

Defining Chemical Injury

A Diagnostic Protocol and Profile of Chemically Injured Civilians, Industrial
Workers and Gulf War

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ABOUT THE AUTHORS

Dr. Heuser practices clinical toxicology. He has seen thousands of patients after toxic chemical exposure and over time developed and used a diagnostic protocol, which objectively documents chemical injury and impairment.

Heuser has published many peer reviewed articles, contributed book chapters,

and has been internationally recognized in his field. He has been invited to present his diagnostic protocol in Australia, before the German government (Bundestag) in Bonn, at the Karolinska Institute in Stockholm (Sweden), and before the Annual Conference of the National Gulf War Resource Center.

Patricia Axelrod directs The Desert Storm Think Tank and Veterans Advocate which is an ad-hoc association of active duty, reserve and retired soldiers, scientists, and researchers working together to assess the impacts and consequences of war in general with a specific emphasis on The Persian Gulf War. Axelrod's work has assisted in American, German and United Kingdom governmental investigation and reform. Her work has received a Project Censored Award from the Sonoma State University, Sonoma, California. She is also the recipient of a 1990-91 John D. and Catherine T. MacArthur Foundation Research and Writing Grant, which helped seed The Desert Storm Think Tank. Her 1993 ground breaking article, «Research Guide for Desert Storm Syndrome (International Perspectives in Public Health Vol. 10, 1994) has been entered into the records of a number of U.S. funded committees for the investigation of Persian Gulf War illness, including those conducted by Senator Donald Reigle, the National Institutes of Health, and the Presidential Advisory and Oversight Committees. In preparation for this article Axelrod traveled to and from post-war Baghdad, Iraq. In addition she has interviewed and debriefed hundreds of Persian Gulf Veterans.

Both Heuser and Axelrod are founding members of the State of California, Reserve Officer Association committee on Persian Gulf War Illness.

Sylvia Heuser is president of EMRIC (Environmental Medical Research and Information Center) which is based in Dr. Heuser's office and supports all his research and writing projects with ideas, literature search, and review of patient files.

INTRODUCTION

Chemical injury can cause severe, often disabling multi-system complaints, which may persist for months and at times years after chemical exposure has ceased. Physicians who see chemically injured patients are frequently baffled

when they face a patient with multiple complaints, which do not fit into a known diagnostic disease category. Furthermore, regular laboratory tests (e.g. CBC, liver function tests, sedimentation rate, urinalysis) are often normal as is a cursory physical examination.

The diagnostic exploration of a chemically injured patient is a new field, which is difficult for the inexperienced physician. Chemically injured patients often complain of impaired cognitive and memory functions, intermittent confusion and disorientation, changes in behavior and mood, word-finding problems, sleep disorders, decreased libido and potency. At times they complain of seizure-like events. They also often report recurrent flu-like symptoms, fatigue and exhaustion, malaise, headaches, and chronic pain. Skin rashes, gastrointestinal complaints, and other health effects may also be present. Different patients may react differently to a given chemical or group of chemicals.

Toxic effects cannot be objectively evaluated unless every involved system is studied with advanced and sophisticated methodology. Without benefit of that process, a chemically injured patient will be dismissed with a diagnosis of post-traumatic stress disorder, somatization disorder or other labels implying that «it's all in their heads» [Davidoff, et al., 2000]. The largest patient population to have received such a diagnosis is that of the Persian Gulf War Veterans. As of the writing of this article, nine years after the armed conflict, several hundred thousand veterans still suffer from a host of symptoms called «Persian Gulf War Illness» which may in large part be due to chemical injury [Jamal, 1998; Everson et al., 1999].

The authors understand that war time in Iraq exposed people not only to chemicals but also to uranium 238, a.k.a. depleted uranium, electromagnetic radiation, experimental vaccines, pyridostigmine bromide, biological warfare agents, and diseases and parasites indigenous to the Middle East e.g. leishmaniasis and brucellosis. Any of these toxins and infectious agents, individually or in combination, may carry with it a host of health effects. The purpose of this paper is not to dismiss those impacts but rather to offer currently available diagnostic techniques which, if applied correctly, will help both patient and physician assess how a toxic environment alone may contribute to illness otherwise dismissed as psychosomatic.

In this paper we will guide the reader through a diagnostic protocol which the senior author has developed and used on thousands of his chemically injured patients. We propose tests and consultations (from experts in their respective fields) which from our experience and research are most helpful in documenting and at times quantifying the effects of toxic chemical exposure.

In discussing our approach, we will take one organ system at a time, discuss and select diagnostic tools and tests appropriate to the evaluation of a given system. Single abnormalities in a single system can have many causes. Abnormalities in

multiple systems can also have many etiologies. However, a careful differential diagnosis (using this suggested protocol) will arrive at a tenable diagnostic impression of chemical injury if multiple objective abnormalities are found and cannot be explained on any other basis. Thus, a diagnosis of chemical injury is arrived at in part by exclusion of other diseases, which may have predated the toxic exposure in question.

