

# Neural Sensitization: The Medical Key to Treatment for Chemical Injury

## Science Based Treatment

### INTRODUCTION

Chemical injury can cause chronic damage to body biochemistry. This involves a biochemical vicious cycle often called “Neural Sensitization” (as discussed below). **This cycle can cause reactive airways (airway inflammation), toxic encephalopathy (toxic brain damage), and chronic inflammation to other mucosal surfaces. This is chemically referred to as the nitric oxide/peroxynitrite cycle.**<sup>1-4</sup>

**Unless and until this biochemistry is healed naturally, inflammation and ongoing damage will occur. Drugs cannot heal these vicious cycles.**

Only science-based treatment with the proper healing substances can help control this cycle, which will otherwise cause ongoing inflammation and further organ damage.

This chemical injury treatment is based on scientific knowledge and patient testing. The treatment is designed to help heal these biochemical changes and the damage they cause. The diagram at the end shows the biochemical vicious cycle.

Mucosal burning is a common sensation in neurogenic inflammation.

For description of exposures that cause the vicious cycle, refer to section titled **Chemical Causes**.

**For examples of more basic concepts, see factsheet HOW CHEMICAL INJURY AFFECTS THE BODY.**

### TREATMENT SUMMARY

Intervention to help control these vicious biochemical cycles includes:

- Natural ingredients to assist cell repair, using bioactive forms.
- Ingredient type and dose is selected to help heal the biochemical cycles that otherwise can lead to chronic severe body changes. This is best done based on the patient’s tested needs.
- Ingredient action is documented in the peer-reviewed medical literature.
- Compounded capsules may be needed. These must be taken throughout the day (with meals) to be effective.
- The meals should contain some essential fat (e.g. egg, seeds/nuts, nut butter, meat, fish, fish oil, olive oil, coconut oil, ghee, etc.) for good nutrition and to help absorption of CoQ10 and other fat soluble ingredients. See factsheet **EATING FOR HEALING**
- For treatment steps, see factsheet **TREATING CHEMICAL INJURY: STEP BY STEP**
- For more summary facts, see **CHEMICAL INJURY TREATMENT: A SUMMARY**
- Testing healing needs through SpectraCell Laboratory
- Exposure controls are **ESSENTIAL**

Scientific information follows for those interested.

### TYPES OF DAMAGE FROM CHEMICAL INJURY

**Toxic encephalopathy** can occur with reduced blood flow to the brain.<sup>5</sup> Brain symptoms include reduced short term memory, poor attention span, difficulty with concentration, balance disturbance, poor coordination, trouble with complex mental tasks. Other nerves can also be affected, called **neuropathy**. Nerve changes can cause numbness, tingling, nerve pain, visual changes, and burning pain. Neural sensitization causes blood vessel lining inflammation, which reduces blood flow to the

brain and other organs. The vicious cycle can cause impaired function of brain and nerve cells.<sup>6-12</sup> See website section: TOXIC ENCEPHALOPATHY.

Chemically induced **reactive airway disease** (**upper and lower** chronic inflammation of the respiratory tract), and **migraines** also have these biochemical changes (**neural sensitization**). Lung effects are sometimes called chemical or irritant asthma. Respiratory effects can also include sinus congestion/pain often with sinus headaches and/or drainage; ear pain from eustachian tube blockage (swelling), burning/sore tongue and throat, hoarseness, bronchial symptoms of coughing, chest tightness and sometimes wheezing, and shortness of breath/difficulty getting enough air. See website section: REACTIVE AIRWAYS.

Neural sensitization also affects the **gastrointestinal tract** (sometimes mislabeled as “irritable bowel”) and **genital urinary tract** (sometimes called “irritable bladder”), and/or vaginal/genital burning (“vulvodynia”), etc.). The **inflammation of blood vessel linings** (endothelium) can reduce blood supply to the heart, causing irregular, rapid or weak heart beat. It can inflame the **conjunctiva** (burning eyes) and **skin** (burning/rash). Other effects can involve liver/gallbladder duct and impair pancreatic digestive enzyme duct function. Both of these interfere with digestion.

Gastrointestinal symptoms include nausea, burning and bloating and symptoms resembling acid reflux. The burning is NOT from excess acid: actually stomach acid is reduced but the inflammation causes burning. Avoid antacids/acid blockers because they further impair digestion.

Blood vessel lining inflammation can cause migraines, visual changes and brain/nerve effects.

Neural sensitization can also lead to increased/abnormal biochemical response to other incoming messages to the brain: noise, light, touch, vibration, electromagnetic fields, etc.

**This widespread inflammation can result in fatigue, aching, adrenal and/or reproductive hormone and other endocrine disturbance (often adrenal and thyroid) and results in depletion of amino acids, minerals and other nutrients.**

This chronic inflammation increases **arteriosclerosis**, **elevates harmful cholesterol** (LDL), increases risk of **neurodegenerative diseases**<sup>13</sup> (such as Parkinson’s, Alzheimer’s, ALS), **other degenerative disease (osteoporosis, arthritis, etc.)** and **autoimmune disease**. It can increase risk of multiple sclerosis.<sup>13</sup> Autoimmune thyroid disease and lupus are common in chemical injury but can improve with environmental controls and this chemical injury treatment. Damage to the heart and other organ function can occur.<sup>13</sup>

## HOW DAMAGE OCCURS

Inflammation and the free radicals from neural sensitization **damage lipid cell membranes**,<sup>14</sup> which are major targets of free radical damage.<sup>14</sup> This impairs substances entering and leaving through the cell membrane.<sup>14</sup> It damages structures on the membrane that regulate hormones, cell messages to other body cells and many other functions.<sup>14</sup>

Damage occurs to **membranes** of mitochondria (**energy production**), ribosomes (which make **proteins, enzymes**), **DNA (genetic material)**, membrane receptor sites (**hormones**, etc.) and other **cell messenger sites** needed for communication within the cell and with other cells and body organs.

