

Working Up The Toxic Patient
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Introduction

Some problems in clinical healthcare are straight forward. The patient might present with low back pain, like a problem such as a strained quadratus lumborum muscle. The patient history matches the physical exam findings and a treatment program is recommended with highly predictable outcome.

The problem with the toxic patient is that they will seldom present with a history of toxic exposure, their symptoms are multisystem and multifactorial, the findings of the physical exam may provide little confirmation of the intake. Proceeding to lab evaluation can be difficult because none of the weather vanes of intake have provided a direction to sleuth. The clinician has absolutely no idea what they are dealing with. Toxin exposure is hard to detect and the effects almost impossible to predict. Toxicity is a highly individual situation based largely on genetics and strength of the toxic exposure(s). It is the authors experience that we have no idea how the human system responds to multiple interacting toxins; this is a common scenario in most “healthy” individuals.

One study¹ found that the combined exposure of toxins by Gulf war veterans created a toxicity cocktail that could not be estimated, the sum of the parts exceeded the whole. In another review article, it was noted that a pair of PCBs have 20 times the capacity to switch the sex of animals than when given each separately.² When endosulfan and dieldrin are combined, they deliver 1600 times the effect of the dieldrin alone. Mercury and lead have shown to have synergistic effects when combined.³ Toxic patients are extremely difficult to assess, diagnose, treat and deliver reliable, predictable results for their presenting complaints. The clinician has to be thorough, think like a detective and look at unlikely areas for sources of toxicity and health problems.⁴

History Of Clinical Therapy

Detoxification therapies have been applied by early practitioners of this approach did not call it “detoxification therapy”. Their methods of hydrotherapy, fasting, regulated diet, and Nature Cure are similar to many modern detoxification methods.⁵ By studying the work of Sebastian Kneipp,⁶ John Harvey Kellogg,⁷ O. G. Carroll, and John Bastyr,⁸ one gets the impression that doctors and

¹ Abou-Donia, et al. “Neurotoxicity Resulting from Coexposure to Pyridostigmine Bromide, DEET and Permethrin: Implications of Gulf War Exposures,” J Toxicol Environ Health 48 (1996): 35–56.

² Raloff, J. “Estrogen? Pairings Can Increase Potency,” Science News 149 (1996): 356.

³ Schubert, J., et al. “Synergistic Effects of Lead and Mercury,” J Toxicol Environ Health 4 (1978): 763–76.

⁴ Debelian GJ et al. Systemic diseases caused by oral microorganisms. Endod Dent Traumatol 1994;10:57-65

⁵ Kilburn KH, Warsaw RH, Shields MG. Neurobehavioral dysfunction in firemen exposed to polychlorinated biphenyls (PCBs): possible improvement after detoxification. Arch Environ Health. 1991;46(4):254-55.

⁶ Watrous LM. Constitutional hydrotherapy: from nature cure to advanced naturopathic medicine. J Nat Med. 1997;7(2):72-79.

⁷ Jackson LS, Dudrick SJ, Sumpio BE. John Harvey Kellogg; surgeon, inventor, nutritionist (1852-1943). J Am Coll Surg. 2004;199(5):817-821.

⁸ _____. On the cover: John Bastyr. J Nat Med. 1991;2(1):39.

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healers found that the best results happened in a setting where the patient could be closely watched. Historically these doctors described their toxic patients as suffering from “auto-intoxication”.⁹ Medical literature now lends credibility to this diagnosis and to the methods used to treat chronically ill patients.

