

# **Medical Evaluation and Treatment of Patients with Chemical Injury and Sensitivity**

**by**

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### **Abstract**

Medical testing was conducted on 30 consecutive toxic injury new patients seen in the author's medical practice. These patients typically had toxic encephalopathy with reactive airways disease. Other abnormalities were quantified by testing, and included adrenal cortisol changes with frequent deficiency; protein deficiency with greatest deficiency in detoxification-related amino acids; changes in Phase II detoxification following challenge, with deficiency of glutathione and superoxide dismutase and increase of lipid peroxides and other free radicals; changes in cell membrane lipid composition to a proinflammatory status; Secretory IgA deficiency with frequent parasites and/or Candida; pancreatic digestive enzyme (chymotrypsin) deficiency; food intolerances; intracellular essential mineral deficiency; reduced antioxidant function; altered energy metabolism; and other nutrient deficiency, the most prevalent being B12 (involved with myelin synthesis). Toxic exposures inducing illness were symptomatic (and repeated, except one patient from a massive propane leak). Other causal agents were solvents, pesticides (organophosphates, pyrethroid, chlordane, benzyl benzoate, other), vehicle exhaust in a building, "sick building" volatiles, adhesives, inorganic chlorines, formaldehyde and glutaraldehyde.

### **Introduction**

Toxic exposure to a variety of petrochemical compounds or combustion products can induce permanent heightened intolerance to chemicals.<sup>i[1]</sup> Toxic induced brain damage, also called toxic encephalopathy, can also induce chemical intolerance.<sup>ii[2],iii[3]</sup> Even relatively short term exposure to petrochemical compounds can cause a significant heightened intolerance to future chemical exposures.<sup>3</sup> Short-term intermittent exposures at even modest levels are capable of causing heightened neural (brain) sensitization by means of the mechanism of time dependent sensitization.<sup>iv[4],v[5]</sup>

### **Toxic Encephalopathy**

Many petrochemical compounds have been shown to cause chronic changes in brain function as documented by testing.<sup>vi[6],vii[7],viii[8],ix[9],x[10],xi[11],xii[12],xiii[13],xiv[14]</sup> Industrial accidents and exposures, sick building exposure and environmental overexposure's are all capable of causing toxic encephalopathy.<sup>xv[15]</sup> Persisting brain damage can be caused by either repeated or single acute symptomatic exposure to combustion products, pesticides, volatile organic compounds, solvents, inorganic and organic chlorines, hydrogen sulfide, and a wide range of petrochemicals.<sup>15,xvi[16],xvii[17],xviii[18]</sup> Even low-level exposure to volatile petrochemical compounds can cause changes in brain function.<sup>xix[19]</sup> Short-term exposure can also cause toxic encephalopathy.<sup>3</sup> Numerous studies document toxic encephalopathy resulting from low level chronic exposure.<sup>xx[20],xxi[21],xxii[22],xxiii[23]</sup> Further exposure after brain damage begins causes additional damage,<sup>xxiv[24]</sup> demonstrating the need for early detection and focusing on neurologic symptoms with exposure at an early stage, such as impaired attention span, reduced memory and/or concentration, headache, balance disturbance or impaired coordination, because these can become permanent<sup>10,11,13,14,xxv[25],xxvi[26]</sup> unless the individual is removed from exposure and/or the exposures promptly controlled to below a symptomatic level.

Because petrochemical compounds are often lipid soluble, they are readily taken up into the brain and concentrate in the lipid part of the brain.<sup>xxvii[27]</sup> Toxic compounds are also capable of entering the brain directly through the nose.<sup>xxviii[28],xxix[29]</sup> The brain also has a special vulnerability to toxic damage because of other factors, including the long shape of nerve cells and the high metabolic rate of the brain so that even minutes of adverse changes in brain metabolism can cause brain cell death.<sup>28</sup> The relatively small number of neurons which utilize the neurotransmitters dopamine or acetylcholine creates increased vulnerability to causing, respectively, profound reductions in coordination and memory.<sup>28</sup> Further, brain cells are unable to regenerate, so that death of a brain cell is usually permanent.<sup>28</sup> Impairment of energy metabolism increases the risk of brain and nerve cell damage.<sup>28</sup> Such impairment is common.<sup>xxx[30]</sup> Impaired energy metabolism is found in the vast majority of chronically ill toxic injury patients.<sup>30</sup> Petrochemicals are also able to attack the membranes of nerve cells, causing damage.<sup>xxxi[31]</sup>

SPECT brain scans on individuals with chronic symptoms following toxic exposure to various petrochemical compounds compared to healthy control subjects show reduced blood flow to the brain and reduced ability of the brain to take up the tracer substance in the early phase of injection.<sup>xxxii[32],xxxiii[33],xxxiv[34]</sup> This is often not evident in the late

phase of injection with SPECT scan testing, emphasizing the need for such scanning to focus on the early phase of injection, which is not always done when this scanning is performed for evaluation of other neurologic conditions. Changes seen in these SPECT brain scans studies involve the frontal, temporal and limbic brain areas. Because of the well known relationship of the limbic brain to emotions, those lacking thorough knowledge of toxic encephalopathy can confuse toxic-induced brain effects with a psychologic condition. However, mood and personality changes which are long-standing have been documented in patients with toxic encephalopathy.<sup>10,11,13,14,25,26</sup> A study which evaluated symptoms in toxic encephalopathy patients secondary to long-term exposure to organic solvents found chronic persisting symptoms of fatigue (90%), impaired short-term memory (94%), reduced concentration (88%), irritability (84%), headaches (81%) and other neuropsychiatric effects.<sup>17</sup>

### **Reactive Airways**

Another mechanism by which toxic injury can cause heightened future sensitivity to chemical exposure is reactive airway disease. Repeated modest or even "tolerable" level exposure to irritants,<sup>xxxv[35],xxxvi[36]</sup> higher dose single<sup>36</sup> or repeated<sup>xxxvii[37]</sup> exposure to irritants can cause permanent reactive airway disease. This induces significant increased respiratory sensitivity to irritant exposures in the future.<sup>35,37</sup> Irritants cause reactive airway disease of upper and/or lower airways by release of the inflammatory substance P and the mechanism called neurogenic inflammation.<sup>xxxviii[38]</sup> Biopsy study has confirmed that irritant exposure can cause loss of the protective nasal epithelial cells, increased permeability (which could allow future irritants to enter more readily), chronic inflammatory changes, and an increase in the number of nerve fiber endings of the olfactory nerve in the nose.<sup>xxxix[39]</sup> These changes would not only affect the respiratory system but would increase the risk of toxins entering the brain directly through the nose. Other scientists have independently confirmed that reactive airway disease can involve the upper as well as the lower airways.<sup>xl[40]</sup>

Reactive airway disease can be induced by volatile organic compounds.<sup>xli[41]</sup> These compounds as well as virtually all other petrochemicals are irritants<sup>xlii[42],xliii[43]</sup> Non petrochemicals such as ammonia and chlorine<sup>xliv[44],xlv[45]</sup> are also irritants. Reactive airway disease can be induced by solvents,<sup>39</sup> pesticides,<sup>39</sup> indoor air pollutants,<sup>xlvi[46]</sup> and inorganic irritants.<sup>39,14</sup> Reactive airway disease is considered a long-standing or permanent phenomenon even after the initial causal exposure has been discontinued.<sup>xlvii[47],xlviii[48],xlix[49]</sup>

Respiratory irritation in humans at even low levels of exposure to a mixture of irritants and/or volatile chemicals shows more than additive effect.<sup>44,45</sup> The degree of hyperadditivity increases with the number of substances present and also with the fat solubility of the chemicals.<sup>41</sup> Prior irritant exposure increases the irritant effect of subsequent irritant exposure.<sup>44</sup> Longer duration of low level exposures and/or higher levels of chemical mixtures increases both adverse response of symptoms as well as sensitization.<sup>l[50]</sup> A key feature of reactive airway disease is heightened respiratory symptoms with exposure to irritants.<sup>35,36,37,41</sup> Nonrespiratory symptoms are also

increased following irritant exposure with reactive airway disease,<sup>41</sup> which is consistent with the inflammatory response and release of inflammatory substances (which increase fatigue, aching, etc.) as well as the reduction of the protective nasal epithelium and thus increased ability for toxins to enter the brain.

Intolerance to chemical irritants has also been reported in persons with asthma<sup>39,li[51]</sup> and in those with rhinitis.<sup>39</sup> Additionally, a community based epidemiologic study of individuals diagnosed with asthma found a higher level of illness exacerbation from irritants such as new carpets, scented products and cleaning products compared to nonasthmatics.<sup>liii[52]</sup> Persons with a diagnosis of hay fever also experience frequent illness exacerbation from irritants such as pesticides and vehicle exhaust.<sup>42</sup> Asthmatics and individuals with hay fever also have significant exacerbation from irritants such as drying paint and passive smoke.<sup>42</sup>

A study of non smoking individuals with reactive airway disease/airway hyperreactivity to irritants showed that testing such as methacholine challenge, chest x-rays and lung function tests were not reliable predictors of reactivity, that symptoms typically involved the upper and lower airways and often failed to respond to (beta 2 agonist) bronchodilators or steroids, and were commonly accompanied by symptoms such as fatigue, headache and/or musculoskeletal aching.<sup>liiii[53]</sup> When these patients were challenged tested, the authors found that the hyper reactivity involved not only the upper and lower airways but also the eyes. Perfume challenge testing below the smell level exacerbated symptoms of airway hyperreactivity in the upper and lower respiratory tract as well as causing headache and fatigue.<sup>50,liiv[54]</sup> This challenge testing also exacerbated eye symptoms. Psychologic causation was ruled out.<sup>50,54</sup> Eye irritation also occurs with irritant exposure at even low levels, and with mixtures of irritants shows more than additive effect on eye irritation in humans.<sup>41</sup>

### **Evaluation of Chemical Exposure**

The author has long been a treating physician for hundreds of toxic injury patients. This paper reflects that experiences as well as the medical literature.

A basic principle of toxicology is that lowering exposure reduces the risk of adverse health effects.<sup>lv[55]</sup> When determining what exposure controls are most appropriate to a particular patient, it is useful to evaluate whether they have toxic related organ changes (see discussion below) and their response to commonly encountered exposures to irritants and other toxins. A questionnaire which is excellent for characterizing the dose response relationship of a particular individual for exacerbating exposures was developed at the Johns Hopkins School

of Hygiene and Public Health by Dr. Davidoff and colleagues and has been validated in the peer-review medical literature.<sup>lvi[56]</sup> The author has used this questionnaire<sup>1</sup> for many years in evaluation of toxic injury patients because it describes the duration of exposure, characterizes an exposure in readily understandable language that helps to assess its intensity, and characterizes the response. It is also useful to ask the question: “how long does it usually take to feel as good as you did before” to assess

recovery time from exacerbations. Another useful assessment instrument which the author has utilized was developed by Dr. Kipen and colleagues<sup>lviii[57]</sup> (Appendix I). This assessment instrument is particularly useful to determine which specific exposures and products are problematic in the home, school or workplace.