There is disproportionate damage and loss of omega 3 essential membrane lipids because these are very vulnerable to free radical damage. Loss of omega 3 essential lipids makes a person more achy, have greater diabetic tendency, and increases risk of arthritis and other inflammatory and degenerative disease.

**Inflammation damage also impairs membranes in the brain and nerve cell coating (myelin).** This makes it harder for messages to pass within the brain and from the brain through nerves. The brain and nerves are high oxygen-demanding organs.<sup>15</sup> The brain is only 3% of body weight but uses 20% of body oxygen at rest. Reduced blood flow to the brain in toxic encephalopathy is documented<sup>5</sup>

and impairs nerve, brain and other body functions, since all body functions depend on oxygen supply and brain/nerve messages.

The **blood vessel inflammation causes reduced blood flow**, and thus reduced supply of oxygen and nutrients to body organs. The red blood cell is 7 microns, but the capillary is only 3 microns, so inflammation causing swelling of the blood vessel lining reduces the blood cell's ability to pass through.

For more detail on body effects, see factsheet HOW CHEMICAL INJURY AFFECTS THE BODY.

### **BIOCHEMICAL VICIOUS CYCLE**

- Neural sensitization occurs by excess **inducible nitric oxide**.<sup>3</sup> This can result from exposure to irritants and/or particle exposure<sup>3</sup> and from other chemicals as discussed below.
- Neural sensitization can also occur by excess activity of brain and nerve cell **NMDA** (N-methyl-D-aspartate), which then increases brain and other organ (inducible) nitric oxide (NO).<sup>8,16,17</sup>
- When this nitric oxide is increased, especially chronic or repeatedly, free radicals are formed from the vicious biochemical cycle set in motion. Free radicals are substances that damage body cells and organs.<sup>18</sup> This cycle is shown in the chemical diagram on page 13.

Below is a detailed discussion of the vicious cycle along with the substances medically documented to control it. This forms the **scientific basis for treatment**. For more treatment details refer to PRACTICAL GUIDE FOR TREATING CHEMICAL INJURY (being revised).

### **Inducible Nitric Oxide**

The cycle begins with inducible nitric oxide (iNOS).<sup>1,3,4</sup> Bioactive B12 works well for reducing excess iNOS.<sup>19,20</sup> Methylcobalamin is a bioactive form and more neurocalming than hydroxocobalamin. Cyanocobalamin should not be used.

Nitric oxide also damages the first detoxification step,<sup>21</sup> allowing chemicals and many drugs to build up more in the body. This further increases inflammation.

Exhaled nitric oxide is a medically accepted marker of airway inflammation.<sup>4</sup> Excess nitric oxide impairs the body's energy capacity<sup>13</sup> and can cause death of energy structures (mitochondria).<sup>13</sup> These mitochondrial changes can lead to fatigue.

Mitochondria are structures in body cells that generate energy by producing ATP. Mitochondrial damage has been documented in the vast majority of patients with chronic illness from chemical injury.<sup>22</sup> This is a major cause of their **fatigue**.

When nitric oxide is increased too much, there can be a decrease in body defense antioxidants such as SOD (superoxide dismutase), catalase and glutathione peroxidase.<sup>23</sup> Healing substances are needed to help these body protections function better.<sup>24</sup>

### **Peroxynitrite Free Radicals**

Inducible nitric oxide forms a tissue damaging free radical known as **peroxynitrite**.<sup>2,8,25,26</sup> This then forms even more nitric oxide. See diagram for biochemical details.

Peroxynitrite is a highly potent free radical that damages proteins.<sup>13</sup> including enzymes, lipids (brain and cell walls), mitochondrial (energy producing) membranes, ribosomal (protein making) membranes, cell messaging membranes (RNA, etc.) and genetic (DNA) membranes.<sup>27</sup> Peroxynitrite weakens the blood-brain barrier, allowing chemicals to enter the brain more readily.<sup>28</sup>

This vicious cycle with increased nitric oxide and peroxynitrite can cause brain cell death and neurodegenerative disease.<sup>8,13,26,29-32</sup>

Antioxidants such as high gamma Vitamin E (tocopherols) reduce peroxynitrite damage in lipid membranes.<sup>33,34</sup> In different cell organ locations, glutathione,<sup>35-37</sup> Vitamin C (ascorbic acid),<sup>14,38</sup> and alpha lipoic acid<sup>39,40</sup> also help protect against these effects.<sup>27</sup> For glutathione function, the body needs selenium<sup>24,41,42</sup> and Vitamin B2<sup>43,44</sup> to help heal damage.<sup>27</sup>

## **SUPEROXIDE FREE RADICALS**

**Superoxide** free radical reacts with nitric oxide, which then increases peroxynitrite. Excess superoxide can damage the mitochondria (energy production) and other body cells. Superoxide is reduced by the body's protective enzyme system, SOD (superoxide dismutase). SOD needs minerals zinc, copper and manganese (in proper ratio) to function.<sup>24,45,46</sup>

### **Damage to Mitochondria/Energy Structures**

Peroxynitrite damages mitochondria and thus also **depletes energy** ATP,<sup>1,13,47</sup> which then further increases sensitization by excess action of NMDA.<sup>32,48</sup> Lack of adequate mitochondrial antioxidants damages the mitochondria and forms more peroxynitrite.<sup>49</sup>

The mitochondria need adequate nutrients to function well to help stop the vicious cycle. These include thiamine, niacin, pantothenate and biotin<sup>24,50-53</sup> as well as coenzyme Q10<sup>40,54-56</sup> and acetylcarnitine.<sup>57-60</sup> Chromium helps glucose enter the cell to be burned for energy,<sup>24</sup> reducing diabetic risk and hunger cravings/obesity. Adequate omega-3 essential fats (EPA/DHA) also helps reduce insulin resistance,<sup>61,62</sup> thus helping glucose enter the cell to generate energy.

