patients with recurrent non-specific small vessel vasculitis (edema, petechiae, spontaneous bruising, peripheral cyanosis) were studied under rigid environmental control. All cleared their symptoms without medications. All patients had their vasculitis reproduced after direct challenge with numerous individual foods and chemicals. Multiple incitants were found in each patient.


Parenterally administered flavonoids decrease endothelaemia in rats as determined by a new method in two ways: in vivo and in vitro. The in vitro effect caused by flavonoids present in blood might interfere with the cell counting and can be eliminated by neutralization of flavonoids with cobaltous ions. The resulting endothelial counts represent the "true" in vivo effect. Using this method it has been shown that the in vitro interference did not modify significantly the previously demonstrated marked effect of a flavonoid (mono-7-hydroxyethylrutoside) on increased endothelial counts after provocation with citrate.
(1976) The question of cholinergic antagonism.


Ten randomly selected patients with recurrent non-traumatic thrombophlebitis of unknown etiology were studied using a comprehensive environmental control method. All cleared their phlebitis without medications. Using withdrawal and challenge of incitants, eight of 10 patients had their phlebitis reproduced. The numerous single triggering agents were common-place inhaled and ingested foods and chemicals.


Exposure of perfused rat lungs to 3.0 ppm of ozone produced a rapid onset of edema and an increased resistance to inflation. Both the Km and Vmax of the enzymic conversion of arachidonic acid to prostaglandins were decreased by ozone exposure suggesting an uncompetitive inhibition of prostaglandin synthetase by O3. Reduced glutathione failed to prevent the inhibition of prostaglandin synthesis by O3.

(1976) Uric acid catabolism in the woolly monkey.
Logan, DC, Wilson, DE, Flowers, CM, Sparks, PJ and Tyler, FH Journal/Metabolism. 25: 517-22.

The degradation and excretion of 2-14C-uric acid were examined in three adult woolly monkeys (Lagotrichix lagotrichia) to determine the basis for the relatively high serum and urinary uric acid concentrations previously reported in this species. Like man and the great apes which lack uricase, but in distinction to most other mammals, these animals converted very little urate to allantoin. Uric acid turnover, as has been reported for other New World monkeys, was several times that of normal man. Renal urate
excretion as well as disposition by extrarenal mechanisms may protect Lagothrix vom hyperuricemia. The capacity to convert urate to allantoin appears to have been lost late in the evolution of New World monkeys. The woolly monkey deserves further study as a primate model for investigations of enzyme replacement strategies.

---------------------------------------------------------------


---------------------------------------------------------------

(1976) Auditory-nerve activity in cats exposed to ototoxic drugs and high-intensity sounds.

The response characteristics of auditory-nerve fibers in normal cats are compared with those in cats exposed to kanamycin and high-intensity sounds. The pathophysiology is characterized by an elevation of the tuning-curve "tips," which is sometimes associated with hypersensitivity of the "tails". Plots of unit thresholds are correlated with patterns of sensory-cell losses in the cochlea. There can be significant shifts in unit threshold without significant loss of hair cells; however, significant hair cell loss is always accompanied by highly abnormal unit thresholds. The presence of inner hair cells seems to be essential for the long-term survival of spiral ganglion cells. An incidental observation is that in the "normal" animal there is almost always a prominent "notch" at 3-4 kHz in the plots of threshold at characteristic frequency, which may have been produced by environmental noise.

---------------------------------------------------------------


A series of spin labeled acetylcholine analogs, in which the number of methylene groups between the quaternary nitrogen and the alcohol oxygen ranged between 1-5, have been examined as inhibitors of electric eel acetylcholinesterase. Evidence is presented suggesting that inhibition of acetylcholinesterase by the spin labeled ACH analogs is due to the high affinity of these compounds for the enzyme, inhibition is competitive and reversible. It has been shown that complex formation is of major
importance in the reaction between spin labeled ACH analogs and acetylcholinesterase. The acetylation step has been shown to occur by demonstrating that the leaving group is released as the reaction proceeds. Complex formation has been demonstrated by means of kinetic criteria. Kinetic parameter have been measured for the five compounds, and correlations with alkaline hydrolysis are discussed.

Abou-Donia, MB and Preissig, SH Journal/Toxicol Appl Pharmacol. 35: 269-82.

(1976) Delayed neurotoxicity from continous low-dose oral administration of leptophos to hens.

(1976) DDT: the degradation of ring-labeled 14C-DDT to 14CO2 in the rat.
Abou-Donia, MB and Menzel, DB Journal/Experientia. 32: 500-1.

Ring fission of p, p'-DDT was studied in the rat following a single oral dose of 0.74 mg kg (1.04 μCi) of uniformly ring-labeled 14C-DDT. Expired air was passed through a solution of ethanolamine-ethylene glycol monomethyl ether (1:2) to trap 14CO2. A total of 1.6% of the radioactivity administered was recovered in the expired air collected continually for 10 days, indicating that while degradation of the phenyl moiety is not a major route of p,p'-DDT metabolism in the rat, it is equal to the urinary excretion. Nevertheless, these results represent the most radical change accomplished in vivo of a residual insecticide yet reported in mammals.

(1976) Physiological effects and metabolism of gossypol.
Abou-Donia, MB Journal/Residue Rev. 61: 125-60.
(1976) Pharmacokinetics of a neurotoxic oral dose of leptophos in hens.
Abou-Donia, MB Journal/Arch Toxicol. 36: 103-10.