Careful evaluation of the home environment is important because of the amount of time individuals spend in the home. The author utilizes a home questionnaire section (Appendix II) and reviews the responses with the patient, obtaining further information as indicated. It has been the author's consistent experience that individuals who have chemical exposures in their community sufficient to exacerbate symptoms on a recurring basis experience significant health improvement by relocating unless the community exposure can be controlled below levels which exacerbate symptoms, eg., when opening windows, being outside near the home.

If the individual is working or attending school, it is important to evaluate whether the workplace or school has exposures which exacerbate symptoms. For occupational exposures, many principles of an occupational exposure history apply. These include the timing of symptoms relative to exposure, such as whether the individual is more symptomatic at home or at work, particularly early in the course of illness. For individuals who have become chronically ill, significant improvement may not occur with being away from exposure for only hours or a few days, so for these individuals information about symptom levels when the individual is away for longer periods of time such as several weeks or more is particularly helpful. It is useful to obtain information about the tasks being performed, with sufficient detail to allow a mental image of the exposure in relation to the individual. Asking the person to provide a diagram is also a helpful aid in clarifying the exposure. Material safety data sheets or other means of obtaining the chemical identity of exposures is useful, and the health care provider can obtain this information with the patient's consent through the OSHA Hazard Communication Standard: 29 CFR 1910.1200. Results from workplace medical monitoring can be obtained through the OSHA Access to Medical Records provision: 29 CFR 1910.0020. This allows the health provider or other designated representative, with the patient's consent, access to any workplace study and personal and/or medical monitoring for which the employer has a copy, thus allowing access for information conducted by consultants as well as in-house studies. Information about the heating, ventilation and air-conditioning (HVAC) system is also useful. Exposure is more likely to affect the individual in work areas that share a common air supply through the air handling system. Air monitoring, HVAC studies etc. are often done after some corrective measures have been taken: this makes them nonrepresentative of original exposures. Common use areas such as entryways, hallways, meeting rooms and restrooms should also be evaluated. Similar principles apply to the school environment, although students, unlike teachers and other school employees, do not have OSHA protection regarding information access. It is often possible to obtain needed exposure information through the individual and/or school administration.

### **Exposure Control**

It is been the author's consistent experience with toxic-induced chronic illness that the most significant factor for future health is the extent to which exposures can be controlled below symptomatic levels. There are four studies in the medical literature which confirm that reduced exposure is the major factor in the long-term outcome of patients who have developed chemical intolerance: Dr. Lax,<sup>lxviii[58]</sup> an occupational medicine physician, found that his patients who had environmental controls did much better than patients without adequate environmental controls. A survey of 305 persons with chemical sensitivity by DePaul University<sup>lix[59]</sup> found that they experienced much greater relief from environmental controls and reducing exposure than with any other form of treatment, and that the use of tranquilizing agents was actually less effective than meditation or prayer. Another study by Dr. Jason<sup>lx[60]</sup> found that individuals were chemically sensitive and had relatively nontoxic housing had much better long term health than those that did not have adequate environmental controls in their housing. This is because once chemical sensitivity is induced, it can be exacerbated by exposures at work, at home, or elsewhere. A fourth study of 206 chemically hypersensitive patients by Dr. Miller and colleagues<sup>lxi[61]</sup> found that reducing exposure to chemicals was very helpful for 71%, but only 17% of the patients who used psychological or psychiatric services/treatment found those to be very helpful. It is important to focus on exposure control in the environments where the person spends the most time: work, school, and home.

Current occupational exposure limits (TLVs) have shown no statistical correlation with health effects.<sup>lxii[62]</sup> Adverse health effects are often reported in the medical literature below these exposure limits.<sup>lxiii[63]</sup> Thus they are often not a reliable guide of the health status of a working environment even for workers without toxic injury, and are thus likely to be less protective for workers who have already developed work-related symptoms.

### **Accommodation**

If the individual has symptoms with a medical condition which significantly interferes with major life activities, they can be considered to have a qualifying condition under various disability legislation and regulations. The most effective approach is to discuss with the individual the exposure situations, utilize knowledge of the health care provider and/or other information sources, and then formulate a request for reasonable accommodation which is planned according to the types of exposures and the degree of severity of the exacerbated response, also taking into consideration the known toxic properties of the substance(s).

Nontoxic and least toxic pest control methods have been developed for virtually all weeds and pests,<sup>lxiv[64],lxv[65]</sup> and should be requested for persons with any disabling symptoms or symptoms which are exacerbated in that environment and/or frequent symptoms. It is the author's experience that pesticide residue, even when weeks old, can exacerbate illness in individuals who have toxic-induced illness and/or heightened intolerance to pesticide residue by history. The reasonable accommodation provision regarding nontoxic pest control would probably not apply to agricultural situations in which the crop is an important source of livelihood, but advance notification can then be

utilized. This provides much less protection but still allows the individual to take some preventive precautions as described below. In the author's experience, chronically ill persons near agricultural pesticide use have significant difficulty achieving significant improvement, despite other medical interventions (which can slow or limit deterioration).

Reasonable accommodation can also be requested and provided for cleaning agents, air fresheners and less toxic renovation and repair products. These also have alternatives which are effective and far less likely to exacerbate symptoms.<sup>lxvi[66]</sup>

Individuals can also be requested to refrain from the use of scented products if they are in an environment sufficiently close to an affected individual to exacerbate symptoms. Because scented product use is often a personal behavior, compliance is often much more successful if persons understand the nature of scented products (Appendix III). Illness reactions in the general population are common to scented products, involving 20 percent or more of the population.<sup>lxvii[67],lxviii[68]</sup> Illness reactions can cause migraine headaches, sinus congestion, hoarseness and/or asthma reactions. Further, scented products residue can cling to hair and clothing for many hours at levels sufficient to exacerbate illness hours later. Like the issue of smoking and passive smoke, altering personal habits may initially be resisted by some individuals, but in the author's experience, when users have adequate knowledge and when decision makers set a positive example and tone, reasonable accommodation can often be achieved.

Other reasonable accommodations for the workplace can include changes in work schedule to reduce exposure to rush hour traffic; and for all environments, conducting the activity in an area with a window that can be opened if the exterior environment is less polluted than the interior environment. Advance notification is also needed for painting or pest control procedures, since even less toxic products may cause a problem, albeit of less severity, for certain individuals. Flexi-place accommodations can be used for home, work and school environments and are medically necessary if the individual's health declines or symptoms aggravated despite attempts to achieve reasonable accommodation or if adequate accommodation is not achievable or not undertaken.

Once the affected individual and their health care provider and/or other information sources have adequately discussed which accommodations are needed and appropriate, a recommended format is that the individual request in writing the accommodations and the health care provider confirms the same if the individual's health declines or symptoms aggravated despite attempts to achieve reasonable accommodation or if adequate accommodation is not achievable or not undertaken.

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Care should be taken in recommending specific filtration devices. Areas with a moisture problem should utilize a device with a HEPA filter, since this is needed to capture mold particles. When mold is not a problem, HEPA filters may be unnecessary and some HEPA filters can create some exacerbation in certain individuals because of their glues. Consideration should be given to the noise level of the device to reduce the risk of gradual hearing loss. Whole house filtration can also reduce noise if properly located. The device also needs to be adequate for the space and contaminant level. Thus for workplaces it is often useful to use a smaller office. For the home, it is helpful to have such filtration at least in the individual's bedroom and major living areas. In many environments it is more effective to leave the filter device running so that pollutants do not build up in the individual's absence. This also avoids the need to turn the device on high, creating a higher noise level during occupant use.

Some individuals experience symptom exacerbation from water which is used for cooking, drinking or shower. This is more common for chlorinated water, since chlorine reacts with organic debris to form chloroform. Individuals with wells near areas of pesticide application also need activated charcoal filtration for shower/bathing and may wish to consider bottled spring water for drinking and cooking. Chronically affected individuals can benefit from whole house activated charcoal water filtration to control chloroform, pesticides etc., which can be used with backup activated charcoal filters on shower and cooking/drinking water for optimal control. The investment in filtration devices may well be offset by a reduction in medical expense and disability. Periodic filter changes are needed, with frequency according to contaminant levels and illness severity.

### **Home Controls**

If relocation is needed or if the individual plans to move, a relatively nontoxic house with electric heat and appliances is recommended. Other important features include relatively nontoxic flooring such as hardwood or tile, a substantial buffer of land, ideally wooded or a body of water, location preferably not closer than one mile from agricultural pesticide use, not closer than one-quarter mile from a major highway, and not close enough to an industrial or other commercial emission source to notice any detectable odor or particulate. Ideally the house should be free standing and under the control of the patient, because of the problem of chemical use in an apartment or condominium. If the house has an attached garage, an impermeable barrier between the garage and house is recommended. Windows that open easily in the bedroom, kitchen

and other major living areas are important. Ceiling fans can be utilized to help reduce the need to close the house during much of the summer. Very major improvement in health occurs with such housing in the author's experience.

Because of the amount of time spent in the bedroom, often about 60 hours per week, extra caution in bedroom exposures typically results in reduced respiratory irritation, fatigue, neurologic symptoms, etc.. Controls here, especially for individuals with frequent symptoms, are recommended to include mattresses or futons without petrochemical flame retardants (which may require a physician's prescription) and without pesticides, which are common in mattresses as mold control agents. Mold can be controlled with a very tightly woven mattress and pillow enclosure called barrier cloth. Because cotton is often grown using a significant amount of pesticides, bedding and mattresses using cotton grown without pesticides often results in reduced symptoms. Because pillows are close to the breathing zone for many hours daily, even small amounts of offgassing from a pillow can exacerbate respiratory symptoms, and affected individuals typically improve noticeably when synthetic pillows are replaced with those containing natural fibers. Patients report that wool containing pillows are more comfortable than those with cotton. If down is utilized, barrier cloth is essential as is ensuring that the individual does not have allergies. New onset allergies are not uncommon in chronically affected individuals and down pillows could potentially initiate allergy to dander, especially if used without a barrier cloth pillow case.

Individuals who experience respiratory congestion with newsprint can utilize a reading box with proper ventilation to reduce illness exacerbation. Non-toxic airtight containers to store printed matter in the house reduces exposure. Some affected individuals experience skin irritation with synthetic clothing and need to utilize clothing made from natural fibers. Storage of food in containers made from glass, metal, or wood derived cellophane can reduce food contamination. Individuals with frequent symptoms following toxic exposure improve when eating foods not grown with pesticides. This avoids the ingestion of pesticide residue, which the body must detoxify.