Culturally we think of detoxification as a medicine or strategy to deal with patients dealing with drugs and alcohol dependency.¹⁰ This is a medical bias which interestingly, does not usually use nutritional strategies to care for those who have “toxic” issues with alcohol and drugs. Ironically, the findings of practitioners who have used nutritional strategies for alcohol detox, can be applied to patients with other toxicity related issues. The findings of these practitioners have shown that the liver is the organ that bears the primary role of breaking down any toxin, exogenous or endogenous.¹¹ The problem of “system overload” is a common consequence of basic health issues, regardless of current pollution and toxin exposure. For this reason, skillful physicians in all cultures have relied on purification strategies to harmonize and balance biochemistry to induce the body into a pattern of self healing. This strategy is a valuable addition to a medical armamentarium because it allows the patient and doctor to deal with a multi system/multi problem approach using a multi-system therapy. Toxicity based clinical problems are embedded within a complex web of an interdependent ecosystem.¹²

Which Patients Are Given Detox Therapy?

The most common presenting chronic complaints presented to a clinical practitioner for which there is no known diagnostic criteria are pain, fatigue and weight gain. Detoxification therapy is indicated in this class of patients.¹³ If the patient is acutely toxic, appropriate diagnosis and treatment is indicated.¹⁴ Working up and treating this type of patient is challenging, the chronically toxic patient is even more so.

A complete clinical detoxification program should focus on three targets:

1. Retrieve gut functioning
2. Reduce heavy metals; and
3. Reduce organic chemicals stored in fat tissue.

This type of program can be applied to a patient with immune disorders, digestive problems, cancer patients and those individual who present with psychoneurological problems.¹⁵ Clinically, the best results are with patients presenting with mild cognitive disturbances.

⁹ Editorial. Intestinal endotoxins as mediators of hepatic injury-an idea whose time has come again. *Hepatology* 1989;10(5):881-891

¹⁰ Libby AF, et al. Methodology: use of orthomolecular techniques for alcohol and drug abuse in a post-detox setting. *J Orth Psych* 1982;11(4):277-288.

¹¹ Bland J, Bralley JA. Nutritional upregulation of hepatic detoxification enzymes. *J Ap Nut* 1992; 44(3&4)2-15

¹² Simopoulos AP, et al. (eds) “Intestinal Flora, Immunity, Nutrition and Health.” *World Rev Nutr Diet*. Basel: Karger, 1993, vol 74,123-148.

¹³ Buist RA. Chronic fatigue syndrome and chemical overload. *Int Clin Nutr Rev*;8(4):173-176

¹⁴ Liang H. Clinical evaluation of the poisoned patient and toxic syndromes. *Clinical Chem* 42, 8B (1996): 1350-55

¹⁵ Bland, J.,S., E. Barringer, R.G. Reedy, and K. Bland. “A Medical Food Supplemented Detoxification Program in the Management of Chronic Health Problems,” *Alternative Therapies* 1, 5 (1995): 62-71.

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Providing assistance in this area can provide a vital enhancement to the quality of life in individuals assessed as “well” in a conventional medical assessment.¹⁶

This type of clinical program can support cellular functioning, improve the filtration capacity of the liver, stimulate the excretion of toxins through the kidneys, bowel, and skin, support gut repair, and improve neuroendocrine balance in the hypothalamic-pituitary system. Studies have shown that poor liver function has a dramatic effect on the level of cognitive functioning.¹⁷ It has been postulated that “recycled” metabolic by-products, which are not cleaned out by the body, contribute to poor cell signaling. The retention of metabolic end products and their effects as toxins act on intermediary metabolism. At the cell membrane level the action occurs. As an example, in uremic patients, there isn’t a single individual compound has been implicated as the uremic toxin.¹⁸ Reviews of medical literature detailing the negative health effects of toxicity demonstrates that it may be important to help certain patients relieve some of the body burden that modern living imposes.^{19,20} Failing to address this issue bodes ill for individuals living in modern society. It is well known that burdens of chemicals damage critical areas of the brain.²¹²²²³ It remains to be seen if detoxification strategies can avert the social epidemic of toxicity and anticipated increase in chronic degenerative health problems. Our health paradigm evolved to treat social epidemics of a different nature.²⁴ Chronic degenerative disease and poisoning from environmental pollution are not specialties of our healthcare system. Clinical detoxification strategies represent a move or transition in medicine from treating acute disease as the main cause of death at the turn of the century to treating chronic degenerative disease as we enter a new millennium. Physicians must skills necessary for this trend rather than relying on “heroic” methods.