In the experience of the authors there is no doubt that chemical exposure (solvents, pesticides, chemical weapons, others) occurred during the Gulf War. In this sense, Gulf War Veterans deserve the same careful evaluation which is indicated in patients who have been exposed to chemicals at home, at work, or elsewhere (e.g. commuting) here in the USA.

The protocol begins with an exhaustive case history, to be followed by a careful physical examination, laboratory tests, and specialty consultations. Patient and doctor should seek out consultants who display interest rather than indifference. Generally an enthusiastic, curious and interested consultant specialist will be a better member of the evaluation team and bring his or her methodology to bear when tackling the problem of diagnosing chemical injury. The evaluation process ends with case definition and a better understanding of the patient's problems and needs. Most importantly, this process will lay the foundation for rational and compassionate treatment.

This paper does not address the experienced clinical toxicologist. Rather, it is meant to help the personal physician to follow a road map of investigation when facing a patient who presents with a history of chemical injury.

This paper is also meant to help the educated layperson who has been chemically injured and is being told that nothing is wrong since nothing abnormal can be found (on minimal testing only!).

In our experience, both the general physician and the educated patient need a guide to follow when trying to understand and evaluate a toxic situation.

This paper is meant to function as such a guide.

The need for a road map is especially urgent since society is pressured by some of its segments to attach a psychiatric diagnosis to some patients and to then hospitalize them with that diagnosis.

HISTORY

Histories as well as the physical examinations are meant to guide the clinician into the process of a differential diagnosis in which certain conditions are tentatively accepted or rejected. Appropriate testing will then follow and rule in or out conditions and diseases in a given patient.

An individual and family history must be carefully obtained from the patient. Past and present conditions and diseases (incl. those of childhood and connected with occupation), as well as past and current occupational, incidental or accidental chemical exposures should be listed. Short-term memory loss is present in many patients and therefore at times makes them poor historians. Thus it is desirable to engage support from family members and significant others to participate in the history, which may then be more correct and complete.

Patients should be encouraged to list what appear to be «allergic» or «sensitive» reactions to chemical substances, which were previously not experienced as harmful. These include chemicals such as gasoline, fumes and perfumes, household cleaners and other chemicals in everyday use. Reactions to these chemicals may include skin rashes, hives, eye and throat irritations, sinus problems, nausea, dizziness, and flu-like symptoms. These may have developed during the initial chemical exposure but may also recur when a patient has become chemically sensitive and now reacts to even low amounts of a given chemical or chemical mixture. This reaction to low level exposure is called Multiple Chemical Sensitivity (MCS) [Cullen, 1987]. If not carefully evaluated, MCS patients will easily be misdiagnosed as suffering from somatization disorder, post-traumatic stress disorder or other psychiatric labels.

Patients with a history of chemical injury may develop chronic fatigue [Behan, 1996; Bell et al, 1998; Buskila, 1999; Dunstan et al, 1995; Heuser, 1993; Tirelli, 1998] (incl. Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), chronic pain (incl. headaches and fibromyalgia), intermittent dizziness and faintness (especially after prolonged standing), and other significant and at times disabling symptoms. A complete history should list all of the above and all additional problems the patient has.

Patients should also be asked to obtain all existing civilian and/or Department of Defense and Veteran Affairs medical records for review.

In the case of Persian Gulf or other veterans, special consideration should be given to wartime duties and experiences including: known or suspected chemical exposures, number of sick bay calls in theater and out, number of times the veteran was ordered to don chemical protective gear, and number of unexplained sightings of dead animals or deceased humans.

PHYSICAL EXAMINATION

A chemically injured patient deserves a very careful physical and especially neurological examination.

The skin should be examined for rashes and scratch marks. Flushing (suggesting a mast cell disorder) should be noted if present during the physical examination. Submandibular lymph node swelling and parotid gland swelling should be noted.

Blood pressure should be examined for orthostatic hypotension, if possible after quiet standing for twenty to thirty minutes (while being attended by a competent observer).

A detailed comprehensive neurological exam should document balance and sway (often impaired), the rapidity and smoothness of rapidly alternating movements (often impaired), and coordination (also often impaired).

If abnormalities are suspected or actually found, the patient should be referred to a specialist for more objective tests.

CENTRAL NERVOUS SYSTEM

Neurotoxic chemicals can reach the brain via the blood following inhalation, ingestion, or through skin absorption. A different route of entry is via the nasal passages into the roof of the nose and then through the nerves in the cribriform plate into the olfactory bulb and beyond (e.g. limbic system, neuro-endocrine system and others).

Every patient who complains of impaired cognitive, memory and other central nervous system functions deserves a detailed neurological evaluation. So does the patient who complains of impaired balance, coordination, speech, and sensory and/or motor nerve function. Finally, a neurological evaluation is also indicated in patients who suffer from tremor, chronic headaches, chronic pain, and intermittent impairment of consciousness. It should be noted that some patients are unaware of their deficits. Therefore, every chemically injured patient deserves a comprehensive neurological and neuropsychological evaluation.