### **NMDA (N-methyl-D aspartate) Receptor**

**NMDA is a neuroexcitation receptor.**<sup>18</sup> When activated, it increases nitric oxide, peroxynitrite, and other free radicals.<sup>13,63,64</sup>

Magnesium calms the NMDA overactivation.<sup>65-67</sup> Magnesium is further depleted by body acidity caused by inflammation.<sup>24</sup>

Pyridoxal phosphate B6 helps form GABA,<sup>68</sup> and taurine supports GABA<sup>69</sup> and is neurocalming,<sup>70</sup> reducing NMDA adverse effects.

## **SUMMARY OF NEURAL SENSITIZATION**

**Neural sensitization thus involves self-perpetuating excess brain/nerve cell neuroexcitation** response to further chemical exposure.<sup>71,72</sup> Since nerve cells communicate with all body organs, increased inflammation can involve many organs. This can cause **hyperactivity** in children and a feeling of being “wired” in all ages, despite fatigue, as well as other changes discussed above.

Antioxidant function in general is usually reduced in chemically ill patients,<sup>22</sup> and increased lipid peroxides and other damaging free radicals are common.<sup>73</sup> These cause ongoing damage if not corrected by the above medical treatment and environmental controls.

**Without adequate antioxidant protection, there is increased risk of inflammation and degenerative diseases,**<sup>14</sup> lung damage,<sup>74,75</sup> and other organ injury.<sup>76</sup>

The vicious cycle **must** therefore be interrupted to the maximum extent feasible. **Symptoms of sensitization “reactions” are warnings that other more silent toxic-induced organ damage of the liver, pancreas, immune system, adrenals, mitochondria, and other organs can be also occurring.**<sup>22,73,77</sup> Thus masking/blocking symptoms of these cycles by drugs is not recommended because it allows silent damage and patient deterioration. It does not heal the disturbed biochemical mechanism. This is like turning off the battery warning light without fixing the battery.

For effective treatment, the **frequency of intake of ingredients** must be adequate to **CONTINUALLY interrupt the biochemical vicious cycle**. Also, interruption in taking protocol ingredients significantly delays the ability to interrupt the biochemical cycle.

## CHEMICAL CAUSES AND EXACERBATING FACTORS

These causes are illustrated in the chemical diagram. All can cause significant worsening: thus the **essential need for ongoing environmental controls**.

### Chemical exposure can cause inflammation and neural sensitization:

- **Pesticides**,<sup>78-80</sup> **fungicides**<sup>78,79</sup> and **herbicides**<sup>78,79</sup> activate the NMDA receptor.<sup>78,80</sup>
- **Pesticides** such as organophosphates and carbamates over stimulate NMDA. This occurs because they inhibit acetylcholinesterase (a nerve cell messenger), and over stimulate muscarinic nerve receptors, which increase nitric oxide. When muscarinic receptors are too stimulated by pesticides, increased calcium is released within cells. This over stimulates NMDA receptors.  
As discussed above, NMDA activation causes excess nitric oxide, producing neural sensitization.
- **Pyrethroids** Pesticides interfere with cell ability to keep out excess sodium. This harms cell electrical balance and activates NMDA receptors.<sup>81</sup>
- **Formaldehyde activates NMDA**.<sup>16,72</sup> Formaldehyde also stimulates the brain vanilloid receptor.<sup>82</sup> This receptor induces sensitization by activating the NMDA receptor<sup>83</sup> and increasing nitric oxide, which then increases peroxynitrite and sets in motion neural sensitization.  
Vanilloid receptor stimulation also increases release of immune substance P.<sup>84</sup> Increased substance P is associated with reactive airway disease.<sup>85</sup>
- **Petrochemicals (VOC's, solvents)** damage energy production (in mitochondria) and increase superoxide free radicals which increases peroxynitrite.<sup>86</sup> This can increase tissue-damaging free radicals in the brain.<sup>87</sup> Peroxynitrite also harms energy production.<sup>1,47</sup> Repeated very low level solvent exposure (e.g., toluene at 1 ppm; far below legally allowed exposure limits) can cause sensitization.<sup>88</sup>
- **Carbon monoxide** Carbon monoxide is released in all combustion: coal, gas, gasoline/diesel, wood, tobacco, and even natural products (beeswax and other candles) and “aromatherapy” (a medical oxymoron). Exposure to carbon monoxide even at “low levels” can increase nitric oxide and cause excess NMDA activity.<sup>89,90</sup>
- **Irritants** Petrochemicals and many other chemicals are irritants.<sup>90</sup> Irritant exposure can cause inflammation. Repeated or high exposure can lead to chronic inflammation.<sup>73</sup> Inflammation results in further elevated nitric oxide and damaging free radicals.
- **Particles** cause inflammation and increase nitric oxide.<sup>4,16,91-94</sup>

## BIOCHEMISTRY OF TREATMENT

Ideally treatment should be customized based on patient testing. Patients can be very deficient in some substances and adequate in others. Progress is best by testing, not guessing. See test guidelines below. Some patients are very inflamed and the sequence discussed here can help them with better tolerance. Very sick patients are often very inflamed and dosing often has to be more gentle and gradual: some is better than none. NEVER PUSH CONCENTRATIONS OR BRANDS that cause discomfort: the PATIENT'S BODY IS WISER THAN ANY DOCTOR.

### 1. NITRIC OXIDE

Cobalamin (B12) is a **nitric oxide scavenger**<sup>19,20</sup> that reduces excess, harmful levels of inducible nitric oxide. B12 (cobalamin) is inadequate in the majority of chemically ill patients.<sup>73</sup> The bioactive

form is methylcobalamin. The cyano form (too often sold) is not recommended (patients don't need cyanide). Cyanocobalamin is not effective in essential enzyme function.<sup>95</sup> Methylcobalamin can also help brain and nerve repair.