Clinical Problems and Assessment

On presentation to the clinic, the doctor should consider all patients as candidates for detoxification therapy. A thorough medical history examining toxin exposure and symptom patterns indicating systemic dysfunction should be approached. In particular patients with fatigue, muscle pain, immune, neuropsychiatric problems should be thoroughly screened. The

¹⁶ Fillit HM, et al. Achieving and maintaining cognitive vitality with aging. *Mayo Clin Proc.* 2002 Jul;77(7):681-96.

¹⁷ Mullen KD. Benzodiazepene compounds and hepatic encephalopathy. *NEJM* 325, 7 (1991): 509–11.

¹⁸ Wills, M. “Uremic Toxins and Their Effects on Intermediary Metabolism,” *Clin Chem* 13, 1 (1985): 5–13.

¹⁹ Institute for Functional Medicine. *Clinical Nutrition*, 2nd Ed., Chapter 9: Environment and Toxicity. Gig Harbor, WA: Institute for Functional Medicine, 2004.

²⁰ Krop J. Chemical sensitivity after intoxication at work with solvents: response to sauna therapy. *J Altern Complement Med.* 1998;4(1):77-86.

²¹ Betarbet, R. and J.T. Greenamyre.. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nature Neuroscience* 2000;3(December):1301-1306.

²² Giasson, B.I., and V.M.-Y. Lee.. A new link between pesticides and Parkinson's disease. *Nature Neuroscience* 2000; 3(December):1227-1228.

²³ Lockwood, A.H.. Pesticides and Parkinsonism: Is there a link between environmental toxins and neurodegenerative disorders? *Medicine and Global Survival* 2000;6(June):87.

²⁴ Glazier, W.H. “The Task of Medicine,” *Sci Am* 228, 4 (1973): 13–18.

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blurr between patients diagnosed with chronic fatigue syndrome, fibromyalgia and multiple chemical sensitivity can be difficult to distinguish and clinically irrelevant.²⁵

First and foremost is determining a good family history. Genetic predisposition to toxin exposure determines the success and out come of therapy. It cannot be stressed enough that individualizing your treatment give better clinical results. Knowing whether your patient has a genetic predisposition such as a sulphoxidation defect offers a chance to protect them from severe chronic degenerative diseases.²⁶ Variations in sulfation and sulfoxidation are inherited metabolic polymorphisms. A significant number of individuals with environmental intolerance or chronic disease have impaired sulfation of phenolic substances from starvation of sulfotransferases for sulfate substrate. Sulfation is a limited capacity xenobiotic conjugation pathway that is present in many tissues. Impaired sulfation may be relevant to intolerance to phenol, tyramine, and phenolic food constituents. This biochemical pathway may be the link to explaining Dr. Feingold's (Feingold, B. *Why Your Child Is Hyperactive*. New York: Random House, 1975) findings that some children react to food colorings and preservatives. This represents a unique consideration of treatment of depletion/disruption of sulfate pool in diet-responsive Feingold patients, autistics, depletion of sulfates might elevate endogenous biocomponents like bile acids and joint glucosamine glycans and primary biliary cirrhosis and rheumatoid arthritis. The sulfate conjugation of phenolics is an important pathway for the detoxification of catacholamine neurotransmitters, steroids, bile acids, phenolic and aromatic drugs, and xenobiotics. Impaired sulfation may cause tyramine headache, poor first pass sulfation of monoamines. Tyramine is a bacterial fermentation product closely related to catacholamine neurotransmitters, found in cheese, wine, etc.