The author does not recommend or urge affected individuals to remain housebound. Human beings are social beings and have a need for personal interaction. Some individuals are so severely affected that until their body can detoxify better, they will voluntarily choose to limit their social excursions, and should not be coerced out. Social interaction can be improved by the use of a proper car filter, by educating friends and social contacts regarding medical needs, and of course when society implements reasonable accommodation in public places, such as least toxic pest control, cleaning agents, and eliminating "air fresheners" from public places, particularly since these are often odor masking agents and commonly contain irritants and/or toxins.

### **Medical Measures**

As an added measure but not a substitute for exposure control, individuals who experience symptom exacerbation with an exposure can take measures to reduce intensity and severity of exacerbations. The author provides a factsheet to patients (Appendix IV)

describing actions they can take. Due to difficulty with memory in toxic injury, written information is especially important. Micellized agents are useful because of the reduced pancreatic enzymes commonly present<sup>30</sup> It is common during significant exacerbations for the body to become more acidic. pH strips to self test urine can be used to determine whether this occurs. Such patients experience improved symptoms with a bisalt or trisalt mixture, such as two parts of sodium bicarbonate to one part of potassium bicarbonate (a drop in potassium levels is also common and determining potassium levels during exacerbation is useful to assess whether this occurs). Patients who experience neurologic, respiratory or cardiovascular symptoms during exacerbations often benefit from oxygen at 3-4 liters per minute using a ceramic mask and Tygon 2075 tubing (to reduce exposure to plasticizing chemicals) until significant symptom improvement occurs. Body temperature can drop further; a well tolerated way to assist this is a yutampo (metal "hot water bottle" in quilted cotton sack.<sup>lixix[69]</sup> It should be filled from tap water, not water heated on the stove, to avoid burns.

The author also recommends a baseline daily broad range antioxidant protection, often 1-11 gm of buffered C powder in water, vitamin E at 300-400 IU, micellized A at 5,000 IU, and broad spectrum bioflavinoids. Improved pH can be achieved by testing and dietary information on foods (Appendix V).

### **Glutathione**

The proper use of glutathione can significantly reduce the severity of exacerbations in the author's experience. Glutathione is the most important intracellular antioxidant in the body. It is ier cloth pillow case.

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The proper use of glutathione can significantly reduce the severity of exacerbations in the author's experience. Glutathione is the most important intracellular antioxidant in the body. It is so close to the breathing zone for many hours daily, of brands and insulation is critical, since glues, certain woods, some insulation materials and various other construction substances can be heated up and actually exacerbate symptoms in these patients. A sauna in which the patient is laying down has more risk of falling asleep. If the patient has such a sauna, it is essential that it never be used without an effective timer and ideally with another individual who would awaken the person.

Petrochemicals are stored in fatty tissues of the body, creating a specific body burden. These chemicals are in equilibrium with blood levels through principles of toxicokinetics such that increased fat levels result in higher levels in blood and other body tissue. Reducing body burden can help improve detoxification. Further, reducing body burden is associated with reduced risk of adverse effects because of the dose-response principle of toxicology.<sup>55</sup>

Multiple epidemiologic studies and clinical case reports confirm both clinical improvement and reduced body burden of various petrochemical and combustion products with use of sauna for chemical injury. Unlike some metals, chelation is not

used, but reduced body burden is the common principle. Chronic illness following PCB overexposure resulted in liver abnormalities and chloracne. Following sauna therapy, symptoms improved and fat levels dropped by over 50%.<sup>lxx[70]</sup> Seven individuals ill following PCB exposure were given intensive sauna therapy for an average of 20 days. There was an average reduction of 21.3% in fat levels of 16 organochlorines tested.

Testing 4 months later revealed a drop of 42.4% from original levels, indicating that the initial drop was not just a shift to other body areas.<sup>lxxi[71]</sup> Electrical workers exposed to PCB's and other biopersistent organochlorines were given sauna therapy and organochlorines compared before and after therapy with electrical workers not undergoing sauna treatment. Treated workers had a mean reduction in organochlorine pesticides of 7.8% after treatment which by 3 months later dropped 21.2% compared to before treatment. Levels in untreated controls actually rose slightly (4.2%).<sup>lxxii[72]</sup>

A study of 103 patients undergoing sauna therapy used a control group of 19 persons untreated but undergoing comparable testing. Neurocognitive function revealed a mean increase in IQ in the treated group of 6.7 points. Symptoms of body aching improved in 11 of 11 persons affected, irritable bowel symptoms in 8 of 9 affected; dermatitis in 7 of 8 affected; migraine in 3 of 4 affected; thyromegaly in 3 of 4 affected, etc.<sup>lxxiii[73]</sup> Fourteen firefighters with PCB and combustion product overexposure showed significant impairment with sauna treatment in neurocognitive testing for memory, visual images, block design, culture fair, trails, reaction time, motor speed, and digits backward compared to unexposed firefighters.<sup>lxxiv[74]</sup> Eleven capacitor workers with PCB and other chemical exposure were given sauna therapy and testing compared with untreated co-workers. Following treatment with sauna, PCB levels in serum and fat dropped by 42% and 30% in those without concurrent disease (6 patients) and 10% in fat in those with disease. Levels in untreated controls actually increased during the same interval. Following treatment, there was significant improvement in symptom severity using a standard rating scale for chloracne, other dermatologic problems, headache, and eye, respiratory, gastrointestinal, musculoskeletal and neurologic symptoms. There was no symptom improvement in the untreated group.<sup>71</sup>

Clinical improvement following sauna therapy has also been documented with case reports in several peer reviewed medical articles. A disabled woman following soot and fire ash overexposure had severe adenopathy, extreme fatigue, pustular acne, sleep disturbance and chronic respiratory symptoms. During sauna treatment a black substance began to daily exude from her pores. Following sauna therapy the acne and adenopathy largely cleared, fatigue and respiratory symptoms greatly improved and sleep returned to normal.<sup>73</sup> There is also some legal precedent that patients cannot be denied reimbursement for sauna when no traditional therapy has been shown to be effective in reducing body burden of petrochemical compounds.<sup>lxxv[75]</sup>

### **Symptom Log**

For individuals who have waxing and waning of symptoms and/or exacerbations, a log of these occurrences can help to identify the particular situations, exposures or other

circumstances chronologically preceding an exacerbation. This log of illness exacerbation may not be needed long term but is helpful until exacerbating factors have been better identified. The illness log should focus on exposures/places/situations in the 6 to 8 hours before the onset of symptoms or before symptom exacerbation. Over time, review of this log can assist both the individual and the health care provider to identify exposures and other situations which precede symptom exacerbation. This facilitates an information-based means of developing strategies to reduce exposures using means described above.

## **Medical Evaluation and Care**

### **Neurologic Evaluation**

It is recommended that patients who describe neurologic symptoms including but not limited to confusion, disorientation, reduced memory and/or concentration, difficulty thinking quickly or clearly, balance disturbance and/or numbness/tingling be evaluated for neurologic and neurocognitive changes. Dr. Kilburn<sup>14</sup> has carefully described evaluation of brain and neurologic function from toxic exposure and that discussion will not be duplicated here. It is important to seriously consider his recommendations, because they were based upon significant experience and careful epidemiologic design evaluating many hundreds of individuals with frequent symptoms following toxic exposures such as hydrogen sulfide, chlorine, hydrogen chloride, arsenic, chlordane, polychlorinated biphenyls, trichloroethylene, diesel exhaust, combustion products with a toluene rich vapor, and vinyl chloride and other contaminants. He found Culture Fair testing of intelligence (2A) and Trail Making B to be the most sensitive of the neurocognitive testing. He also found that neurophysiologic testing was often more sensitive than neurocognitive testing, and that the most sensitive neurophysiologic testing to assess toxic injury was balance testing (he quantitated by sway speed), blink reflex latency, visual fields, and simple and choice reaction time. Not all toxins will affect the brain in an identical way nor cause identical changes on testing, but review of his findings from epidemiologic studies of the above exposure situations provides vital guidelines for selecting the most sensitive testing approach. Sensitive testing is important to detect brain and neurologic injury at the earliest stage to avoid further damage.

Neurocognitive tests results can be utilized as a basis for focusing cognitive rehabilitation. This can help the patient to better cope with damaged brain functions and utilize less affected areas. This is obviously not a substitute for controlling exposure and early detection. Following principles of occupational medicine,<sup>lxxvi[76]</sup> when individuals describe cognitive, neurologic or other symptoms which may be related to exposure, exposure removal is recommended to ascertain whether symptoms improve. If this principle is widely implemented early in symptom onset, much chronic and disabling toxic injury can be prevented.

### **Hyperbaric Oxygen Treatment**

Toxic brain injury, also called toxic encephalopathy, is associated with reduced blood flow to the brain<sup>lxxvii[77],lxxviii[78],lxxix[79],lxxx[80],lxxxi[81]</sup> on SPECT scan and therefore brain ischemia. HBOT therapy has been shown to reduce ischemia and its damage in a wide range of tissues, including but not limited to the nervous system.<sup>lxxxiii[82]</sup> Increased lipid peroxides are present in the majority of toxic injury patients.<sup>lxxxiii[83]</sup> Hyperbaric oxygen therapy (HBOT) reduces lipid peroxides.<sup>lxxxiv[84]</sup> It also facilitates healing of damaged nerves in the brain as well in the peripheral nervous system.<sup>85</sup> Increased formation of lipid peroxides occurs with toxic injury (directly through detoxification changes<sup>lxxxv[85]</sup> with increased free radical production and indirectly through inflammation). Cytochromes are essential to detoxification and can be disturbed by toxic exposure. Cytochrome disturbances can improve with hyperbaric oxygen therapy.<sup>85</sup> Superoxide dismutase is an enzyme important for clearing toxins from the body and is commonly reduced in toxic injury patients.<sup>84</sup> HBOT helps stimulate production of this enzyme.<sup>85</sup> It has been the author's experience that significant and long-lasting improvement in brain function typically occurs with HBOT which often also acts to improve multiple other symptoms. For improvement to occur, HBOT must be properly administered. Ideally, the chamber should be metal rather than plastic or other synthetic material. Pressure levels of 1.3 to 1.5 atmospheres are recommended except for patients with a history of seizures, for whom 1.25 atmospheres is preferred. No significant complications have been described at these pressure levels in the hyperbaric literature.<sup>81,83</sup> To avoid exacerbation, for patients with heightened intolerance it is necessary to utilize a chamber that does not use disinfectants which are irritants or petrochemicals or leave any such residue. Many hyperbaric chambers are now used for the treatment of resistant infections, utilizing significantly higher pressure levels as well as disinfectants. A toxic encephalopathy patient of the author who mistakenly sought treatment in such a chamber experienced no improvement, in contrast to significant improvement seen in all patients treated in a nontoxic chamber and relatively nontoxic facility. This patient experienced significant improvement with treatment at 1.5 Atm without germicidal use in the chamber. A treatment of one hour duration can be conducted daily. Follow-up is recommended during the course of therapy: after a few treatments to ensure that improvement is occurring and there are no problems with the treatment or facility, occasional follow-up during the course of therapy to assess ongoing progress, (which should be occurring if the treatment is effective), and follow-up before the treatment is terminated. Severely affected patients may require up to two months of treatment, with lesser duration needed for more mildly affected individuals. Once the physician can be sure that maximum improvement has been reached, treatment can be discontinued. In the author's experience, benefits are typically long-lasting unless a significant exposure occurs (an exposure sufficient to exacerbate symptoms for weeks or months).