**Since the nitric oxide excess is a major starting step in the vicious cycles, methylcobalamin use is essential.**

Sublingual forms of methylcobalamin at 5 mg per tablet are convenient and portable. They can be used 1-2 per dose, repeating until exacerbating symptoms clear. Rapid entry into the blood stream with symptom reduction, using 2 tablets at a time under the tongue until exacerbations clear has been demonstrated in many patients.

Nebulizer use also builds body levels, but is less convenient and less portable. If a patient cannot tolerate sublingual tablets, pure methylcobalamin can be compounded at 1-5 mg/drop and placed on the tongue. This liquid will then absorb through the upper tongue surface into the blood stream. Very inflamed patients may need to dilute it further, e.g. in a 4-5 ml pharmacy bottle to start, moving up the concentration as able. It can be added to 1-2 ml of water in the nebulizer if preferred.

Past research shows effectiveness of cobalamin. For example, nasal cobalamin is rapidly absorbed, well tolerated<sup>96,97</sup> and increases body levels.<sup>97</sup> Nasal cobalamin reduces frequency and severity of migraines, by reducing excess nitric oxide.<sup>98</sup> Because of lack of a barrier between the nose and brain, nasal use can improve brain levels.<sup>99</sup>

Bioactive folate (MTHF) can also help reduce abnormal levels of nitric oxide.<sup>100</sup>

## **2. HIGH GAMMA TOCOPHEROL**

**Natural Vitamin E with high gamma tocopherol protects lipid membranes.**

Gamma tocopherol reduces peroxynitrite damage on lipid membranes.<sup>33,34</sup> It complements alpha tocopherol, which activates glutathione<sup>76</sup> and protects cells from injury.<sup>101</sup> Roughly equal amounts of each form are needed.<sup>102</sup> Thus "mixed tocopherols" with mostly alpha do not function as well for inflammation control because of low gamma levels. Avoid all synthetic tocopherol e.g. dl-tocopherol: it is useless and competes for tocopherol receptors. Beware of being misled by "vitamin E" studies using synthetic or unspecified tocopherols.

Tocopherols are lipid soluble: Dr. Ziem has not seen much benefit from dry forms, using retesting.

Respiratory lipid membranes directly encounter airborne irritants, so high gamma tocopherol protection is vital. Occasionally, patients may want or need to puncture the capsule immediately before use, emptying contents on food or tongue, or even start with a drop or two and slowly increase concentration.

## **3. GLUTATHIONE**

**Glutathione is the most important antioxidant in the body.**<sup>46,103</sup> Glutathione helps protect brain cells from nitric oxide-peroxynitrite damage.<sup>13</sup> It reduces upper and lower respiratory inflammation.<sup>35,37</sup> It reduces NMDA activity<sup>36</sup> and scavenges peroxynitrite. **Glutathione together with cobalamin can reduce body damage from chemicals.**<sup>104</sup>

Glutathione can now be taken orally as S-acetyl glutathione capsules, (e.g. Xymogen), a fat soluble form not broken down by digestion but able to enter the blood stream through the small intestinal wall. Preliminary research, patient response and testing are very promising. It must be taken with fat for absorption (e.g. a bit of olive oil, fish oil, coconut oil, ghee, etc). Other oral forms are disappointing. Other glutathione routes are discussed below.

Improving glutathione levels in the upper and lower respiratory tract (nose, throat, bronchial tubes, lungs, etc.) can help reduce respiratory responses to irritants<sup>35,37</sup> and help to reduce the severity and duration of the patient's reactions. This means less congestion, burning and mucous in the nose,

eustachian tubes, throat, sinuses, bronchial tubes, and lungs.

**Glutathione can also be absorbed through the lungs by nebulizer,**<sup>105</sup> as an aerosol **and is able to cross the blood-brain barrier.**<sup>106</sup> This reduces the need of IM/injection use. The nebulizer used should generate particles of 5 microns (the size of the smallest airways) to enter the lungs and blood stream. AeronebGo brand nebulizer makes smaller particles of mist that enter the body easier from the lungs. Use of buffered nebulized glutathione improves symptoms and lung function in people with chronic lung inflammation<sup>35</sup> compared to double blind placebo of persons not on the treatment.

Nebulized or injectable glutathione is easily oxidized (damaged) and must be compounded by an experienced pharmacy with expertise in proper glutathione compounding, packaging and shipment. It must be refrigerated and usually oxidizes after 2 months even with proper care.

Patients with more inflammation who have irritation with oral S-acetyl-glutathione or nebulizing initially can begin with injectable, e.g. 200mg/ml, 1 cc 1-2 times a day. If desired or needed, they can later try the oral or nebulized form.

A nasal spray form of compounded glutathione may be used for reactions that would otherwise harm brain function. **Glutathione nasal spray also reduces symptoms of chronic rhinitis.**<sup>37</sup> **There is no blood-brain barrier between the nose and the brain.**<sup>15</sup>

Oral S-acetyl-glutathione is easier to use for many patients. All glutathione works best in patients who have adequate selenium for glutathione to function.

**Glutathione also reduces excess brain cell “excitotoxicity”** (also called neural sensitization), **helping prevent impaired function and death of brain and nerve cells.**<sup>36</sup>

If any irritation is experienced with glutathione, the concentration is too high for the level of inflammation at that time (nasal or nebulized). Stop immediately and promptly dilute with safe (clean, nontoxic) water to below irritation level or try injectable. As healing improves, the concentration can gradually be increased. NEVER ignore irritation symptoms: the body will let you know the amount it can handle well. For severe inflammation VERY dilute amounts are needed, or use S-acetyl-glutathione capsules.