This clinical assessment may provide special considerations for those with neurodegenerative disease, especially in the prevention of its development.²⁷ Patients presenting with chemical sensitivity may be heralding the potential for more serious diseases. Christopher Reading, M.D., has evaluated the case histories of over 5,000 patients and strongly advises doctors and patients to draw up family trees showing diagnosed illnesses. He discovered that it is extremely important to draw up a family tree. It is important to study the various ways certain genetic disorders are inherited. For example, a father cannot pass on an X linked disorder to his son because his son only gets the Y chromosome from his father but all the daughters are at risk. Dr. Reading found one family where the manic depression was X linked with an additional X linked B12 deficiency. The B12 deficiency was later found to be due to wheat allergies, a common inherited trait. He treated this family with vitamin B12 and a gluten free diet. Their anemia and manic depression resolved.²⁸ A good family history can even find those at a higher risk for cigarette smoking.²⁹

²⁵ Buchwald, D., and D. Garrity. "Comparison of Patients with Chronic Fatigue Syndrome, Fibromyalgia and Multiple Chemical Sensitivities," *Arch Int Med* 154 (1994): 2049–53.

²⁶ McFadden, S.A. "Phenotypic Variation in Xenobiotic Metabolism and Adverse Environmental Response: Focus on Sulfur-Dependent Detoxification Pathways," *Toxicology* 111 (1996): 43–65.

²⁷ Williams, A.C., G.B. Steventon, and R.H. Waring. "Hereditary Variation of Liver Enzymes Involved with Detoxification and Neurodegenerative Disease," *J Inher Metab Dis* 14 (1991): 431–35.

²⁸ Reading, C. "Family Tree Connection: How Your Past Can Shape Your Future Health: A Lesson in Orthomolecular Medicine," *J Orthomol Med* 3, 3 (1988): 123–34.

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Lab Work-up

After an initial visit, the key strategy to rule out co-existing disease. Doing a CBC, Chem screen, urine analysis, hair analysis, serotype type helps to provide a prescreening protocol. Depending on the case, Urine amino acids, heavy metal excretion, intestinal permeability, digestive analysis, and food allergy IgG/IgE can be specifically chosen.

Urine Amino Acids

Urine amino acids have been investigated in patients with chronic fatigue syndrome.³⁰ Essential amino acids provide precursors cycle for ATP production as well as precursors for neurotransmitters. Supplementation of amino acids can significantly affect these process. The key point is to assess levels of amino acids critical for biotransformation. It is recommended to screen most patients with a heavy metal challenge test.

Mercury and Heavy Metals

Mercury and lead body burdens must be determined as co-existing toxicity related health issues. Primarily because mercury preferentially disables the body's natural detoxification organs.³¹ To assess mercury levels, a provoking or chelating agent is needed, one that has a high degree of binding affinity.³² DMPS (2,3-dimercapto-1-propane-sulfonate) provides an excellent challenge substance because of its high degree of sulphhydryl bonds.³³ For diagnostic purposes IV or oral dosing is appropriate. If testing for mercury, clinically it is appropriate to screen for lead, cadmium and other heavy metals at the same time. Even though DMPS enhances excretion of a wide number of metals, many clinicians opt to combine chelating agents in the same challenge test. This remains a wide and unexplored area of detoxification medicine.

Intestinal Permeability

It is well established that patients with inflammatory bowel disease have a six-fold increase in gut permeability.³⁴ Patients with chronic immune and digestive problems commonly have a compromised gut barrier.^{35,36,37} The gut damage and subsequent downstream health problems

²⁹ Nebert, D.W., et al. "Human AH Locus Polymorphism and Cancer: Inducibility of CYP1A1 and Other Genes by Combustion Products and Dioxin," *Pharmacogenetics* 1 (1991): 68–78.

³⁰ Bralley JA, and Lord RS, "Treatment of Chronic Fatigue Syndrome with Specific Amino Acid Supplementation." *Journal of Applied Nutrition*. 1994. 46(3): p. 74-78.