It is also important to insure that the patient will be returning to a relatively nontoxic home environment, since benefits of hyperbaric treatment can be lost if there is significant contamination in or near the home or if significant workplace or school exposures have not been corrected. It may also be useful to time the hyperbaric treatment after some reduction in body burden and after treatment for the treatable complications of toxic injury as described below.

## **Hyperbaric-like oxygen**

Prior to use of the hyperbaric chamber treatment, the author used an approach designed to create increased oxygen availability for toxic brain injury. Blood plasma is capable of carrying oxygen at levels which are equal to those which can be carried by the red blood cell,<sup>82,83</sup> if sufficient oxygen is available. This technique includes a mask designed by a respiratory therapist, with metal for the mask and tygon tubing for the face seal. Other equipment includes tygon 2075 tubing, a glass jar as a water reservoir, and a wood-derived cellophane humidity mixing chamber.<sup>lxxxvii[86]</sup> Oxygen is given at 6 liters per minute for two hours daily, which requires added humidity to avoid drying the respiratory passages. On the first day, an arterial oxygen blood draw is recommended while the oxygen is running and after one hour of oxygen running at 6 liters per minute. The author recommends an arterial paO<sub>2</sub> of 250 mm of mercury for optimal effect: oximetry testing is not satisfactory for this assessment. Virtually all patients with toxic brain effects treated in this manner by the author for 6 to 8 weeks experienced sustained improvement in cognitive function, but the extent of improvement was less than that seen with the above described HBOT chamber treatment. The author feels that HBOT by chamber is preferred when possible, but this alternative is better than no measures to increase brain blood flow. A longer duration may be needed for more severely affected patients.

## **Patient characteristics for subsequent data discussion**

One of the most exciting developments for the author has been the growing understanding that some aspects of toxic injury are treatable and that such treatment can be scientific, i.e., test-based. To further illustrate abnormalities which are more common with toxic injury, all available test data was analyzed for 30 consecutively tested *new* patients who had chronic illness, defined as two or more daily symptoms following toxic exposure. The toxic cause of exposure was evaluated with these criteria: 1) the patient was relatively healthy, able to work/conduct daily activities prior to exposure; 2) symptomatic exposure with symptoms occurring during exposure and improving away from exposure on multiple occasions (except for one patient with a single massive propane leak exposure who had only one exposure incident); 3) symptoms consistent with the type of exposure; and 4) onset of chronic illness within hours or days of a symptomatic exposure to the toxin(s). There is no overlap between these patients and those for whom test data was described earlier by this author.<sup>30</sup>

Of these 30 patients, the most common situation of exposure was sick building/building related, involving 9 patients. Two of the sick building exposures involved mold and could have also involved chemical agents to remediate mold exposure. Mold is capable of

releasing volatile compounds not unlike those encountered in other sick building environments.<sup>lxxxviii[87],lxxxviii[88],lxxxix[89],xc[90]</sup>

The most common chemical class was pesticides, involving 9 patients and including organophosphates chlorpyrifos (two patients), and diazinon; the synthetic pyrethroid resmethrin; a benzyl benzoate containing dust mite spray which was utilized on four (symptomatic) occasions by the patient to spray home carpet; disinfectant glutaraldehyde and occupational handling of plants which had been pesticide treated. Two of the pesticide exposed patients involved chlordane, although they came from a very large family where chlordane had been illegally used to treat the home by a nonprofessional applicator. To avoid skewing the data results, I randomly selected two individuals from the family.

Solvent exposure was involved with 7 patients, two of whom work in laboratories (one of whom also had exposure to sterilizing agents and formaldehyde). Two patients were secondary to inorganic chlorine compounds. One of these involved passive occupational exposure to a 10% solution of chlorox used to clean floors. The other was exposed to sodium hypochlorite in a poultry processing operation. She was one of fourteen individuals exposed and chronically ill from working in the evisceration department of the same plant. Two patients were exposed to adhesives: one a carpet adhesive, the other a drywall adhesive containing n-hexane. Three patients were exposed to vehicle exhaust: two to diesel exhaust entering into a building while idling at open warehouse loading doors and one with gasoline powered vehicles used in a building.

One of the patients was exposed to ultraviolet inks containing acrylates and epoxies. This patient has the most severe exacerbation by light of any patient the author has ever encountered, verified both by history and testing. Even his balance testing when facing the window with blinds pulled and wearing sunglasses was much more impaired than when facing away from the window. This is strongly suggestive of a persisting body burden. One of the patients was exposed to medical cleaning towlettes used occupationally in a health care setting. Some patients had multiple symptomatic causal exposures to toxins that met the above criteria. Of the 30 patients, 25 (83%) were of occupational origin, four were a consequence of home contamination and one was a consequence of removing contaminated items from an office involving diazinon treatment in an office of a chronically ill family member (who is also the author's patient).

### **Adrenal Function Testing and Treatment**

Reactive airway disease as well as chemical sensitivity are associated with increased inflammation.<sup>30,40</sup> Petrochemicals when metabolized generate free radicals<sup>xc[91]</sup> which can perpetuate inflammation. Inflammation often causes pain, which induces cortisol release from the adrenal gland. Inflammation on a chronic basis can deplete adrenal reserve, leading to adrenal insufficiency.

Like other hormones, the vast proportion of cortisol is protein-bound when assessed in the blood. The bound portion is not only less active but can be affected by other factors such as the protein status, often deficient in toxic injury patients.<sup>30</sup> Blood assessment also involves venipuncture, which can induce stress and may thus alter results. The cortisol

daily rhythm is clinically important as a basis for medical decisions, making venipuncture impractical for assessing the rhythm beginning in the early morning and concluding at bedtime. Fortunately, salivary cortisol levels show excellent correlation with plasma levels<sup>xcii[92],xciii[93],xciv[94]</sup> Salivary cortisol is collected by placing a cotton pad in the mouth to pick up saliva as excreted without sucking motion (since sucking can alter the composition of saliva) at 7-8 am; 11 am to noon; 4-5 pm and 11 pm to midnight, with one sample collected during each of those four time intervals.

Of the 22 consecutively tested *new* patients in this group described above (Table1), a total of 15 (68%) had reduction of morning cortisol with 9 (41%) having changes suggesting significant adrenal insufficiency. Of the remaining five individuals, three had elevations of two or more daily cortisol levels, one had a single modest elevation and only one had a normal rhythm. This is further evidence of involvement of the hypothalamic-pituitary-adrenal axis. HPA impairment makes the individual more susceptible to physical and psychologic stressors.<sup>xcv[95]</sup>

The mean value of dehydroepiandrosterone (DHEA) of those patients with two or more cortisol elevations was 3.0, while the mean for those with two or more suppressed values was 2.1, compared to a normal range of 3 to 10 ng/ml. DHEA is a precursor to formation of estrogen and testosterone.

It has been the author's experience that patients who have test-documented reduction in morning cortisol typically experience reduced fatigue with morning cortisol (hydrocortisone) supplementation until the adrenal gland can sufficiently heal. It is important to endeavor to keep added amounts to within physiologic range, striving for levels of slightly below average in order to avoid impeding ACTH activity and ultimate recovery of adrenal function. In this group, 32% had elevated nighttime cortisol levels, with a mean of 9.4 nM (lab reference range of 1-4 nM for this time interval). This nighttime elevation can exacerbate sleep disturbance. Phosphatidylserine may reduce the cerebral response to this cortisol elevation when taken 30 minutes prior to the evening meal, and can be given as a trial, but the goal is to normalize adrenal function.

To help heal disturbed adrenal function, several measures are helpful. 1). Reducing exposure is essential to reduce inflammation which elevates cortisol and exacerbates pain, another factor in cortisol elevation. 2). Pain control also requires identifying and correcting other causes of pain. Pharmaceutical intolerance in most toxic injury patients often leads to impaired ability to utilize pain control medication. Pharmaceuticals are typically detoxified through pathways also used for other petrochemicals. Intestinal inflammation can be exacerbated by parasites, candida and food intolerance, all of which are common in these patients as discussed below: testing and test-based treatment of these is important. A proinflammatory state can be exacerbated by an imbalance of essential fatty acids: these should be tested and returned to a non proinflammatory state. 3). Daily walking or very gentle activity for up to forty minutes daily is important, although it is essential for effectiveness in the author's experience that this be conducted in an area without significant irritants or pollutants. The individual should always begin gradually and never push the pace or duration to a level which results in increased fatigue

following the activity, since fatigue exacerbation or walking in pain will not correct cortisol disturbance. 4). Low glycemic carbohydrates are critical because insulin release drops body glucose, stimulating cortisol release. Carbohydrates should be balanced with adequate protein for meals and snacks: up to a 1:1 ratio in protein deficient persons, while 2:1 may be preferable without protein deficiency. 5). Daily/frequent measures which reduce adrenal attempts to excrete cortisol excess (which can exacerbate depletion) can include relaxation, comedy, meditation, biofeedback, etc.<sup>xcvi[96]</sup> according to what is preferred as relaxing by the individual.

### **Amino acids:**

Testing of plasma amino acids was conducted on 27 consecutively tested chronically ill toxic injury new patients. As seen in Table 2, the majority of these patients with amino acids had significant deficiencies. Furthermore, the distribution of deficient amino acids was far from random. The most prevalent deficiency was taurine, an amino acid that is utilized in Phase II of detoxification. It is a sulfur containing amino acid: at least two other Phase II pathways also utilize sulfur: sulfation using inorganic sulfates and glutathione conjugation. The second most prevalent deficiency was in glutamine, a Phase II detoxifying agent and also used by the body to make glutathione (the body's most important intracellular antioxidant and a Phase II detoxification essential substance). The third most deficient was glycine, which is also used in Phase II detoxification directly, to make glutathione, and to make body purines, (for genetic material).<sup>xcvii[97]</sup> It appears unlikely to be coincidental that the rate of deficiency was highest among the detoxification amino acids, since many amino acids were tested. The prevalence of methionine deficiency in this group is also instructive: methionine can be converted through biochemical steps to cysteine (needed to make glutathione) or taurine. Both of these latter agents are used in detoxification Phase II. Methionine is also a methyl donor, used in methylation (another Phase II detoxification pathway).