No single test, not even a neuropsychological evaluation, can tell the whole story. This is why one has to rely on history obtained from the patient and witnesses, record review, observation during office visits, a neurological examination, and evaluation of brain function with tests, which are added to the neuropsychological evaluation. The choice of these additional tests (e.g. Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), evoked response studies) depends not only on the clinical indications but also on the availability of advanced technology and interested and knowledgeable expert physicians [Heuser, 1992].

Neurological and neuropsychological functions may fluctuate, making challenge tests desirable whenever possible. Trying to solve mathematical or other problems can constitute such a challenge.

Structural effect on the brain is assessed by Magnetic Resonance Imaging (MRI). In some cases (e.g. in suspected multiple sclerosis and brain and pituitary tumours) a more sensitive evaluation uses the MRI after injection of a contrast medium (e.g. gadolinium) which «lights up» the affected part of the brain.

Lesions resembling those seen in multiple sclerosis and vascular (ischemic) disease are often seen in patients after chemical injury.

MRI scanning of the brain should be done in every patient with neurological problems. MRI is preferable to Computed Tomography (CT) since an MRI sees soft tissue (e.g. brain) better than CT and also avoids exposure to radiation.

In our experience SPECT and/or PET are often abnormal while MRI is more often within normal limits. Certainly, functional impairment far exceeds structural impairment in chemically injured patients. It is commonly assumed that brain function is symmetrically affected by chemical exposure. In our experience, this is not true. More often than not, abnormalities are asymmetrical in distribution [Heuser and Mena, 1998].

Function of the brain can be assessed by a variety of tests. The choice of these tests is often dictated by their availability in a given community and by VA, DOD or civilian insurance coverage. A brief discussion of available functional tests follows:

A neuropsychological evaluation [Hartman, 1995] is mandatory in each patient after neurotoxic exposure. A competent neuropsychologist will also be able to test for malingering and for a psychiatric disorder. In addition he or she will be able to predict which areas of the brain are most likely effected. This prediction can then be correlated with other function tests.

The EEG sees only activity of the cortical layers of the brain. Therefore, it is unable to detect abnormalities deep inside the brain. Recording time should be at least thirty minutes and may well have to extend to an hour or longer. Routinely, recording is done while the patient is alert, during spontaneous sleep, and before, during and after hyperventilation and photic stimulation. All these conditions and measurers can bring out abnormalities which may not be seen during a resting EEG. While the tracing is subjectively «eyeballed» by the examiner, it is obtained over a considerable time interval and may therefore detect abnormalities, which are not seen during other tests. A well-executed EEG will give valuable information about left-right hemisphere differences, normal vs. abnormal frequencies, and episodic discharges (e.g. seizure activity). EEG abnormalities may be asymmetrical after chemical exposure, which can cause slowing, dysrhythmia, and also occasionally seizure activity. Long-term effects were first described by Duffy et al. in 1979. If seizure activity is suspected, an EEG together with PET scanning is the optimal approach. The senior author has found hypermetabolism, raising the suggestion of seizure activity, in the deep subcortical (e.g. amygdala) areas of the brain after chemical exposure [Heuser, 1999; Heuser and Wu, 1999, 2000].

EEG, PET and also prolactin levels should be done as close (in time) as possible to an actual or suspected seizure. Prolactin levels have been described as being elevated shortly after a seizure [Bauer, 1996].

EEG studies during sleep are necessary if a sleep disorder (esp. sleep apnea) is suspected. This can occur after chemical exposure [Ulfberg et al., 1997] and can cause elevation of blood pressure, chronic fatigue, headaches, and other symptoms.

A quantitative EEG (qEEG) analyses a short epoch of a given EEG tracing by computer. Very few investigators are properly trained in analyzing a qEEG. Also, no published data are available after toxic exposure.

Evoked response studies measure the speed of electrical conduction of a given stimulus (e.g. a light flash or sound click or electrical stimulus) to the appropriate brain region. The resultant electrical activity in the target area of the brain builds itself into a waveform, which has positive and negative peaks. These normally occur after a given number of milliseconds. Abnormalities can be seen after neurotoxic exposure when symmetrical or asymmetrical delay of peaks and change in waveforms can occur.

A different evoked response evaluation is the P300 study in which regularly occurring clicks are interrupted by a random click. The positive deviation of the curve - which normally occurs 300 milliseconds after the auditory click - then becomes a measure of central nervous system function. This is a well-studied response, which is known to correlate with cognitive function. Dysfunction can be found after neurotoxic exposure [Morrow et al., 1992].

SPECT consists of inhalation and/or subsequent intravenous administration of a radioactive compound. As the compound circulates through the brain, the computer constructs a color image in which colors have been calibrated to represent varying blood flows (perfusion) through the region of interest. A typical finding after neurotoxic exposure may be hypoperfusion in the frontal, temporal and parietal areas of the brain, usually in an asymmetrical distribution [Heuser and Mena, 1998]. This finding in chemically injured patients is indicative of impaired blood flow and oxygen delivery to a given part of the brain. Hypoperfusion of the temporal lobes can be correlated with impairment of short-term memory, which is known to be laid down in the temporal lobes. Of particular interest to Persian Gulf Veterans is the work of Dr. John Vento who found a high percentage of SPECT abnormalities amongst his memory and cognitively impaired Gulf War veteran population [Vento et al., 1997].