³¹ Hahn LJ et al. (1990). Whole-body imaging of the distribution of mercury released from dental fillings into monkey tissues. *FASEB J*, 4 (14) 3256-60.

³² Patrick, L. Mercury Toxicity and Antioxidants: Part I: Role of Glutathione and alpha-Lipoic Acid in the Treatment of Mercury Toxicity *Altern Med Rev* 2002;7(6):456-471.

³³ Gonzalez-Ramirez D et al. (1995). Sodium 2,3-dimercaptopropane-1-sulfonate challenge test for mercury in humans: II. Urinary mercury, porphyrins and neurobehavioral changes of dental workers in Monterrey, Mexico. *J Pharmacol Exp Ther*, 272 (1) 264-74.

³⁴ Pearson, A.D., et al. "Intestinal Permeability in Children with Crohn's Disease and Celiac Disease," *BMJ* 285 (1982): 20–21.

³⁵ Rooney PJ, et al. A short review of the relationship between intestinal permeability and inflammatory joint disease. *Clin Exp Rheum* 8:75-83, 1990.

³⁶ Smith, M.D., R.A. Gibson, and P.M. Brooks. "Abnormal Bowel Permeability in Ankylosing Spondylitis and Rheumatoid Arthritis," *J Rheumatol* 18 (1985): 299–305.

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probably results from local immune mediated inflammatory reactions to food and dietary antigens.³⁸ In one study children were assessed to be allergic to foods.³⁹ Intestinal permeability testing proved to be a non-invasive way to monitor patients. There are many protective factors in the intestinal mucosa intraepithelia; lymphocytes, secretory IgA, other immune globulins, mucosal coat, microvillious membrane. Even though the milk reaction is a local event involving the complex web of protective factors, cow's milk allergy symptoms are commonly found elsewhere besides (but also including) the gut; in the respiratory tract and skin. Intestinal permeability can be an excellent measurement for cow's milk food allergies.

Once damage is initiated it becomes a critical strategy to address from the standpoint of liver detoxification.⁴⁰ Since every patient has bacteria in their gut, if it is leaking they are by definition leaking bacteria and bacterial toxins. Gut leaked enteric bacteria and endotoxins play a role in multiple organ failure.⁴¹

Bacteria and their endotoxins have a major impact on the host's immune system. Bacterial translocation causes decreased systemic immune responsiveness.⁴² Failure of the gut barrier results in further impairment of host defenses thereby leading to increased survival of translocated bacteria. Endotoxins management is a primary strategy in assessment and treatment of a patient. The lipopolysaccharide (LPS) macromolecule of the outer walls of gram-negative bacteria who have died can transit the gut in patients with intestinal permeability. Endotoxemia has gained favor as an explanation for the multiple organ failure with severe trauma and sepsis and is associated with Crohn's and neonatal enterocolitis.

Integrity of detoxification and immune system is critical in the response to endotoxins. Complications in chronic liver disease can be induced or aggravated by LPS because LPS are scavenged by Kupffer cells, this then depresses p450 and impairs mitochondrial function. Alcohol is known to aggravate LPS toxicity. Strong injurious products are released by macrophages exposed to LPS causing the need for antioxidants.⁴³

Digestive Analysis

An examination of the patients stool can provide clues as to the extent of dysfunction and dysbiosis in the bowel. A thorough digestive analysis will measure complex sets of interdependent relationships:

³⁷ Madara, J.L., et al. "Structure and Function of the Intestinal Epithelia Barrier in Health and Disease," *Brit J Rheu* 9 (1990): 306–24.

³⁸ Carini C, et al. Immune complexes in food induced arthralgia. *Ann Allergy* 1987 (59) Dec, 422-428

³⁹ Jalonen, T. "Identical Intestinal Permeability Changes in Children with Different Clinical Manifestations of Cow's Milk Allergy," *J Allergy Clin Immunol* (5 November 1991): 737–42.