Forty-six percent of patients exhibited deficiency in one or more of the branched chain amino acids: leucine, isoleucine and/or valine. Branched-chain amino acids can be reduced in chronic liver disease and can function as neurotransmitters. They are also the only amino acids which can enter the inner mitochondrial membrane<sup>xcviii[98]</sup> where energy generation occurs. Tryptophan (deficient in a third) is utilized to form serotonin, which is in turn converted to melatonin,<sup>96</sup> essential for healthy sleep. This is another biochemical factor in sleep disturbance: reduced melatonin by testing is common in toxic injury patients of the author. Deficiencies in phenylalanine and tyrosine are also critical. Phenylalanine is converted to tyrosine, which can then be converted into thyroxine, (a thyroid hormone) or through a series of steps to neurotransmitters: first to L-dopa which is converted to dopamine, then converted to norepinephrine which is in turn converted to epinephrine. Regarding tyrosine, an additional 5 (20%) were borderline deficient.

Amino acid supplementation is ideally done with a mixture that addresses the specific tested deficiency profile. Extra amounts can be used as indicated: extra support for detoxification is often useful. As with all supplementation, the focus is to correct deficiency to ample but not elevated levels while dietary measures and environmental

controls are implemented to maintain adequate levels. It is the author's experience that amino acids and minerals are difficult to bring to adequate levels (at least average as a minimum for repair of toxic injury) without stabilization of disturbed adrenal function using the approaches described above.

The author's treatment approach has been to base repletion on test results. This can be done with a formulated powder whose composition is modified according to the precise deficiencies present. Unless environmental and other controls are adequately eliminated to control most exacerbations, or in patients using medications (the vast majority of which are detoxified through similar pathways as nonpharmaceutical petrochemical compounds), additional supplementation of amino acids necessary for detoxification is often useful.

### **Energy metabolism:**

Foods are converted into energy through a multistep process in the intracellular structures called mitochondria. The author earlier documented disturbances of energy metabolism in all of 20 additional consecutively tested patients who were chronically ill following toxic exposure<sup>30</sup> by measuring metabolites in the urine from each of the multiple steps in energy metabolism, (often known to physicians as the Krebs or TCA cycle of energy metabolism). Recently a more cost-effective test was introduced which assesses energy metabolism only. As of this date, only six energy metabolism test results are available from the patient group described in this paper. While this is a small number, all 6 had impaired energy metabolism, with 5 having impaired function at two or more steps in the energy production cycle. Lactate levels were normal in all six and pyruvate reduced in one (other 5 normal). However, all 6 had reduced hydroxymethylglutarate, which was found in half of the previously tested group.<sup>30</sup> Despite the small numbers, the results have striking similarity to the earlier tested group, even though the two groups were tested in different laboratories, lending further support to validity.

The results from energy metabolism can be utilized by a health care provider with some knowledge of the biochemical cofactors which are necessary for the various steps. As a clinical example, one of the patients tested low in alpha ketoglutarate, which feeds directly into the electron transport chain of energy generation, which is vital to all body functions. The immediate preceding step, isocitrate, requires vitamin B3 (as NADH), magnesium and manganese. Mineral testing on this patient showed reduced magnesium and a low normal manganese. With this particular test, a diagram is provided to the physician listing necessary cofactors so the results can be readily compared with other testing to determine the extent of clinical significance for energy generation in fatigue patients who have either deficient or low levels, guiding the supplementation process and dietary recommendations.

Energy metabolism testing is also useful to help determine biochemical causes of fatigue and to assess, following treatment, whether energy production has reached more normal levels. Because hydroxymethylglutarate is necessary for the formation of coenzyme Q10, a vital antioxidant for energy production in the inner mitochondrial membrane,<sup>97</sup>

supplementation with coenzyme Q10 is useful to address this disturbance until/unless the more basic problem can be corrected. The above discussed deficiencies of branched chain amino acids are also important for energy metabolism, because these are the only amino acids which cross the inner membrane of the mitochondria where energy metabolism occurs.<sup>99</sup> Additionally, carnitine is essential as a shuttle to allow fatty acids to pass into the mitochondria to be utilized for energy metabolism, so carnitine deficiency can also interfere with energy metabolism. It would thus be useful to have a more direct measurement of carnitine adequacy. Increased adipate or suberate (medium chain fatty acids) often occur with carnitine deficiency. For the 20 previously evaluated toxic injury patients,<sup>30</sup> adipate was increased in 30 percent, with none of the patients showing decreased levels, suggesting that carnitine deficiency could also be a factor in reduced energy metabolism in toxic injury patients.

A wide range of toxic substances have been documented to impair energy metabolism, including phthalate plasticizers, styrene, polychlorinated biphenyls, toluene, trichloroethane, 2,4,6-trichlorophenol, pentachlorophenol and other pesticides. For example, toxic injury patients with fatigue could have exacerbations from food/beverage containers with phthalates (soft plastic) and medical equipment using such plastics: soft IV bags, much IV tubing, many oxygen masks, etc.<sup>99</sup>

### **Detoxification:**

Detoxification capability was assessed in 21 consecutively new tested patients (Table 3) and, as for all other tests, data is presented for all of the 30 patients who completed the respective tests by the time of the manuscript preparation. Detoxification of petrochemical compounds typically involves two steps or phases: Phase I involves the cleaving of part of the molecule to create a free radical which must then be linked with another substance in the second step, often called Phase II.

The first step involves the cytochrome p450 system, which has several dozen subtypes. For this assessment of detoxification, which is a true challenge testing, 200 mg of caffeine is taken by mouth (tablet) to assess a common p450 isomer: only three patients had disturbed function, with two of those having increased function and thus likely to form increased free radicals. This does not rule out abnormal Phase I function for other p450 isomers.

Four Phase II pathways were assessed using a single dose of acetaminophen of 650 mg to assess glutathione conjugation, sulfation and glucuronidation; and 650 mg of aspirin (two aspirin tablets) to assess glycine conjugation. Urine is collected for metabolites 10 hours after acetaminophen and aspirin challenge. In this group of new patients, excess activity of Phase II was the predominant abnormality, and was found in the majority of patients, with four patients actually having excess activity in all four tested Phase II pathways. It is felt that excess activity is likely to precede reduced activity, the latter occurring when depletion of the necessary substances such as glutathione, glycine, sulfate, etc. occurs. Other Phase II conjugation pathways which cannot be assessed with these challenge substances include conjugation with glutamine, taurine, methyl groups (such as from

methionine, folate etc.), and conjugation with an acetyl group.<sup>55,97</sup>

The increased lipid peroxides found in over one-third of tested patients is of grave concern: lipids comprise nearly two-thirds of the content of the brain, as well as forming membranes for body cells, for the billions of body mitochondria (energy metabolism occurs in the mitochondrial membrane), and membranes around genetic material (DNA). Obviously, converting these essential lipids into peroxides damages their function. All cell nutrients must pass through the lipid/essential fatty acid cell membrane and all waste products must pass out of this membrane. Damage to such lipids may be repaired by the body using the wrong fatty acid/lipid in an attempt to prevent cell death, but normal lipid/essential fatty acid composition has been altered. This concept is discussed further below.

The large portion of patients who had glutathione deficiency is a further indication of the need to preserve glutathione levels, by reducing exposure, utilizing nebulized glutathione and conserving the reduced (active) state of glutathione by adequate levels of buffered vitamin C. Alpha lipoic acid also helps to conserve glutathione and is able to access water and fat-soluble body tissues. Glutathione cycling in the body requires an adequate selenium level<sup>99</sup> but excess can be toxic, so testing is useful.

Superoxide dismutase (SOD) functions as an antioxidant to reduce tissue damage from free radicals and was reduced in 33%. Necessary cofactors for its adequate functioning include copper, and manganese,<sup>99</sup> emphasizing the need to evaluate mineral status to identify factors underlying reduced SOD functions. Despite ample or excess activity in Phase II pathways in these tested patients, over half had a high level of free radicals, emphasizing the need for antioxidant protection. Increased free radicals have been associated with degenerative and chronic diseases,<sup>xcix[99]</sup> stroke and heart disease,<sup>c[100],ci[101]</sup> cancer,<sup>cii[102],ciii[103]</sup> cognitive decline,<sup>civ[104],cv[105]</sup> the rate of aging,<sup>cvi[106]</sup> and can damage enzymes and other proteins, cell membranes, nerve cells and virtually any other body tissue.

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### **Essential Fatty Acids in Cell Membranes**

Following the publication of Dr. Simpson,<sup>cvi[107]</sup> a world renowned researcher on red cell morphology, the author undertook an evaluation by submitting samples on 20 chronically ill toxic injury patients, to be interpreted by Dr. Simpson without any knowledge of diagnosis. All 20 had altered red blood cell morphology, all with a reduced proportion of discoid cells and an increased proportion of flat cells. This alteration in RBC morphology would impair the ability of the cells to pass through the capillary, because the red cell is about 7 microns in diameter and a capillary is only 3-4 microns. The cell must therefore flex to pass normally through capillaries, and disc shaped cells flex much better than flat ones. The study with Dr Simpson also showed a substantial minority of patients with even more bizarre forms of altered morphology.

After the author's patient testing by Simpson, the author began to assess RBC membrane lipid composition, in an attempt to improve brain blood flow and other cell functions. Some preliminary information was published earlier.<sup>30</sup> Impaired tissue perfusion in the brain has been documented in toxic injury patients by several authors.<sup>32,33,34</sup>

All patients in this group of 30 who had completed RBC membrane essential fatty acid testing have data displayed in Table 3 (25 patients); 17 of these had specimens sent to one laboratory<sup>cviii[108]</sup> and eight patients in another laboratory.<sup>cix[109]</sup> Because the first laboratory reported results in weight percent, while the second in micromoles, the data were displayed separately.

Omega 3 essential fatty acids include alpha linolenic (ALA), eicosapentanoic (EPA), and docosahexanoic (DHA) The proportion of patients from the two laboratories which had a deficiency of one or more of these Omega 3 essential fatty acids was 76% and 88% respectively, while none of the 25 patients had an increase in either laboratory.