PET yields an additional measure of brain function. It provides color scalimaging of an intravenously injected radioactive compound (commonly a glucose derivative). As the brain requires glucose for its activity, its accumulation in various parts of the brain is a measure of brain function. Decreased activity is

often seen in the cortical areas while increased activity may be seen in the deep sub-cortical areas in chemically injured patients [Heuser, 1999; Heuser and Wu, 1999, 2000].

Magnetic Resonance Spectroscopy (MRS) is a procedure developed to display the presence of neurotransmitters in the brain [Ross et al., 1992]. This is an evolving specialty, which has a lot of promise. Recently, yet unpublished definite abnormalities were described in Gulf War Veterans

Functional MRI (fMRI) is a research tool that does not require the administration of a radioactive compound. As yet, no data are available on the effects of neurotoxic exposure.

Prior to any functional testing, the patient should again be asked what drugs or other preparations he or she is on. Since they may affect the function tests, they should be discontinued if at all possible. Most investigators will be satisfied when a patient has not taken any nonessential drugs for one week. Ideally, the patient should be off all nonessential drugs for more than a month prior to any functional testing.

PERIPHERAL NERVOUS SYSTEM

Frequent complaints after neurotoxic exposure are numbness, tingling, burning and crawling sensations, weakness and pain.

The standard approach is to test peripheral nerve function by doing ElectroMyoGram (EMG) and nerve conduction studies. We have found however that Current Perception Threshold (CPT) studies constitute a more comprehensive approach. While the literature on the use of CPT after neurotoxic exposure is still sparse [Bleecker et al, 1997], CPT is well established as a test for peripheral sensory nerve function [Katims, 1998]. In our opinion, CPT is a more sensitive test of peripheral nerve function since it also examines small (e.g. C) fibers that cannot be examined by nerve conduction velocity studies. The most recent CPT equipment employs a double blind approach and has therefore become increasingly objective. Biopsy of the sural nerve may supply additional information.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system controls functions such as temperature, perspiration, vascular tone (including blood pressure), heart rate, smooth muscle tone (including intestinal and bladder) and others.

The hypothalamus (i.e. neuro-endocrine system) interacts with the autonomic nervous system. Chemicals can impair both hypothalamic and autonomic nervous system functions.

Tilt table testing [Rowe and Calkins, 1998] is becoming a recognized test for assessment of autonomic nervous system function, especially in patients with CFIDS which often develops as a result of chemical injury.

EYES

An eye examination is recommended for every patient with a history of chemical injury.

Patients frequently complain of eye irritation after toxic chemical exposure. While this may simply be due to an inflammatory response to the irritating chemical, it can also be due to dryness.

Intermittently blurred vision is another frequent complaint that can be due to a dry eye syndrome. In our patient population, Sjogren's syndrome is very rare, while dry eye syndrome secondary to chemical exposure is frequent.

After studying (unpublished data) several hundred patients we have found that tear quantity and tear quality are impaired in more than one half of chemically injured patients. Quality tears are produced by the goblet cells. Their quantity can be assessed by the Schirmer test, their quality by examining tear break-up time [Franck and Boge, 1993; Sommer et al., 1994; Bulbulia et al., 1995].

Goblet cell mucous secretions enhance tear quality by providing viscosity and eye lubrication independent of the lacrimal tear gland, which provides tears for crying. Therefore, a patient can still cry copious tears even with a dry eye syndrome. It should be understood that in our experience (Sadun and Heuser, unpublished data) dry-eye syndrome may continue for years, may be life-long, and can best be relieved with the use of artificial tears. Chemically produced dry eye syndrome should not be confused with Sjogren's syndrome which also causes dry eyes and can be ruled out with appropriate tests [Bell et al., 1999; Manoussakis and Moutsopoulos, 1999; Rice, 1999]. A routine eye examination does not include a test for dry eye syndrome which therefore often goes undiagnosed. Typically, tear quantity is measured by the Schirmer test in which a filter paper is placed between the globe of the eye and the lower lid. A yellow liquid (fluorescein sodium and benoxinate hydrochloride ophthalmic solution) is dropped into the eye and its advance on the filter paper is measured after a five-minute interval. An advance of less than 10 millimeters indicates insufficient tear production.

Color vision is also often affected after chemical exposure. This however has to be tested by using the Lanthony D-15 [Mergler et al., 1987; Mergler, 1994] rather than the usual tests for color blindness.

Visual field defects, increased electric and sunlight sensitivity, accommodation inertia and other abnormalities have been described and should therefore always be tested for.

EARS, NOSE, AND THROAT (ENT)

Patients frequently complain of intermittent nosebleeds, sore throats, dryness, change in sense of smell, congestion, intermittent cough, impairment of voice (hoarseness), sinus problems, and other ENT symptoms. Vertigo and dizziness are also frequent complaints.

When complaints persist, a competent ENT evaluation is mandatory. Here again, some patients are unaware of their deficits. Thus, every patient should ideally be tested after toxic exposure. This will involve:

Inspection of the nasal mucosa which is often atrophic, brittle, dry, and shows a cobblestone pattern [Meggs et al., 1996].