⁴⁰ O'Dwyer, S.T., et al. "A Single Dose of Endotoxin Increases Intestinal Permeability in Healthy Humans," *Arch Surg* 123 (1988): 1459–64.

⁴¹ Dietch, E.A., et al. "Bacterial Translocation from the Gut Impairs Systemic Immunity," *Surgery* 109, 3 (1991): 279–76.

⁴² Editorial. "Intestinal Endotoxins As Mediators of Hepatic Injury: An Idea Whose Time Has Come Again," *Hepatology* 10, 5 (1989): 881–91.

⁴³ Sword, J.T., et al. "Endotoxin and Lipid Peroxidation in Vivo in Selenium and Vitamin E Deficient and Adequate Rats," *J Nutr* 121 (1991): 258–64.

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- Digestion
- Absorption
- Detoxification
- Immune recognition
- Ecological balance of bacterial flora

Chronic enzyme and HCl deficiency disturbs gut pH and bacterial ecology of the small intestine. It also impairs nutrient digestion and absorption. The humble act of chewing and eating slower can go a long way in remedying some enzyme deficiencies. Chewing stimulates the secretion of a growth factor that prevents intestinal permeability.⁴⁴

The ecology of the bacterial flora can be the source of many chronic immune related diseases. Inhibitors of detoxification might be coming from gut flora.⁴⁵ For example, encephalopathy in cirrhotic patients develops after a meal where they cannot metabolize the amino compounds produced by gut flora. The gut flora produces a wide array of chemicals which cause reactions with all organs in the body. In susceptible individuals with reduced hepatic enzymes, these partially metabolized metabolites of gut flora pass into systemic circulation to produce symptoms at distant parts. It is well known that IBS can come on after surgery, radiation, gastroenteritis, and the use of antibiotics, all of which may change the bowel flora. Food allergy may not be an immunologic disease but a disorder of bacterial fermentation and enzyme deficiency.

Enteroadherent E. coli are present in the stool in a high percentage of patients with a variety of food related autoimmune problems such as Crohn's disease. Abnormal bacteria are also found in patients with RA, ankylosing spondylitis. HLA B27 is synthesized by the fecal flora and associated with facultative anaerobes, klebsiella and proteus.⁴⁶

Food Allergy Testing

Patients with chronic gut/liver/immune problems respond by identifying immune mediated food sensitivities and using an elimination and rotation program.

Salivary Hormone Testing

Patients under chronic stress have gut/liver dysfunction. Identifying clinically significant hormone abnormalities and treating appropriately facilitates better clinical results.

Organic Acid Analysis

Altered organic acids in the urine can be found in patients with dysbiosis.

Detox Therapy

The essential steps of this clinic-based program are:

- brief water fasting (two days),

⁴⁴ Playford RJ, et al. Effect of luminal growth factor preservation on intestinal growth. *Lancet*. 1993;341: 843–50.

⁴⁵ Hunter, J.O. "Food allergy or enterometabolic disorder," *Lancet* 338 (1991): 495–96.

⁴⁶ Ebringer, R.W., et al. "Sequential studies in ankylosing spondylitis. association of *Klebsiella pneumoniae* with active disease," *Ann Rheum Dis* 37 (1979): 145–51.

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- oligoantigenic diet (five days) and slow reintroduction of omitted foods,
- saunas and hydrotherapy (one month), and
- nutritional supplements (one month).
- chelation therapy for appropriate metals (one-five years)

Using all these elements together gives reliable results for restoring the balance in the system and reducing burdens of toxins on organ systems of vital importance.

Fasting

Fasting on water for a short period can be an important clinical therapy for some toxic patients. By stopping all food, the metabolic machinery of the body can focus on cleaning the blood and lymph.