The Omega 3 essential fatty acids are anti-inflammatory.<sup>cx[110]</sup> ALA can be converted to EPA which then may be converted to DHA. Further, DHA has a high concentration in the cerebral cortex, comprising about 30% of the essential fatty acid in phosphatidylserine and phosphatidyl ethanolamine.<sup>109</sup> Because the enzymes which convert ALA to the other essential fatty acids could be impaired by free radical damage, it is recommended that essential fatty acids be tested separately, as was done for these patients. ALA appear to be involved with the transfer of oxygen from air into the lungs, across the red cell membrane to hemoglobin, and appears to hold oxygen in the cell membrane where it can assist as a barrier to viruses, bacteria, etc.<sup>cxii[111]</sup> Cell membrane rigidity/fluidity is also affected by essential fatty acid composition of cell membranes, with Omega 3 essential fatty acids creating a less rigid membrane.<sup>109</sup> Thus the reduction in Omega 3 essential fatty acids in the RBC membranes of toxic injury patients could impair the ability of the red blood cells to pass through and flex in the capillary, reducing tissue perfusion and nutrient/waste product exchange between the blood and other body cells.

GLA is the precursor of dihomo-gamma-linolenic acid (DGLA), which is also anti-inflammatory, being a precursor for the series one anti-inflammatory prostaglandins in the body.

Arachidonic acid (AA), is an essential fatty acid that when found in excess can be proinflammatory.<sup>111</sup> Arachidonic acid forms proinflammatory leukotrienes, which attract white blood cells called phagocytes and polymorphonuclear white cells during inflammation.<sup>111</sup> As can be seen in Table 4, a high proportion of patients showed increased proinflammatory arachidonic acid, while none of the 25 showed reduced levels. The combination of a high proportion with reduced anti-inflammatory essential fatty acids and a high proportion with increased proinflammatory arachidonic acid is consistent with the proinflammatory symptoms in these patients: increased aching, respiratory congestion, etc..

The author's approach to correcting membrane essential fatty acid composition is to base recommendations upon test data. EPA, DHA and GLA are available in a micellized form that is absorbed without the necessary activity of digestive pancreatic enzymes, which are often deficient in toxic injury patients<sup>30</sup> and further documented below. Essential fatty acids can be damaged by contact with light, heat or air, so sealed containers are advisable and refrigeration is recommended. Dietary recommendations are an important part of patient care. The richest dietary sources of EPA and DHA are naturally grown cold water fish such as mackerel, salmon, sardine, blue fish, herring, trout, and whitefish.<sup>111</sup> Up to four grams daily of omega 3's may be needed to suppress excess inflammatory response.<sup>111</sup> Because individual food preferences vary, the author's approach is to encourage increased consumption of such fish, but as with any food, not to urge consumption for individuals who have a dislike of the specific fish or other foods. Fish oil may be more useful than aspirin and other cyclooxygenase (COX) inhibitors in suppressing chronic inflammation.<sup>111</sup> The source of fish is important in its omega-3 content, because fish who eat omega 3 algae and phytoplankton in the wild are likely to have a higher omega-3 content than farm-raised fish without an ample level of omega-3 in their diet. Arachidonic acid is rich in red meat and shellfish, but does not appear to be the sole and perhaps not a primary source of these elevations, since some of the patients were vegetarians and others did not eat these foods.

### **Gastrointestinal testing**

Table 5 illustrates gastrointestinal abnormalities found in all consecutively tested new toxic injury patients. Secretory SIgA was evaluated in the stool, and was deficient in 87% of those tested, with striking similarity to the high portion reduced as reported earlier by the author on other toxic injury patients.<sup>30</sup> SIgA levels on many patients were severely deficient. This could increase the potential for infection, which was also commonly found as illustrated on Table 5. The potentially ulcer-inducing parasite, *H. pylori*, was evaluated by IgG antibodies specific to *H. Pylori*. *Entamoeba histolytica* was evaluated by salivary secretory IgA specific antibodies which are more likely to detect amoeba-induced intestinal infection which is invasive. *Toxoplasma* was assessed by secretory IgA-specific antibodies to *toxoplasma*: the test had only been introduced recently, but over half of the 7 tested patients were positive. *Giardia* and *cryptosporidium* were both assessed by organism-specific antibodies. Evaluation for *Clostridium difficile* utilized toxins A and B, which is more sensitive than the use of a single toxin alone. While the use of the parasite testing approach described is considered more sensitive in parasite detection than viewing the stool samples under the microscope (in the hope of detecting the evidence of a parasite in a tiny drop of stool specimen), the laboratory utilized three microscopic evaluations for ova and parasites in addition. The original contact source for the various parasites could have been food and/or water, depending in part upon the specific parasite's life cycle.

Parasites were treated by antibiotics, and retesting was conducted to verify cure. The specific antibiotic regimen was varied slightly to improve the ability of these patients to tolerate treatment. The author does not recommend herbs to kill these parasites because

of concern not only regarding efficacy but also because some parasites, such as *E. Histolytica* and toxoplasma can migrate to other body organs.

The following are treatment regimens recommended by the author.

Toxoplasma has responded well thus far to Mepron at 750 mg (1 teaspoon liquid) twice daily with food for 21 days. With use of Mepron, liver function testing (SGOT, SGPT, GGT) before treatment and after 7-10 days of treatment is recommended. For *E. Histolytica*, a triple therapy is recommended to clear the parasite from the intestine and any organisms that have spread to other body areas, using Yodoxin 650 mg three times daily and generic tetracycline (which is retained largely within the intestine) at 500 mg three times daily for 10 days, then Tinidazole 500 mg three times daily for 7 to 10 days. Tinidazole is closely related structurally to metronidazole, but the former appears better tolerated and, based upon retesting results, appears effective. *H. Pylori* appears to respond well to a regimen including Tinidazole 500 mg three times daily with meals and Bismagel one teaspoon 30 minutes before meals, taking both for 10 days, and Amoxicillin 500 mg three times daily with meals for 10 days. The recommended treatment for cryptosporidium is Tinidazole 500 mg three times daily for 10 days. Following antibiotic therapy, the author has used human strain probiotics (*acidophilus*, *bifidus*, etc.), which, unlike the nonhuman strains comprising the vast majority of available brands, appear to remain functional because they can multiply and sustain their population in the human intestines.

Like an earlier tested group of toxic injury patients,<sup>30</sup> a substantial proportion of these patients had *Candida*, usually *Candida albicans*. This was assessed on culture, although microscopic examination was also done by the laboratory (microscopic results for *Candida* were not added to Table 5). *Candida* are opportunistic organisms and are sufficiently ubiquitous in the environment that reinfection is likely unless the factors which allow them to flourish in the gut are addressed. These factors include adequate digestive enzymes (deficient in 73% of those tested in this group and 60% of an earlier tested published group<sup>30</sup>). Gastric acid deficiency, insufficient human strain *acidophilus* and/or *bifidus* (which secrete enzymes to help digest sugars) are also factors which allow *Candida* to flourish. In the author's experience, evaluating and controlling these risk factors as well as a *Candida* diet has been adequate to control *Candida* without the use of antibiotics such as Nystatin, Diflucan, etc., except for a very few patients who had been placed on steroids for medical conditions such as autoimmune disease (not including patients in this group of 30).

Chymotrypsin is a marker enzyme for pancreatic digestive enzyme output: low chymotrypsin levels suggest reduced pancreatic output of other pancreatic digestive enzymes. Digestive enzyme deficiency can impair the ability to obtain adequate nutrient content from food, because food must be adequately digested through pancreatic enzyme action. In the author's experience, reduced chymotrypsin often persists for years in toxic injury patients. Digestive enzyme supplementation with food at mealtime is recommended. Reduced digestive enzyme output could lead to food intolerances, because incompletely digested foods are more likely to be antigenic. As demonstrated on

Table 5, the majority of tested patients showed secretory IgA specific antibodies to one or more of the foods evaluated: milk, soy, and egg. Food intolerance assessed by other means, such as ELISA-ACT and IgG-specific antibodies show multiple food intolerances in the vast majority of tested toxic injury patients of the author, although this data has not been quantified. Avoiding foods to which an individual has intolerance has improved symptoms in the author's experience, particularly fatigue and aching. After an interval of avoiding the food, some patients can tolerate reintroduction of the food on an occasional basis. Clinical nutritionists often recommend an interval of up to once every four days, based upon the three-day transit of food through the intestinal tract. For patients testing as gliadin (gluten) positive, elimination of gliadin-containing foods would include those containing wheat, rye, barley, oats and kamut. Such patients may eat corn, and may tolerate quinoa and amaranth in modest amounts because of the small and well tolerated glutens in these grains. Patient response to food reintroduction after a three to six month interval of elimination can utilize the illness log approach discussed above, if the patient understands that foods remain in the intestines for about three days, so that symptom exacerbation can occur on a delayed basis.

### **Red Blood Cell Minerals**

Intracellular mineral levels was used as the preferred technique because it is less influenced by recent dietary intake and because these minerals have passed the cell membrane, the composition of which is disturbed as described above. Patients were tested using one of two different laboratories as indicated on Table 6, depending in significant part on the Medicare status of the patient, although the author prefers more comprehensive testing of laboratory one.

Calcium was found deficient in none of the tested patients and is generally uncommon in toxic injury patients. Calcium is widely used as a supplement in the general population and is often added to foods as a supplement.

Chromium was deficient or borderline low in a substantial proportion of patients tested. The assessment of borderline low was a clinical judgment of the author based on test results: these patients were well below the lower 25 percent of the normal range. Levels needed to repair toxic injury are felt to be above average level and may well be in the ample range although intracellular levels in the excess range are not recommended.