A nasal smear, especially for eosinophils. These cells are typical of allergy and are not typically found after chemical exposure.

Biopsy of the mucosa of the middle turbinate. This will distinguish between a chemical and an allergic change. One change occasionally seen on nasal mucosal biopsy is the presence of squamous metaplasia. This is definitely not a sign of allergy but is a sign of chemical exposure. Patients with this finding deserve close follow-up since squamous metaplasia may potentially develop into cancer.

Videolaryngoscopy. This will examine vocal cord appearance and function. Both may be impaired from chemical exposure and/or reflux but also because of impaired function of the nerves supplying the vocal cords.

Platformography and other sophisticated tests to evaluate a patient for balance problems and vertigo.

ElectroNystagmoGram (ENG) and other specialized tests for evaluation of dizziness. Vestibular dysfunction was recently described [Roland et al., 2000] in Gulf War Syndrome.

CT scanning of the sinuses if sinusitis is suspected.

IgA content of saliva. One function of the inner lining of the nose, the throat, the lungs, the gut and the bladder is to defend the body against intruders. IgA (an immune antibody) is one of these defense mechanisms. A saliva specimen is usually representative in the sense that IgA levels measured in the saliva may be assumed to be similar all the way through the mucosal system. Salivary IgA is

often decreased after chemical exposure [Ewers et al., 1982]. This decrease may explain the low defense of a given individual against external intruders.

A saccharin test by which saccharin is placed inside the nose and beyond the middle turbinate. One then asks the patient when he or she first notices a sweet taste. The time elapsed between the placement of a small saccharin crystal and the sweet taste is an indicator of mucociliary function which is often impaired after chemical exposure [Andersen et al., 1974; Capellier et al., 1997; Schafer et al., 1999].

NASAL AND PULMONARY PASSAGES

Patients frequently complain of:

Shortness of breath and dyspnea on exertion which can be due to nasal congestion with a Reactive Upper Airway Dysfunction Syndrome (RUADS), Vocal Cord Dysfunction (VCD) with Reactive Laryngeal Dysfunction Syndrome (RLDS), and hyperreactive airways (incl. Reactive Airways Dysfunction Syndrome (RADS), and of course, other conditions contributing to shortness of breath (e.g. anemia, heart disease, and others).

Cough (intermittent) which can also be due to RLDS, bronchitis, and asthma (incl. RADS) and other conditions. Here again a careful differential diagnosis is mandatory.

Pulmonary function may be impaired as a result of chemical exposure.

Hyperreactive airways with abnormalities suggestive of obstructive impairment are often found. The most sensitive indicator is the Forced Expiratory Flow (FEF) 25 -75% measurement, which is part of a complete pulmonary function test. This measurement is often decreased after chemical irritant exposure and has the additional advantage of being generally independent of the effort the patient makes. This indicator is of course only one measure of a necessary comprehensive pulmonary function test.

A methacholine test will often help to diagnose hyperreactive airways.

Restrictive airways from impairment of the elasticity of the lungs leading to reduced ability to take a deep breath are also often found after chemical irritant exposure. Asbestosis is a disease that typically causes restrictive and also obstructive airways disease.

A chest x-ray will be part of the process of the differential diagnosis.

A CT scan of the lungs is indicated whenever restrictive disease is suspected.

In the 1980s a number of patients were described who had suffered from very short exposure to inhaled irritating chemicals and then developed an asthma-like condition for years thereafter. This has been termed RADS [Brooks et al., 1985, Brooks, 1995]. In some cases, RADS has been found to continue for more than ten years after short-term exposure [Piiirila et al., 1996].

When the upper nasal airways have become reactive from a previous chemical exposure, the term RUDS has been introduced [Meggs, 1994; Meggs et al., 1996].

When shortness of breath is caused by problems within the vocal cord area (vocal cord dysfunction), the term RLDS (Reactive Laryngeal Dysfunction Syndrome) applies. This term was introduced by the senior author [Heuser et al., 1998] to describe patients who have voice problems after an initial chemical irritant exposure and then continue, sometimes for years, to have voice problems whenever exposed to even small amounts of irritating chemicals. In addition, these patients may develop shortness of breath.

One of the functions of the lungs is exchange of oxygen. The resultant level of oxygen saturation in the blood can be measured by oximetry. This may be low when lung function is impaired (and also for other reasons). Therefore, oximetry is routine in our office in all patients who have a history of toxic inhalation exposure.

GASTROINTESTINAL SYSTEM

Patients often have acid indigestion incl. GastroEsophageal Reflux Disease (GERD), irritable bowels including Irritable Bowel Syndrome (IBS), and food allergies. These conditions are frequently diagnosed but are not specific for chemical exposure.

Additional complaints include abdominal cramping, intermittent constipation and/or diarrhea, and also intermittent nausea and vomiting. Unfortunately, a given toxic chemical leaves no diagnostic signature in the gastrointestinal system. Therefore all the above complaints are usually considered as nonspecific. Nevertheless, the term Reactive Intestinal Dysfunction Syndrome (RIDS) has recently been introduced [Lieberman and Craven, 1998].