While water fasting may not be suitable for severely compromised patients research has shown calorie restriction and fasting to alleviate hypertension,^{47,48} diabetes,⁴⁹ epilepsy,^{50,51} and rheumatoid arthritis.⁵² Recent research has shown that calorie restriction may be the most powerful way known yet to extend lifespan.^{53,54} Studies have shown that high glucose and insulin damage mitochondria, and calorie restriction (fasting) reduces the total amount of oxidative stress within the cellular mitochondria.^{55,56}

Fasting may improve liver function. Fasting has traditionally been thought to enhance the liver's ability to clear out metabolic byproducts from the blood stream, and regenerate the liver's ability to function in a healthy way. There are indications from a few animal studies that dietary restriction may help to reduce the risk of age-related diseases associated with impaired lipid

⁴⁷ Michalsen A, Weidenhammer W, Melchart D, et al. [Short-term therapeutic fasting in the treatment of chronic pain and fatigue syndromes—well-being and side effects with and without mineral supplements.] *Forsch Komplementarmed Klass Naturheilkd.* 2002;9(4):221-7.

⁴⁸ McCarty MF. A preliminary fast may potentiate response to a subsequent low-salt, low-fat vegan diet in the management of hypertension – fasting as a strategy for breaking metabolic vicious cycles. *Med Hypotheses.* 2003;60(5):624-633.

⁴⁹ Kimura KD, Tissenbaum HA, Liu Y, Ruvkun G. daf-2, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans*. *Science.* 1997;277:942-6.

⁵⁰ Greene AE, Todorova MT, Seyfried TN. Perspectives on the metabolic management of epilepsy through dietary reduction of glucose and elevation of ketone bodies. *J Neurochem.* 2003;86(3):529-537.

⁵¹ Mantis JG, Centeno NA, Todorova MT, McGowan R, Seyfried TN. Management of multifactorial idiopathic epilepsy in EL mice with caloric restriction and the ketogenic diet: role of glucose and ketone bodies. *Nutr Metab (Lond).* 2004;1(1):11.

⁵² Iwashige K, Kouda K, Kouda J, et al. Calorie restricted diet and urinary pentosidine in patients with rheumatoid arthritis. *J Physiol Anthropol Appl Human Sci.* 2004;23(1):19-24.

⁵³ Lee C-K L, Weindruch R. Calorie intake, gene expression and aging. In *Functional Medicine Approaches to Endocrine Disturbances of Aging*, 8th International Symposium on Functional Medicine, 2001. Gig Harbor, WA: Institute for Functional Medicine.

⁵⁴ Guarente L, Kenyon C. Genetic pathways that regulate ageing in model organisms. *Nature* 2000;408:255-262.

⁵⁵ Merry BJ. Oxidative stress and mitochondrial function with aging—the effects of calorie restriction. *Aging Cell.* 2004;3(1):7-12.

⁵⁶ Lambert AJ, Merry BJ. Effect of caloric restriction on mitochondrial reactive oxygen species production and bioenergetics: reversal by insulin. *Am J Physiol Regul Integr Comp Physiol.* 2004;286(1):R20-21.

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metabolism.^{57,58} However, caution is indicated because long-term fasting or fasting in a polluted environment can deprive the body of nutrients that are critical to a patient's health. Fasting should be done for short periods of time in a pure environment and, in my practice, I recommend taking vitamin C during fasting in the range of one to four grams per day.

Fasting may benefit cognitive functioning. Several studies have shown that as severe liver toxicity progresses, the patient fails to break down valium-like compounds that create a toxic state.^{59,60} One might hypothesize a continuum of such effects for patients who are not nearly so ill. Patients who fast do often report a sense of renewal and clearer thinking. Fasting allows the liver to reduce the presence of recycled chemical messengers like adrenalin and other stress hormones, which often have a second chance to restimulate the nervous system when they are not biotransformed and excreted appropriately.