N-acetyl cysteine often does not help much and is seldom a “rate limiting step”, based on Dr. Ziem’s review of thousands of SpectraCell tests where glutathione is low and cysteine ample. When cysteine tests low, N-acetyl cysteine in capsule form is often useful. Cysteine needs adequate B6 to not be neuroexcitatory.

#### 4. SUBSTANCES THAT IMPROVE GLUTATHIONE FUNCTION

Vitamin C (ascorbate) reactivates glutathione in water-based body fluids.<sup>14</sup> It also helps protect from effects of chemical injury.<sup>75</sup> Vitamin C reduces free radicals in water-based body fluids like the blood stream and inside cells, but not brain, nerve myelin or lipid cell membranes.<sup>14</sup>

Selenium is essential for function of the enzyme glutathione peroxidase, which reduces tissue damaging “free radicals”<sup>14,107</sup> and helps glutathione to function.<sup>24,41,42</sup>

Alpha lipoic acid is a potent and lipophilic antioxidant that keeps glutathione in active form in all body areas.<sup>39,40,108</sup> It protects lipid membranes<sup>109</sup> of cells and membranes of cell structures (including the energy-generating mitochondria), protein/enzyme-making structures (ribosomes), genetic DNA and all other cell structures.<sup>109</sup> It also protects brain/nerve cell myelin.<sup>110</sup> It has been used in Germany for decades to treat neuropathy.<sup>111</sup> Alpha lipoic acid (the effective form is also called dihydrolipoic acid) keeps many other antioxidants active in all body areas, including glutathione, vitamin C, flavonoids and tocopherols (natural vitamin E).<sup>39,112-114</sup>

Riboflavin (B2) is essential in reactivating glutathione. It does this by acting (in its bioactive form of FAD) as an essential cofactor of the enzyme, glutathione reductase.<sup>24</sup> This enzyme keeps glutathione

in its active form. With even minor reduction of riboflavin there is reduced function of this enzyme.<sup>43,44</sup> Riboflavin has also been shown to be effective in preventing migraines.<sup>115</sup> Migraines are a blood vessel form of neural sensitization. Riboflavin is typically low in people with chemical illness.<sup>77</sup> The Ziem neural protocol contains riboflavin in the form the body can promptly use: riboflavin-5-phosphate.

## 5. SOD (Superoxide Dismutase) PROTECTIVE ENZYME

Superoxide dismutase (SOD) is a protective body enzyme that helps interrupt the vicious cycle.<sup>46</sup> SOD needs adequate zinc, copper, and manganese to function.<sup>24,45,46</sup> It stops damaging superoxide from forming more peroxynitrite and also protects the mitochondria from damage.

SOD also has other antioxidant actions.<sup>14</sup> SOD cofactors of zinc, copper and manganese are often reduced in chemically injured patients.<sup>73</sup> These mineral cofactors must be properly balanced as too much of one will reduce the other. SpectraCell testing greatly helps balance these minerals and they should be replaced in well absorbed and transported forms, for example, picolines.

## 6. METHYL DONORS TO CONTROL PEROXYNITRITE

Trimethyl glycine (betaine) is recommended as a methyl donor to reduce the damage of peroxynitrite. Betaine (trimethyl glycine), liquid phosphatidyl choline (e.g., Phosphaline), MTHF, and other methyl nutrients can reduce chemical effects.<sup>116</sup>

Adequate genetic enzyme MTHFR is needed to make bioactive folate. This enzyme often has impaired function. If folate is reduced, the genetic ability for MTHFR can be tested for this enzyme function. The two genes are often called “677” and “1298”. Thus the neural protocol provides oral bioactive folate: MTHF. This acts as a methyl donor to reduce damage from peroxynitrite.

## 7. PEROXYNITRITE SCAVENGERS

Natural Vitamin E as high gamma tocopherol (e.g. Thorne Ultimate E, Xymogen HG) is discussed above because it is essential for all vicious cycle patients and easily tolerated by almost everyone. Dr. Ziem has used Metagenics E Complex 1:1 as a treatment in patients with difficulty swallowing or children because of the very small capsule size and has observed improvement in swallowing ability as inflammation decreases.

A mixture of carotenoids is also needed to scavenge peroxynitrite. Carotenoids can be more organ-specific. An inclusion of gingko<sup>117,118</sup> (brain), silymarin<sup>53,119,120</sup> (liver), bilberry<sup>121,122</sup> (collagen stabilizing, capillary permeability, vision), cranberry<sup>123,124</sup> (urinary) and other mixed carotenoids<sup>125,126</sup> is recommended. Carotenoids like lutein, zeaxanthin and astaxanthin are lipid soluble and improve neurologic function<sup>127</sup>

Silymarin scavenges peroxynitrite and also enhances the body's detoxification enzyme superoxide dismutase (SOD) activity in cells.<sup>107,128</sup> SOD is important to help control the neural sensitization vicious cycle.

Bilberry is a potent flavonoid antioxidant that reduces blood vessel and capillary fragility and permeability,<sup>129</sup> and improves damaged neurologic function.<sup>130</sup> Bioflavonoids help body cells make more glutathione,<sup>131</sup> the body's essential antioxidant.<sup>44,132</sup>

Lycopene protects from nitric oxide damage.<sup>133</sup>

Taurine has been shown to reduce lipid damage (forming of lipid peroxides) from peroxynitrite.<sup>134</sup>

Astaxanthin is a separate lipid soluble antioxidant that can help nerves and brain.<sup>127</sup>

## 8. SUPEROXIDE SCAVENGERS

**Superoxide radical** is also produced, feeding into the vicious cycle (see chemical diagram). To prevent this tissue damaging cycle, superoxide scavengers are needed. The following are available to be compounded into the protocol.