Malabsorption with weight loss may occur in some patients after chemical exposure. In this context, patients should be evaluated for non-tropical sprue [Murray, 1999].

Liver function tests should always be done on every patient who gives a history of past or ongoing chemical exposure. Here again, toxic chemicals do not usually leave a signature, which is diagnostic of chemical exposure.

Low salivary IgA levels may be representative of an impaired mucosal intestinal defense mechanism after chemical exposure.

KIDNEYS AND URINARY SYSTEM

After chemical exposure patients often complain of urinary frequency and urinary discoloration. The former is not usually due to diabetes insipidus or urinary infection and therefore remains unexplained at this time in these patients.

Chemicals can cause hematuria, often microscopic [Gun et al., 1998].

Kidney function can be affected after chemical exposure [Lauwerys and Bernard, 1987; Mutti et al. 1992; Fowler, 1993; Hook and Goldstein, 1993] which in the extreme can cause kidney failure.

Creatinine clearance and twenty-four hour urine collections for protein (incl. globulin fractions) may become necessary to follow patients with significant impairment.

SKIN

Recurrent rashes (with or without itching), hives, welts, «blood blisters» and other skin changes (incl. visible flushing) are frequent complaints after chemical exposure and can continue for a long time after exposure has ceased.

Here again, inspection reveals no signature, which would be specific for toxic exposure.

Many of our patients carry a diagnosis of rosacea. This is usually considered to be of unknown origin. If chemically induced or aggravated rosacea indeed exists, it has no distinguishing characteristics from a diagnostic point of view.

Also of note is in our observation that chemical exposure of the skin appears to at times accelerate sun induced aging of the exposed skin.

In addition to inspection our consulting dermatologists will also obtain a skin biopsy in unaffected areas. This frequently shows perivascular dermatitis and the presence of mast cells. The latter may be indicative of a mast cell disorder which can develop after chemical exposure and then explain allergies, sensitivities to chemicals, sun light and ultraviolet light, and other reactions (incl. flushing) which may all be found in our patient group [Heuser and Kent, 1996; Heuser, 2000].

Contact and other dermatitis should be evaluated with appropriate tests [Marks and DeLeo, 1997; O'Malley, 1997]. Dermal uptake of solvents was studied by Brooke et al. (1998) and others.

Very sophisticated dermatopathological changes after exposure were described by Prof. Johansson's group [Gangi and Johansson, 1997; Liang et al, 1998; Rossi and Johansson, 1998].

IMMUNE FUNCTION

Sensitivity to allergens (incl. foods) and/or chemicals (incl. drugs) is a frequent complaint in our patient population. This can be further analyzed with appropriate tests. However, changes in immune function are often not clearly related to specific symptoms and signs and yet may be so profound that they should always be tested for.

When patients develop allergies after chemical exposure, these should be evaluated by an allergist with skin testing and other appropriate tests. We routinely order total IgE and check for eosinophils. If elevated in blood (IgE, eosinophils) and nasal smears and/or biopsy specimens (eosinophils), a diagnosis of allergy is justified.

The immune system consists of many cells that can be counted in a blood sample. Function of these cells (e.g. mitogenesis, natural killer cell function) can be tested only in specialized laboratories.

A rapid increase in TA1 (CD3+, CD26+) and T3 positive (CD3) cells can be a very sensitive indicator of chemical exposure. While increased TA1 cells can be seen in auto-immune disease (e.g. multiple sclerosis), they more frequently show a temporary increase after exposure, particularly if the patient is sensitive to chemicals [Heuser et al., 1992].

It should be stated at this time that different organ systems can have a different sensitivity to chemical exposure. For instance, the immune system may react much more than the brain and other organs (or vice versa).

Among immune function tests the test for natural killer cell function is particularly important. This function is measured by bringing live natural killer cells in contact with live human leukemia cells. Normally aggressive natural killer cells will attach to these leukemia cells and dissolve them.

The result is expressed in *lytic units* and often shows impairment of this function after chemical exposure. Long-term impairment increases cancer risk. This is why we routinely test for killer cell function. If impairment is found, it may be corrected with vitamin C [Heuser and Vojdani, 1997].

The immune system also releases certain cytokines and other factors, which may become indicators of chemical exposure. In our experience and that of others [Blackwell, 1999; Luster et al., 1999; Scheumann and Tiegs, 1999] this is true of

Tumour Necrosis Factor (TNF-alpha) which is elevated in many of our patients after toxic exposure.

When chemicals attach themselves to some of the body's proteins, the immune response may become confused and become an autoimmune response. This is frequently found after immunotoxic exposure [Bigazzi, 1997; Rich, 1996]. A positive ANA titer, positive rheumatoid factor, and positive tissue (e.g. thyroid, myelin, smooth muscle, parietal cells, and others) antibodies are examples of that response [Gard and Heuser, 1990; Heuser et al., 1992]. It is important to realize that auto- antibodies may appear after chemical exposure but may go away once the exposure has ceased (Heuser, unpublished data).