Chromium losses are increased through tissue trauma.<sup>111</sup> Chromium is probably transported in the blood by plasma protein known as transferrin.<sup>111</sup> With the widespread protein deficiency in these patients, carrier proteins could be reduced. Chromium deficiency is associated with glucose intolerance and elevated cholesterol and triglycerides.<sup>111</sup> The density of insulin receptors is enhanced by chromium supplementation, and cholesterol elevation is significantly reduced.<sup>111</sup> Dietary levels are often insufficient<sup>111</sup> and thus diet changes are difficult to utilize as a sole means of correcting chromium deficiency. Inorganic chromium salts are poorly absorbed,<sup>111</sup> and like other minerals, chromium is better absorbed as an amino acid chelate (the specific chelate can be selected using those deficient in the cellular energy testing, for example

citrate, aspartate etc. or linked to picolinate. Picolinic acid is considered the binding agent secreted by the pancreas to assist mineral transport.<sup>cxiii[112]</sup>

Deficiency of copper is significant because it is essential for the function of the detoxification substance superoxide dismutase,<sup>99,111</sup> often deficient as displayed on Table 3. Copper is also a necessary component of some cytochrome oxidase hemoproteins which are an essential component of the mitochondrial system of generating energy.<sup>98,111</sup> Copper may compete with zinc for absorption,<sup>111</sup> although that does not appear to be the cause of copper deficiency in this patient group, given the low levels of zinc on testing. Copper requires carrier proteins, first using albumin and later ceruloplasmin.<sup>111</sup> Carrier proteins could be affected by the widespread protein deficiency in these patients as illustrated in Table 2. Copper is also incorporated into liver enzymes,<sup>111</sup> which could be affected by exposure to hepatotoxic agents. Copper absorption is an energy-dependent process,<sup>111</sup> and impaired energy metabolism as discussed above in toxic injury patients could affect absorption. Copper is also involved in the healing of inflammation and tissue repair.<sup>111</sup> Therefore there could be multiple mechanisms of copper deficiency in toxic injury. Copper deficiency may contribute to cholesterol disturbance, particularly elevation of low-density lipoprotein (LDL), the “bad cholesterol”.<sup>111</sup> Only one of the tested patients showed elevation of copper, suggesting the need to evaluate supplementation and/or Wilson’s disease. Copper is also best absorbed as a chelate which increases water solubility. Foods rich in copper include whole grains, nuts, and legumes as well as avocado.<sup>111</sup>

Magnesium was the most common essential mineral deficiency in these patients. Magnesium absorption is reduced with intestinal malabsorption.<sup>98,111</sup> Magnesium loss is increased by acidosis, which is also common in toxic injury. Twenty percent of these patients had urinary pH at first visit of less than 5, and an additional 40% were at 5 pH. Clinical nutritionists consider a urinary pH of 6 to 7 optimal. Magnesium deficiency enhances muscle irritability;<sup>111</sup> symptoms of muscle twitching, cramping, jerking and/or muscle spasm are common in the author’s toxic injury patients. When present, these often improve within 30-40 minutes with a rapidly absorbed form of oral liquid magnesium chloride/acetate designed for rapid absorption in heart patients. The rapid action assists in evaluation of magnesium’s role in the symptoms. Magnesium deficiency can exacerbate smooth muscle constriction, with implications for blood pressure.<sup>111</sup> High blood pressure in magnesium-deficient patients may respond to correcting magnesium deficiency, as may other conditions involving vascular spasm. This has applied in the author’s patients with angina, using nitroglycerin, oxygen etc. as well. Once magnesium deficiency is corrected, nitroglycerin need may decline, particularly if vasospasm was the primary mechanism inducing angina. Magnesium is also required for many ATP-dependent enzyme reactions<sup>111</sup> and is a necessary cofactor for the conversion of carbohydrates and fats into energy and for at least 2 steps of the energy metabolism cycle. Adequate magnesium is also necessary for normal bone mineral metabolism,<sup>109</sup> and the majority of the body’s magnesium content is located in the bone.<sup>111</sup> It is important in toxic injury patients to utilize well absorbed forms of magnesium when needed for supplementation to prevent loose stools. Forms can include magnesium glycinate, which also can improve glycine levels for detoxification, or an

amino acid chelate, particularly using substances necessary for energy metabolism such as citrate, etc.. Magnesium in the diet can be increased by increasing magnesium-rich foods such as whole grains, nuts, seeds and chlorophyll rich leafy plants.<sup>98,111</sup>

Manganese is essential for energy metabolism, the detoxification substance superoxide dismutase, the formation of essential substances for cartilage (hyaluronic acid and chondroitin sulphate), for bone mineralization, and for formation of membrane phosphatidylinositol.<sup>111</sup> Blood distribution probably involves transferrin proteins,<sup>111</sup> with implications for protein deficiency. Absorption may be increased by citrate and reduced by calcium, iron and phytates in the diet.<sup>111</sup> Good food sources include whole grains, nuts, and leafy vegetables. The richest grain source is in the germ.<sup>111</sup>

Molybdenum deficiency was particularly common in these patients in both testing laboratories. It is used to detoxify aldehyde compounds.<sup>111</sup> It is also necessary for the conversion of cysteine to sulfate for detoxification: cysteine to sulfate ratios were decreased in over a third of the tested patients, as illustrated in Table 3. It is also required for inactivation of the otherwise destructive sulfite compound<sup>111</sup> and in other oxidase enzymes containing flavin.<sup>111</sup> Molybdenum is found in the germ of grains and probably the legumes (beans).<sup>111</sup> For supplementation it is best absorbed as an amino acid chelate or picolinate.<sup>111</sup> Dietary absorption is good except in the presence of sulfate or enhanced sulfur containing proteins (which may be necessary for toxic injury patients), so timing of intake should be adjusted accordingly.

The vast majority of body potassium is located within cells, not blood plasma,<sup>111</sup> so the commonly utilized medical measurement of potassium in plasma could significantly underestimate intracellular deficiency (although plasma levels are also essential to control for medical reasons). Potassium is essential for normal membrane function including but not limited to nerve cell and neurotransmitter function.<sup>111</sup> Potassium listed on Table 5 was not drawn during episodes of exacerbation. In the experience of the author, potassium may drop during exacerbation following exposure, but because of the relatively narrow range of safety for potassium supplementation, it is useful to assess whether this occurs. Many potassium supplements can be irritating to the intestinal tract, which may often be avoided by using potassium chloride as a salt and/or potassium bicarbonate in patients who are acidic during exacerbations. As discussed above, pH levels are a useful guide for decisions regarding bicarbonate compounds during exacerbation.

Selenium deficiency interferes with glutathione peroxidase<sup>111</sup> and deficiency can thus reduce levels of glutathione, commonly deficient as illustrated in Table 3. Glutathione peroxidase plays a role in the detoxification of peroxides and free radicals.<sup>111</sup> Selenium is also necessary for the deiodinase enzyme that converts the less active thyroid hormone T4 to the active thyroid hormone T3. Glutathione peroxidase activity improves with selenium supplementation, as selenomethionine,<sup>111</sup> although selenium can also be administered in well absorbed amino acid chelate or picolinate. Food content of selenium depends significantly upon soil content.<sup>111</sup> Selenium rich foods include garlic and onion family foods, asparagus, grains grown in selenium-adequate soils, meats and seafood.<sup>111</sup>

Vanadium may bind to glutathione.<sup>111</sup> It is important for glucose metabolism, being able to mimic the effect of insulin on fat cells, although subsequent metabolism may prefer the pentos pathway more than insulin.<sup>111</sup> Vanadium may also stimulate mineralization of bone by promoting osteoblasts, and may also be important in cholesterol metabolism.<sup>111</sup> Vanadium is carried by the plasma protein transferrin,<sup>111</sup> like certain other essential minerals discussed. Vanadium has a low efficiency of absorption and the American food supply often contains low levels, but such levels can vary by several orders of magnitude,<sup>111</sup> which can reflect soil content. Since vanadium is potentially more toxic than chromium,<sup>111</sup> the author prefers to address chromium adequacy first prior to vanadium supplementation, because chromium helps to spare the body's vanadium reserves.

Zinc deficiency was common, as illustrated in Table 6. Zinc is essential for normal function of the detoxification substance superoxide dismutase<sup>99,111</sup>, commonly deficient in these patients as illustrated on Table 3. Superoxide dismutase, which requires both copper and zinc, is present in all body cells. Red blood cell levels play an important role in controlling superoxide free radicals,<sup>111</sup> helping to protect other cells from this free radical. Zinc is necessary for the activity of more than 100 body enzymes, including those associated with carbohydrate and energy metabolism, protein synthesis, synthesis of other vital body structures and pancreatic digestive enzymes,<sup>111</sup> which were often deficient as illustrated on Table 5. Zinc is also necessary for normal function of vitamin A (an antioxidant) and is critical to normal immune function.<sup>111</sup> It may also be required for normal activity of adrenocorticotrophic hormone (ACTH),<sup>111</sup> which is secreted by the pituitary to stimulate adrenal cortisol production, the latter being commonly deficient in toxic injury patients as discussed above. Increased zinc loss can occur with injury.<sup>111</sup> Pancreatic insufficiency can also cause zinc deficiency.<sup>111</sup> Increased loss from the body can also occur with liver disease, porphyrin disturbance and parasitic infection.<sup>111</sup> Porphyrin disturbance is common in toxic injury<sup>1</sup> as is parasitic infection,<sup>30</sup> as further illustrated on Table 5. There are thus multiple potential mechanisms for zinc deficiency in toxic injury.

Essential minerals deficiency was thus common by testing of toxic injury patients. Chronically elevated cortisol leading to adrenal insufficiency (see discussion above) can deplete minerals as well as proteins. Reduced carrier proteins for some minerals could reduced effective transport to body cells. Impaired digestive enzymes as illustrated on Table 5 can impair adequate breakdown of food, making minerals less bioavailable for absorption. Chronic gastrointestinal inflammation can reduced absorption and/or accelerate loss of minerals. Such inflammation could be secondary to intestinal parasites (common as illustrated on Table 5) and in earlier work by this author,<sup>30</sup> and also increased through a generalized proinflammatory state as illustrated in Table 4. Further, neurogenic inflammation in toxic injury involves the gastrointestinal tract and genital urinary tract as well as the respiratory tract because of its systemic nature.<sup>40</sup> The detoxification role of zinc and copper (in superoxide dismutase) and molybdenum (in converting organic to inorganic sulfates for Phase II sulfation) are further mechanisms of mineral deficiency in toxic injury.

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### **Other Nutrients**

The other nutrients displayed on Table 7 were tested with a different technology that involves assessing, for each nutrient, the ability of lymphocytes to divide and form new cells. Unlike nutritional assays relying on plasma levels, transport in the bloodstream and cellular uptake is taken into consideration with this technology. With the membrane disturbances described above (Table 4), this is particularly important. Further, lymphocytes traverse through lymphatic fluid, which is lipid based, with increased potential for exposure and effects of lipid-soluble chemicals. Such chemicals can affect other lipid tissues such as the brain, with its high lipid content, and cell membranes as discussed above. Further, nutrient need for repair of tissue damage is higher than the mere maintenance of healthy body function, and levels alone do not readily take into consideration nutrient need. This is a factor, however, with this particular lymphocyte assay, because the function of cell division is a demanding one and reflects nutrient need. The technique has been further described in the medical literature.<sup>cxiii[113]</sup>

Thiamine is important in two steps of energy metabolism and converts to a coenzyme (thiamine pyrophosphate) for these functions as well as for essential metabolism of all cells including the brain.<sup>111</sup> Reduced levels can exacerbate impaired attention span, memory, and peripheral neuropathy.<sup>111</sup> It may also play a separate role in brain cell viability, i.e. ability to survive.<sup>111</sup> The brain is a high energy utilizing organ.