Grape seed proanthocyanidin has shown superoxide scavenging ability.<sup>135</sup> The Ziem protocol uses the same brand (Activin) shown effective in research<sup>135-137</sup> scavenging free radicals<sup>136</sup> and helping cells survive.<sup>137</sup>

Catechins have also shown superoxide scavenging ability in multiple studies<sup>138-141</sup> with (-)-epigallocatechin gallate (EGCG) likely the most effective.<sup>138-140</sup> Catechins also reduce peroxynitrite radical damage.<sup>141</sup> These catechins are a form of flavonoid.

Silymarin, discussed above, also helps with superoxide scavenging by improving function of the body's SOD defense mechanism.<sup>142,143</sup> Vitamins C and E also have some superoxide protection.<sup>141</sup> Folate also reduces superoxide by stabilizing nitric oxide (reducing excess enzyme nitric oxide synthase).<sup>100</sup>

## 9. REDUCING NMDA ACTIVATION AND IMPROVING GABA FUNCTION

Magnesium levels must be ample. Deficiency is very common with toxic injury<sup>77</sup> and this allows MNDA activation. **Magnesium acts as a blocker of the NMDA nerve receptor,<sup>65-67</sup> thus reducing nerve pain and its inflammation.**<sup>144</sup>

Reducing NMDA activation helps reduce damaging peroxynitrite.<sup>6,10,12,13,63</sup> Magnesium is also a calcium channel blocker and can help bronchoconstriction.<sup>65</sup> Low magnesium is common in the U.S. population.<sup>24,145,146</sup>

Taurine helps make GABA.<sup>147</sup> GABA calms NMDA excess, and thus relaxes respiratory tightness<sup>69</sup> e.g. bronchial constriction, throat tightness etc. Taurine reduces breakdown of the relaxing brain messenger GABA.<sup>148</sup> It also binds to GABA, increasing the brain calming GABA effect.<sup>70,149</sup> Improving GABA function reduces these vicious cycles (neural sensitization) and also improves sleep. Taurine is taken in the evening without protein for better adsorption and sleep: midevening for difficulty falling asleep and bedtime for nighttime awakening.

Bioactive vitamin B6 (pyridoxal-5-phosphate) lowers excess NMDA activity. It can do this in two ways. It helps convert glutamate (excitotoxic) to GABA,<sup>24,68</sup> a relaxing neurotransmitter (nerve messenger substance). It thus protects nerve cells from damage of glutamate.<sup>132</sup> It helps convert excess cysteine (which can be excitotoxic) to taurine (which is calming). It calms the vicious cycle<sup>36</sup> and helps bronchoconstriction.<sup>150</sup> Pyridoxal-5-phosphate, the bioactive form, is more effective than other forms of B6.<sup>151</sup> The bioactive form is used in the Ziem chemical injury treatment (neural protocol).

## 10. ENERGY/MITOCHONDRIA FUNCTION

Acetyl-L-carnitine is more active than L-carnitine<sup>57</sup> and it enters cells, including brain/nerve cells better. It helps energy metabolism.<sup>58-60,152</sup> This helps provide adequate energy needed for reducing the excess NMDA over-activation.<sup>110,153</sup> Thus acetyl carnitine is needed to stop the vicious cycle and allow healing from chemical injury.

Manganese is used because it is needed for function of the protective enzyme SOD<sup>24</sup> that works in the energy-generating mitochondria and helps protect from chemical injury.<sup>154</sup>

Thiamine,<sup>24</sup> riboflavin<sup>24</sup> (discussed above), bioactive niacin as niacinamide, lipoic acid, chromium<sup>24</sup> and magnesium<sup>24</sup> are all also needed for normal energy metabolism.<sup>155</sup>

Pantethine is the bioactive form of B5.<sup>24</sup> Pantethine is essential for energy metabolism<sup>24</sup> and essential for healing membranes and brain/nerve myelin.<sup>24</sup> Low pantethine often indicates adrenal strain and bioactive pantethine helps adrenal function.<sup>156</sup> Better adrenal function helps reduce inflammation.

Coenzyme Q10 is essential to making energy.<sup>54-56</sup> It also protects the energy producing mitochondria from free radical damage<sup>55,56</sup> and is needed for energy structure (mitochondrial) repair.<sup>157</sup> Coenzyme Q10 helps protect from chemical injury.<sup>154</sup>

Molybdenum also helps the body make energy and helps the body detoxify (get rid of chemicals).<sup>24</sup> It is needed for many body enzymes<sup>158</sup> including but not limited to sulfite oxidase<sup>159</sup> to process essential body sulfur compounds.<sup>160</sup> Patients who have trouble with sulfur containing foods (cabbage, broccoli, other crucifers, onion/garlic family) may lack adequate manganese (200 mcg daily is usually adequate).

Biotin is essential for energy metabolism.<sup>50,52,157,161</sup> It is produced by healthy intestinal bacteria<sup>157</sup> and can be depleted by antibiotics.<sup>24</sup> Absorption is reduced by raw egg white.<sup>157</sup> Deficiency can cause fatigue, dry skin, scaly dermatitis, muscle aching and other symptoms.<sup>24</sup> Biotin is also needed for the (elongase) enzyme that helps the body make EPA, DHA, GLA and other essential body fats<sup>161</sup> for cell membranes and nerve myelin.

These substances act biochemically in different ways in the complex energy process of making electrical energy from food nutrients.

## 11. MYELIN, BRAIN, NERVE AND CELL MEMBRANE REPAIR

The brain and nerves to your muscles, joints, skin, etc. have a protective coating of myelin essential for nerve function. Free radicals damage myelin. Myelin requires omega-3 EPA, DHA, phosphatidylcholine (Phosphaline) and other phospholipids (dry forms don't work).