Interestingly, full-blown autoimmune disease (e.g. Systemic Lupus Erythematosus and Multiple Sclerosis) is rarely found in our patients after chemical exposure which however seems to push patients in the direction of such diseases.

After chemical exposure, gamma globulins may be low. This is why we often obtain IgG subclasses. If abnormal, the patient may benefit from i.v. gamma globulin infusions.

Typically the sedimentation rate (ESR) is normal or even low normal after chemical exposure unless infections or autoimmune disease are the result.

Antibodies to certain chemicals can also be looked for and may, if positive, constitute a lead as to what exposure has caused the immune system to react [Thrasher et al., 1987].

In our opinion, immune system testing and testing for auto-immunity should be routine in all patents after toxic exposure.

ENDOCRINE SYSTEM

Chemical exposure can cause significant, at times disabling, chronic fatigue. While these patients usually end up with a diagnosis of CFIDS, one should nevertheless consider other causes of chronic fatigue. In this context, hypothyroidism has to be ruled out with appropriate tests (e.g. TSH, thyroid antibodies) which may have to be repeated.

While hypothyroidism seems to be a relatively frequent occurrence after chemical exposure, adrenal insufficiency is rare. However, we have seen cases of chemical sensitivity, which could, in retrospect, be explained on the basis of a well-documented adrenal insufficiency. When this was adequately treated, the chemical sensitivity disappeared. An early morning cortisol level is a good screening test, so is a twenty-four hour urine collection for this compound. More detailed testing and consultations by endocrinologists will be necessary,

particularly if the patient complains not only of severe fatigue and exhaustion and weakness but also allergies, nausea and headaches.

Women often complain of loss of sex drive and of irregular menstrual bleeding. The latter can sometimes be explained by the estrogen-like effects of many chemicals (solvents, pesticides) [Colborn et al., 1997; Barnard and Heuser, 1998].

DeHydro-Epi-Androsterone (DHEA) levels are frequently low in patients who suffer from chronic fatigue. This often responds to appropriate replacement therapy.

Men frequently complain of loss of libido and potency.

The most striking finding in our male population is a high percentage of abnormal shapes on examination of sperm in the ejaculate. Abnormal morphology is a more frequent finding than a low sperm count [Heuser and Marik, 1996]. A number of authors have addressed changes in sperm in this context [Auger et al., 1995; Bujan, 1998; Indulski and Sitarek, 1997; Tielemans et al., 1999; Var. authors, 1995]. Prolactin levels may be increased shortly after a seizure [Bauer, 1996]. They may also be chronically increased in some patients with pituitary tumours and hypothyroidism.

The pituitary master gland governs most endocrine glands. This in turn depends on the hypothalamus for its function. The hypothalamus has connections to all other parts of the brain and therefore is subject to impaired function after neurotoxic exposure. Nasal pathways transport a neurotoxic stimulus and/or chemical into the olfactory bulb and then on to the limbic system and hypothalamus resulting in neuro-endocrine problems after neurotoxic exposure.

REGULAR LABORATORY STUDIES

An astute clinician will carefully select tests needed to go through a differential diagnosis of a patient's complaints. Of particular importance are conditions and diseases that can cause multi-system complaints similar to those of toxically exposed patients.

Some infections occur independently of toxic exposure (e.g. Lyme disease, HIV and others). Others (e.g. viral, fungal) have been postulated to be the result of chemical exposure as have mycoplasma infections [Baseman and Tully, 1997; Vojdani et al, 1998].

Anemia, diabetes mellitus, hepatitis, and other conditions can cause chronic fatigue.

Vitamin B12 deficiency can cause neurological problems.

While porphyria is very rare in our patient population, abnormalities of porphyrin metabolism [Downey, 1999] are relatively frequent but usually not severe enough to explain symptoms. A study of porphyrin metabolism is in our opinion more meaningful if it is done more than once and is timed in relation to exposure.

The above are just a few of the conditions and diseases which have to be considered and ruled out in order to arrive at a correct diagnosis.

A comprehensive laboratory evaluation is a necessary part of the differential diagnosis and therefore mandatory in our patient population.

Laboratory technicians should be advised of possible allergic responses to alcohol, band-aid tape, metallic and/or rubbers materials employed in blood drawing and other techniques.

TOXICOLOGICAL CONSIDERATIONS

Route of Entry. Chemicals can be absorbed by inhalation, swallowing, and via the skin. It should be stressed that chemicals can irritate and/or enter the brain via the intranasal route to the olfactory bulb and on to other structures including the limbic system and the hypothalamus.

Dose-response. Most pure toxicologists stress the dose while we, as clinicians, stress the response part of the dose-response curve. Regulatory agencies (e.g. OSHA) suggest certain limits of exposure. These limits apply to healthy adult males who work an average eight-hour day for five days a week. They do not apply to females, children, the elderly, and any already impaired individuals. Nor do they apply to individuals who spend most of their days and all night at home where they might be exposed.

In view of the above, a low dose (even below government suggested limits) exposure can cause significant health affects in some people.

When there is ongoing toxic chemical exposure, blood, urine or fat tissue measurements of suspected chemicals or their metabolites are in order. Once time has passed, these measurements may lose their significance. Certainly, long term disabling conditions can develop and continue after the triggering chemical has long disappeared from body fluids and tissues.