A pharmacokinetic profile of [14C] leptophos was determined in laying hens following a single oral dose of 400 mg/kg (0.58 μCi). Most of the radioactivity was excreted into the urine and feces. After 15 days, the total radioactivity recovered in the combined urinary-fecal excretion was 73.5% of the administered dose. A major part of the absorbed leptophos was concentrated in the eggs. The total 14C radioactivity in egg albumen was 7.29% of the administered dose as compared to 4.67% in egg yolk. The half-life for the disappearance of radioactivity from the birds' bodies following the administration of [14C] leptophos was 11.55 days. A correlation between the pharmacokinetics of leptophos and the susceptibility of the hen to delayed neurotoxicity is discusses.

(1975) Introduction to the theme: women and health.

(1975) Sulfonamide resistance mechanism in Escherichia coli: R plasmids can determine sulfonamide-resistant dihydropteroate synthases.

Several natural isolate E. coli strains highly resistant to sulfonamides and antibiotics are shown to contain a sulfonamide-resistant dihydropteroate synthase (2-amino-4-hydroxy-6-hydroxymethyl-7,8-dihydropteridine-diphosphate:4-aminobenzoate 2-amino-4-hydroxydihydropteridine-6-methenyltransferase, EC 2.5.1.15) in addition to the normal sensitive enzyme. The resistant dihydropteroate synthases examined are determined by an R plasmid and are smaller and less heat stable than the normal sulfonamide-sensitive enzyme. One synthase resistant to any sulfonamide tested, and to sulfanilic and arsanilic acids, was still inhibited by several non-sulfonamide analogs of p-aminobenzoate. Citrobacter and Klebsiella pneumoniae strains also show similar mechanisms of sulfonamide resistance.

(1975) Spin labeled acetylcholine analogs: studies of cholinergic receptor.

Some spin-labeled acetylcholine analogs, in which the number of methylene groups between the quaternary nitrogen and the ether oxygen ranged between 1-5, were synthesized to study drug interactions with acetylcholine receptors. None of the compounds tested, with the exception of the one that contained 2 methylene groups (SL-2) had any cholinergic activity. SL-2 was not capable of producing any nicotinic cholinomimetic activity. On the other hand it proved to have a very weak nicotinic cholinolytic activity on the receptors of the frog satorius muscle. This compound exhibited strong antagonism against muscarinic receptors of the isolated frog heart. The muscarinic cholinolytic action of the spin-label ACh analog is discussed in terms of the molecular perturbation theory of drug action.


Using the scratch test with self-made chrysanthemum pollen extract of 32,700 PNU/ml, a positive response was elicited in 60 of 316 patients (18.9%) with allergic rhinitis and bronchial asthma, and was positive in 42.5% adults with allergic rhinitis. On the other hand a 4.7% positive response was obtained in 84 non-allergic subjects. With the intracutaneous test, a threshold value was determined in 7 cases with 0.327 PNU/ml; 12 with 3.27 PNU/ml; 8 with 32.7 PNU/ml; and 8 with 327 PNU/ml, as opposed to one positive in 84 controls with 327 PNU/ml (1.3%). P-K tests were successfully done in 15 out of 16 cases. Furthermore, the results of in vitro neutralization tests using chrysanthemum and other compositae pollen extracts indicated the absence of sharing antigenic determinants between them. Provocation tests were conducted in 4 cases of allergic rhinitis and 3 cases of bronchial asthma with positive response in all the patients. From these results it was found that chrysanthemim pollinosis indeed exists in Japan, particularly in the mountainous districts.

(1975) A kinin model of mediation for food and chemical sensitivities: biobehavioral implications. 
Bell, IR Journal/Ann Allergy. 35: 206-15.

The plasma peptide hormone bradykinin is hypothesized to be a major mediator of the multiple-system functional symptomatology of adverse food and other chemical reactions. It is postulated that native foods as organic chemicals could act cumulatively with other stresses to mobilize directly the kinin-forming enzyme system.

(1975) [Influences of some agents on the enzyme-inducing activity of PCB (author's transl)].

(1975) Kinetic measurements of the release of prostaglandins from perfused rat lungs.

Prostaglandins released from isolated ventilated and perfused rat lungs were measured by a simple modification of the Vane technique using the rat stomach fundus as a continuous bioassay tissue. Exogenously supplied arachidonic acid was converted mainly to PGF2alpha which was determined by bioassay. A novel method for mixing a stream of inhibitors with the perfusate was used to determine PGF2alpha in the presence of substrate amounts of arachidonic acid. Using this system the apparent Km for PGF2alpha production with arachidonic acid as the substrate was found to be 1.90 X 10(-4)M, while the Ki for aspirin was found to 2.47 X 10(-4)M. These kinetic parameters are close to those reported for cell free systems and subcellular fractions suggesting that both substrate and inhibitor have ready access to the site of prostaglandin synthesis. The method appears to be generally useful to determine the effect of drugs and environment factors on the release of prostaglandins by the lung.


Abou-Donia, MB, Lyman, CM and Dieckert, JW Journal/Lipids. 5: 938-46.

(1968) The metabolism in vivo of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (DDD) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) in the chick by embryonic injection and dietary ingestion.

(1968) Chick microsomal oxidases. Isolation, properties, and stimulation by embryonic exposure to 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane.
Abou-Donia, MB and Menzel, DB Journal/Biochemistry. 7: 3788-94.