Phospholipids in lipid form help nerve function.<sup>162</sup>

Myelin also needs saturated fats from organic sources. A “low fat” diet can damage myelin. Avoid all synthetic fats (margarine and other trans fats, hydrogenated fats, deep fried, heated fat oils, olestra, etc.). Heating or cooking with oils, even olive oil, forms damaging trans fats. These impair cell and myelin function. For cooking use organic coconut “oil”, butter, ghee, or lard/animal fat.

Phosphatidyl choline is essential for membrane and myelin function.<sup>116</sup>

Xymogen Phosphaline and Body Bio PC liquid provides excellent phosphatidyl choline ready for the body to use. Xymogen Phosphaline 4:1 provides phosphatidyl choline and phosphatidyl inositol for patients with Spectracell of below average “choline” and “inositol”.

Omega 3 essential fatty acids helps reduce excess nitric oxide<sup>163-165</sup> and lower inflammation effects.

Tocotrienols may also be needed. They protect similar to vitamin E but are better able to enter the brain.

Phosphatidyl serine in lipid form helps memory<sup>166</sup> and a DHA-conjugated form (e.g. Neurokrill) avoids risks of bovine-transmitted infection. The krill form appears more effective than soy based.<sup>167</sup> Phosphatidylserine linked to EPA/DHA significantly improved cognitive function.<sup>162</sup>

Phosphatidyl serine may be needed if “serine” tests below average on SpectraCell, especially if neurologic symptoms are present and/or neurocalming is needed (e.g. sleep, “hyper” effects).

## 12. TESTING

### SpectraCell Testing

Testing helps make treatment with the neural protocol even more science-based and is the best way to fit patient needs accurately. **SpectraCell Lab is CLIA certified.** Only SpectraCell testing measures **repair needs** of each patient tested, on the micronutrient testing panel.

Using one dose range for all patients is similar to selling all woman size 7 shoes and all men size 10 shoes. Individual needs vary greatly for cell repair, even more than body shoe size.

Nutrient needs and cell repair need should be measured and followed by testing through SpectraCell Laboratories (800-227-5227). **This testing tells whether the cell has enough of each nutrient to divide and form new cells.** This is essential even with people who feel “healthy”. Nutrient levels must be ample for healing chemical injury, for detoxification and all body functions. SpectraCell functional nutrient testing is available for glutathione, lipoic acid, total antioxidant function, immune function, B12 (cobalamin), folate, B1, B2, B3, B5, B6, biotin, carnitine, choline, selenium, coenzyme Q10, E, magnesium, copper, manganese, zinc and body stores of vitamin C. At this time lymphocyte cell division testing is only available through SpectraCell Laboratories.

Lymphocytes are involved in irritant and toxic effects.<sup>168-179</sup> Cell repair requires that cells can divide and form new cells (mitosis). SpectraCell testing uses mitosis.

SpectraCell test kits for blood draw come with a prepaid overnight mailing box and envelope. They can be ordered by a doctor and sent to the doctor or patient for local blood draw. For best results, the patient should complete the form before blood draw and mail the blood the same day in the provided FedEx envelope so it arrives at the lab the next day for accuracy.

### **Urinary pH Testing to Reduce Acidity**

Inflammation causes increased body acid. The body must buffer this acid and it does so by binding them to minerals. This causes mineral loss and also contributes to osteoporosis. The acidity also impairs the ability of the body to detoxify. Preventing this is greatly helped with diet- see ALKALINE DIET FOR HEALING Factsheet. Inflamed patients may need extra help in correcting acidity: see CORRECTING EXCESS ACID IN THE YOUR BODY factsheet.

## **13. EXPOSURE CONTROL**

### **Exposure controls are essential for healing.**

Medical treatment is not a substitute for exposure controls at home, work and/or school: places where the person spends most of his/her time. Humans are social beings, and the medical measures above gradually increase the person’s ability to enjoy the company of others and use public places. When society is adequately informed and does public health reasonable accommodation at work, home (e.g. apartments, condos, etc.), at schools, and public places to reduce irritants and toxins in personal and commercial products, this further promotes health and reduces chemical injury for everyone.

The book Less Toxic Alternatives by health educator Carolyn Gorman (214-361-9515) is recommended. Also look at the “Environmental Control Plan” and other resources (including reasonable accommodation) at [www.chemicalinjury.net](http://www.chemicalinjury.net). Use less toxic pest control: [www.beyondpesticides.org](http://www.beyondpesticides.org). Get help locating less toxic products, housing at [www.CIIN.org](http://www.CIIN.org). The book The Endangered Brain (626-798-4299) lists less toxic products and explains brain problems in plain English. Sources of less toxic pest control products include [www.gardernsalive.com](http://www.gardernsalive.com) and [www.arbico-organics.com](http://www.arbico-organics.com). The book Fungus, Mold, and Mycotoxins by Carolyn Gorman is valuable because molds are irritants and toxic. They multiply and spread: see MOLD section on [chemicalinjury.net](http://chemicalinjury.net).

## **14. LONG TERM TREATMENT**

For persons without nontoxic environmental (chemical and mold) controls at home, work and school, long-term protocol treatment may be needed. Persons who have frequent but not disabling exposures/illness may need long term treatment to avoid disability. Others with frequent symptoms often need treatment for two years, uninterrupted as much as possible.