Sensitization and kindling. Some chemicals are known sensitizers and thus become damaging in even very small doses. Neurophysiological research has shown that pain pathways can be sensitized [Willis and Westlund, 1997]. As a result, a patient can perceive pain even when the stimulus is very small.

Kindling [Bell et al. 1997] refers to the fact that repeated stimulation with subthreshold electrical current can eventually bring about a seizure disorder in

animal models. Certain chemicals can result in similar effects when repeatedly administered into the extended amygdala region of experimental animals in subthreshold doses [Albertson et al., 1985; Gilbert, 1995]. Our PET findings may support a kindling mechanism [Heuser and Wu, 1999, 2000] and also explain the emotional changes found in patients after chemical injury [Aggleton, 1992]. Considering these findings, one should be much more careful to diagnose functional disorders [Barsky and Borus, 1999] in chemically injured patients. Furthermore, cytokines are released after chemical exposure and may in turn cause behavior changes [Anisman and Merali, 1999].

The above are but a few examples of the fact that low dose exposure can cause significant health effects in some patients. These patients deserve the full protocol, even if the dose has remained ill-defined or was considered to be too low to have caused health effects.

Chemical injury versus chemical sensitivity. In our experience almost all patients who claim MCS have objective evidence of chemical injury in one or more organ systems. This is why our protocol will usually detect objective abnormalities in these patients.

Chemical injury is defined as a long lasting impairment of a given function during and/or after toxic exposure.

Chemical sensitivity (incl. MCS) and intolerance are defined as a recurrent temporary impairment of function after exposure to a low concentration of chemicals (so low that it does not effect the normal population).

While MCS needs to be documented by using challenge tests, evidence of chemical injury is almost always present in these patients and can therefore be documented at any time by using the protocol developed by the senior author.

Chemical mixtures. In real life situations most patients are exposed to mixtures of chemicals rather than a single chemical. In this case guidelines given by OSHA, NIOSH and other agencies may not apply since interaction between chemicals in the chemical mixture may have unexpected or exaggerated effects [Feldman et al.; 1999, Pollak, 1993; Yang 1994].

CONCLUSIONS

Patients who have suffered a chemical insult may develop long-lasting, at times disabling, conditions. If the examination is limited and cursory, a chemically injured patient will be mislabeled as suffering from a somatization disorder, conversion reaction, psychosomatic or psychiatric illness. This then is a tragic mistake and misdiagnosis.

Frequently, patients with a history of toxic exposure and continuing symptoms develop multi-system impairment. It is the resulting constellation of symptoms and impairment, which in the opinion of the senior author is typical of toxic exposure (incl. Persian Gulf War Illness).

A diagnosis of toxic chemical injury can be made if:

Impairment developed during or after toxic exposure(s).

A typical constellation of multi-system impairment is established with objective tests. Rarely (e.g. in RADS) is only one system effected.

Other diseases and conditions that are known to cause multi-system impairment have been ruled out.

The protocol presented in this paper, using a comprehensive evaluation, will prove or disprove, with objective and recognized tests, the presence of physical injury after toxic chemical exposure.

SUMMARY

In this paper, a comprehensive protocol for the clinical evaluation of a chemically injured patient is described.

It is noted that an in depth evaluation often shows objective evidence of physical injury while a limited cursory examination may not.

It is stressed that exposure to toxic chemicals can cause severe functional impairment in many organ systems while the organ structure may remain intact. This impairment may continue for months or years after exposure has ceased.

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ABBREVIATIONS

ALS Amyotrophic Lateral Sclerosis

ANA Anti-Nuclear Antibody
CBC Complete Blood Count
CFIDS Chronic Fatigue Immune Dysfunction Syndrome
CPT Current Perception Threshold
CT Computed Tomography
DHEA DeHydro-Epi-Androsterone
EEG ElectroEncephaloGram
EKG ElectroKardioGram
EMG ElectroMyoGram
ENG ElectroNystagmoGram
ENT Ears, Nose, Throat
qEEG Quantitative ElectroEncephaloGram
FSH Follicle Stimulating Hormone
GERD GastroEsophageal Reflux Disease
IBS Irritable Bowel Syndrome
IgA Immunoglobulin A
LH Luteinizing Hormone
MCS Multiple Chemical Sensitivity
MRI Magnetic Resonance Imaging
fMRI Functional Magnetic Resonance Imaging
MRS Magnetic Resonance Spectroscopy
MS Multiple Sclerosis
OSHA Occupational Safety and Health Administration
PET Positron Emission Tomography
RADS Reactive Airways Dysfunction Syndrome
RIDS Reactive Intestinal Dysfunction Syndrome
RLDS Reactive Laryngeal Dysfunction Syndrome
RUDS Reactive Upper airway Dysfunction Syndrome
SLE Systemic Lupus Erythematosus
SPECT Single Photon Emission Computed Tomography
TNF Tumour Necrosis Factor
TSH Thyroid Stimulating Hormone
VCD Vocal Cord Dysfunction

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