Riboflavin is also critical to energy metabolism.<sup>111</sup> It functions as part of two co-enzymes (FAD, and FMN). Riboflavin is also essential for the production of the critical energy substance adenosine triphosphate (ATP).<sup>111</sup> In patients with more severe deficiency, redness or inflammation of the tongue and/or the corners of the mouth may be seen,<sup>111</sup> but this is insufficiently sensitive to serve as a substitute for testing.

Niacin is also called nicotinic acid. It is converted by the body to an essential substance called nicotinamide adenine dinucleotide (NAD), which is essential for energy metabolism, and for the utilization as well as the synthesis of essential fatty acids.

Thus thiamine (vitamin B1), riboflavin (B2) and niacin (B3) are all involved in energy metabolism, which is essential to the function of every cell, enzyme and other body function. Forty-three percent of the patients tested were deficient in one or more of these nutrients. Deficiency was defined by the laboratory as less than two standard deviations below the mean of a large comparison control population,<sup>114</sup> and patients with low normal levels were also very prevalent for these nutrients.

Pantothenate (B5) is essential for coenzyme A, which is necessary for energy metabolism and burning of fats by the mitochondria.<sup>111</sup> It is also essential for the body's synthesis of phospholipids needed for the brain and other cell membranes.<sup>111</sup>

Pyridoxine (B6) is necessary for the formation of transaminase liver enzymes. It is also critical to the formation of other amino acids from essential amino acids through transaminases.<sup>111</sup> Further, it is needed for the formation of neurotransmitters serotonin and gamma-amino butyric acid (GABA), porphyrin metabolism, synthesis of brain lipids, taurine synthesis and glycine synthesis.<sup>111</sup> As discussed earlier, both taurine and glycine are used for detoxification.

Cobalamin (B12) was deficient in the majority of these patients, having a higher rate of deficiency than any of the other B vitamins. Vitamin B12 is needed for the maintenance and repair of myelin, the essential coating of nerve cells. It is also a key nutrient in the s-adenosylmethionine (SAM) cycle which provides methyl groups for detoxification in Phase II methylation.<sup>99</sup> Deficient levels can also impair melatonin secretion.<sup>cxiv[114]</sup> Adsorption is more complex than for other vitamins, and requires a carrier protein.<sup>111</sup> Other carrier proteins are required for transport in the blood.<sup>111</sup> Deficiency exacerbates neurologic function.<sup>98,111</sup>

Total antioxidant function is an evaluation of the combined antioxidant capability of various individual antioxidants, with methodology more completely described in the literature.<sup>114</sup> Nearly three-fourths of the tested patients showed deficient levels with numerous others at below optimal capability, particularly given the significant proportion with increased free radicals (Table 3).

### **Other Endocrine Changes**

Melatonin levels at night have been low in a high proportion of the author's previously tested toxic injury patients. Melatonin functions as an antioxidant for hydroxy free radicals<sup>cxv[115]</sup> (increased in one third of these patients, Table 4). Patients with reduced melatonin could benefit from several measures. Ensuring tryptophan at adequate levels provides the precursor for melatonin generation.<sup>98</sup> Tryptophan containing foods include eggs, low-fat milk, beef, chicken, turkey, soy products, nuts, tuna, beans, banana, and oatmeal. Indirect sunlight (15 minutes in the spring and summer, 45 minutes in the fall and winter) and full spectrum daytime lighting can help improve melatonin daily rhythm.<sup>116</sup> Reducing evening light levels and electromagnetic fields, especially near bedtime, is useful. Thus electric blankets, L. E. D. clocks at the bedside, etc. may exacerbate sleep in affected patients, and a trial without these is useful. Melatonin is excreted by the body after passing through Phase II sulfation and to a lesser extent, glucuronidation.<sup>98</sup> The author is cautious about exogenous melatonin administration. If the above measures do not suffice, 1 mg, ideally sustained release can be used. In animals, excess exogenous melatonin can have adverse effects on other endocrine functions.<sup>116</sup> At this time, the extent of melatonin recovery is unknown in toxic injury. Melatonin levels decline with aging,<sup>116</sup> and free radicals accelerate aging, as discussed above. Free radicals are common as illustrated on Table 4.

Reproductive hormones in the author's tested toxic injury patients have shown significant disturbance. For women of reproductive age, lack of ovulation is present in a substantial

majority, and estrogen dominance is very prevalent. The latter is also common in postmenopausal toxic injury patients tested by the author. This has major implications. Estrogen dominance has been associated with increased risk for breast and some other reproductive cancers.<sup>116</sup> Estrogen dominance can also exacerbate migraine. Exogenous estrogen administration is commonly done by physicians for postmenopausal women, and this can exacerbate estrogen dominance of toxic injury patients. Progesterone deficiency is often but not always present with estrogen dominance in these patients. Because reproductive hormones affect many body functions, levels should be kept within physiologic range.<sup>116</sup> This requires testing prior to hormone administration. Since synthetic hormones are not readily tested regarding their physiologic effect on patients, natural hormones are preferred because levels can be evaluated post-treatment by testing. Natural hormones also appear to be better tolerated in these patients. Reduced testosterone is not uncommon in the author's tested patients; this change can lead to reduced muscle strength as well as lower libido in males and females.<sup>116</sup>

Thyroid autoimmune disease is the most common autoimmune disease in the author's toxic injury patients. Further quantification of thyroid changes is useful, particularly given fatigue in these patients. Thyroid hormone treatment is not recommended without thyroid testing. Low body temperature can have other causes. The author does not use the practice of thyroid hormone treatment to elevate low body temperature without testing thyroid function. With limited energy metabolism and high energy needs of the brain and heart, taking limited energy reserves to elevate body temperature by above physiologic thyroid stimulation seems unwise. Further, the author's patients temperatures tend to return to more normal levels as their health improves.

The average (mean) sublingual body temperature (assessed for all 30 patients) on initial visit was 97.4°, with 80% having a temperature under 98° and 23% under 97°. This is consistent with impaired energy metabolism. It also illustrates the fallacy of using temperature alone to make decisions on thyroid hormone treatment.

### **Other Changes**

Medication intolerance is common. Sicker patients often experience sufficient side effects that for many medications intended for symptom relief, the patient often feels side effects outweigh benefits. For medications that are essential for correcting a condition, reduced dosage is often effective and lowers side effects.

The decision of whether antibiotics are needed is more complex than with most other patients. The patient whose temperature usually runs in the 97° range will, when feverish, often not achieve temperatures near 100°. The author encourages patients to periodically monitor their temperature when they feel at their usual symptom level to establish a baseline. If later the patient feels feverish and their temperature at that time is elevated about a degree or more above baseline, this suggests their body may be going into a fever mode. Total white count often runs low to low normal in sicker patients, and during bacterial infection often does not rise to exceed laboratory range. Again, periodic baseline measurement is useful. During bacterial infection, however, the percent of

neutrophils rises, which the author has found to be a valuable assessment. Culture and sensitivity is particularly important in antibiotic selection, given low Secretory IgA and medication side effects.

Some patients describe irregular heart rhythm during exposure. Here a Holter monitor before, during and after a typical exposure (eg., going into work) can be useful. A peak flow meter can be used in the same way (before, during, after) if there is a question whether a particular situation or condition is exacerbating lung function.

In the author's experience, a minority of patients with toxic injury develop increased blood pressure. Of those who do, however, the predominant pattern is normal pressure when not exposed and elevations only with exacerbating exposures. If blood pressure is elevated only in a medical setting, elevated levels are typically seen with this pattern, which involves measuring levels after vehicle exhaust, etc.. Home blood pressure monitoring is recommended to determine whether the blood pressure elevation also occurs at home prior to a decision on medication.

## **Summary**

Exposure control is the single most important intervention for toxic injury, focusing on locations where most time is spent (work, school, home). Medical providers can assist in obtaining necessary reasonable accommodation, placing primary emphasis on the patient's health. Exposure controls are also needed as a basis for all other treatment.

Toxic brain injury can also be treated with hyperbaric oxygen at proper pressure levels and other precautions and ensuring adequate nutrients for energy generation and other functions. Cognitive rehabilitation helps, coping with residual effects. Some residual often occurs with toxic brain injury. Autonomic neuropathy can be associated with irregular heart rhythm and/or rapid rate. These usually improve with oxygen, or preferably HBOT. Mitral valve prolapse is common in toxic injury patients of the author as an autonomic neuropathy, and should improve with HBOT.

Other disturbances in patients chronically ill from exposure to petrochemical compounds, combustion products, and other irritants include disturbance of adrenal cortisol daily rhythm, energy metabolism, amino acids, detoxification (with lower glutathione levels and increased free radicals), altered membrane lipids, reduced secretory IgA with increased prevalence of parasites and Candida, reduced pancreatic enzymes (using chymotrypsin as a marker), increased food intolerances, reduced intracellular minerals, and reduction of other nutrients such as B vitamins involved in energy metabolism and other body functions, frequent reduction in B12 and reduced total antioxidant function (using lymphocytes mitogenesis as an indicator of need following lipophilic toxin exposure).

Reproductive changes in earlier tested toxic injury patients include common lack of ovulation in women of reproductive age and estrogen dominance in pre- and

postmenopausal women. Testosterone deficiency is not uncommon. Melatonin deficiency and disturbed melatonin daily rhythm is also common. Testing for abnormalities should use the most sensitive available technology as described, and patients treated according to test results.

For nutritional supplementation, a helpful principle is to introduce only one supplement at a time, beginning with very small dose levels and increasing as tolerated. The author has typically avoided IV nutrient administration: benefit is short-lived, and veins should be conserved for necessary IV use. The goal is to develop a diet which helps replace deficient nutrients, avoids food intolerances, has adequate protein and antioxidants, and is low glycemic for adrenal disturbance and Candida control.

Due to low body temperature, fever should be evaluated by an elevation of a degree or more over the patient's usual temperature and the patient's sensation of feeling feverish at the time of temperature elevation. Before use of antibiotics, WBC differential is recommended. WBC total runs low in toxic injury patients and is often not elevated with infection, but increased *percent* of polymorphonuclear cells suggests likely bacterial infection. Due to the lower rate of medication clearance in these patients, antibiotics can be used at about two-thirds of usual dose, and other pharmaceuticals at about half dose, or even less for symptom reducing medications.

Due to cognitive disturbance, medical providers should give patients written information whenever possible, in addition to answering questions (with a spouse or friend present if possible to assist in recall, etc.). Initial evaluation can require two hours or more, and follow-up often requires one to two hours. However, the treatability of toxic injury is important and can be scientific and test-based. No longer do medical providers need to tell toxic injury patients that they can't be treated or will not get better. Early detection of warning symptoms and awareness by medical providers, managers, and the general public can often help prevent disability by early removal from exposure and correcting exposure to below symptomatic levels.

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