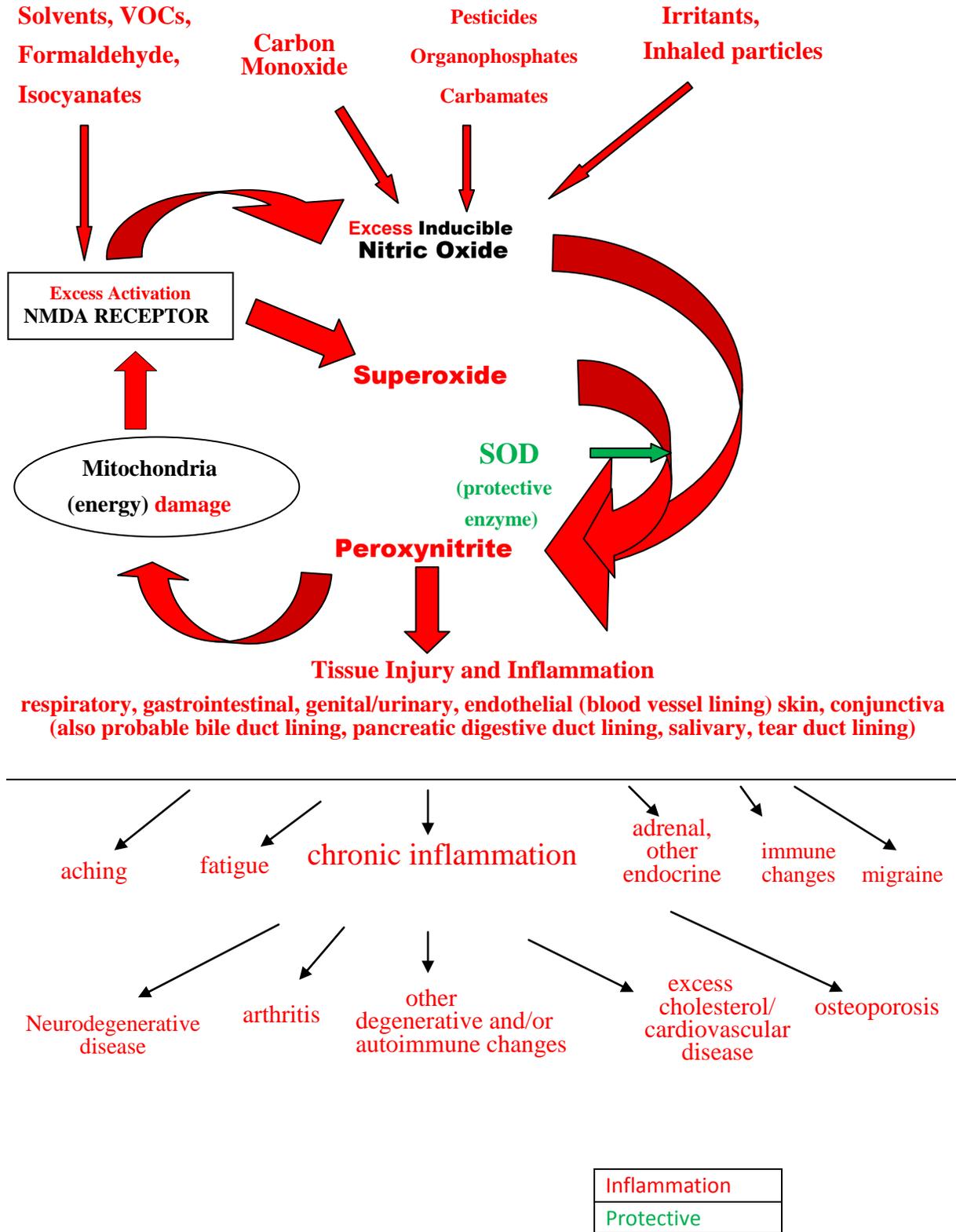
For above persons, SpectraCell testing every 6-10 months is best to see what is and is not working.

After frequent symptoms improve and become occasional or less, yearly SpectraCell testing (with treatment of below average levels ( do not raise copper above average) and keeping B12 in upper 10-20%) ensures that degenerative processes will be greatly reduced. Remember that D3 is a prohormone, and using levels above 400IU can suppress magnesium, thus increasing NMDA activation and worsening the vicious cycle. SpectraCell testing allows easy comparison to balance calcium and magnesium using the scatter plot always keeping magnesium ample (magnesium glycinate without flow agents appears to be very well absorbed, e.g. Moss Nutrition).

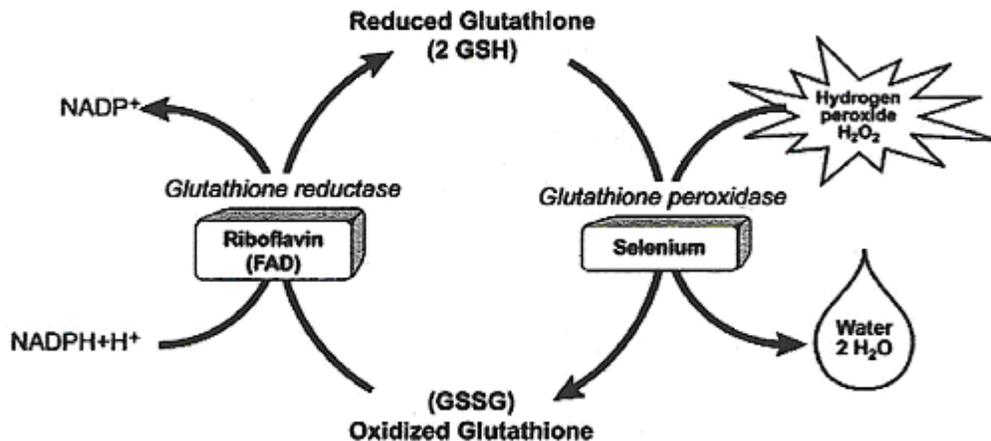
**For everyone, minimizing this vicious cycle is vital to health.** You can greatly reduce all inflammatory and degenerative disease and also greatly reduce cancer risk. Only periodic SpectraCell testing shows what substances you need. Other testing (bone scans, cholesterol, etc.) just document damage but do not tell you how to help heal the disease process.

**YOUR YEARLY PHYSICAL SHOULD BE HEALTH BASED.** This is how to do that. It saves you money and misery!

## NEURAL SENSITIZATION: VICIOUS BIOCHEMICAL CYCLE



## HOW GLUTATHIONE FUNCTIONS AND IS AGAIN ACTIVATED



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