Caloric restriction improves immune function. Caloric restriction, which can be achieved by short-term fasting, appears to have measurable benefit for the immune system.^{61,62} It rests the intestines and liver, both key sites of immune function. It is estimated that 60% of our immune system resides in our intestines. By resting this major site of immune function with fasting, the patient's immune function may be potentiated. A fast of 36 or 60 hours significantly increases the power of white blood cells to destroy pathogenic bacteria.⁶³ Conversely, eating can depress immune function and have a proinflammatory effect,^{64,65} whereas energy restriction may restore the impaired immune response.⁶⁶ Studies have shown that a glucose challenge increases the generation of reactive oxygen species (ROS), while nutritional restriction can inhibit ROS generation by leucocytes.^{67,68}

⁵⁷ Mulas MF, Demuro G, Mulas C, et al. Dietary restriction counteracts age-related changes in cholesterol metabolism in the rat. *Mech Ageing Dev.* 2005;126(6-7):648-54.

⁵⁸ Araki S, Goto S. Dietary restriction in aged mice can partially restore impaired metabolism of apolipoprotein A-IV and C-III. *Biogerontology.* 2004;5(6):445-50.

⁵⁹ Basile AS, Hughes RD, Harrison PM, et al. Elevated brain concentrations of 1,4-benzodiazepenes in fulminate hepatic failure. *NEJM.* 1991;325(7):473-78.

⁶⁰ Mullen KD. Benzodiazepine compounds and hepatic encephalopathy. *NEJM.* 1991;325(7):509-11.

⁶¹ Sun D, Krishnan A, Su J, et al. Regulation of immune function by calorie restriction and cyclophosphamide treatment in lupus-prone NZB/NZW F1 mice. *Cell Immunol.* 2004;228(1):54-65.

⁶² Jolly CA, Muthukumar A, Avula CP, et al. Life span is prolonged in food-restricted autoimmune-prone (NZB x NZW)F(1) mice fed a diet enriched with (n-3) fatty acids. *J Nutr.* 2001;131(19):2753-2760.

⁶³ Sanchez A, Reeser JL, et al. Role of sugars in human neutrophilic phagocytosis. *Am J Clin Nutr.* 1973;26:1180-1184.

⁶⁴ Aljada A, Ghanim H, Mohanty P, et al. Glucose intake induces an increase in activator protein 1 and early growth response 1 binding activities, in the expression of tissue factor and matrix metalloproteinase in mononuclear cells, and in plasma tissue factor and matrix metalloproteinase concentrations. *Am J Clin Nutr.* 2004;80:51-7.

⁶⁵ Aljada A, Mohanty P, Ghanim H, et al. Increase in intranuclear nuclear factor κB and decrease in inhibitor κB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect. *Am J Clin Nutr.* 2004;79:682-90.

⁶⁶ Lamas O, Martinez JA, Marti A. Energy restriction restores the impaired immune response in overweight (cafeteria) rats. *J Nutr Biochem.* 2004;15(7):418-25.

⁶⁷ Mohanty P, Hamouda W, Garg R, et al. Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. *J Clin Endocrinol Metab.* 2000;85(8):2970-73.

⁶⁸ Dandona P, Mohanty P, Hamouda W, et al. Inhibitory effect of a two day fast on reactive oxygen species (ROS) generation by leucocytes and plasma ortho-tyrosine and meta-tyrosine concentrations. *J Clin Endocrinol Metab.* 2001;86(6):2899-902.

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Fasting benefits arthritis. It has been demonstrated in research settings that fasting benefits arthritis.⁶⁹ The best results in treating autoimmune arthritis are achieved when a short fast is combined with a change to a vegetarian diet, and foods to which the patient is sensitive or allergic are removed.^{70,71} Fasting may be involved in changing the bacterial flora in a favorable way for patients with rheumatoid arthritis. Abnormal bacteria or microflora are present in the stool in patients with a variety of autoimmune problems such as Crohn's disease,⁷² rheumatoid arthritis,⁷³ and ankylosing spondylitis.⁷⁴ Anaerobic bacterial species such as Klebsiella and Proteus have been implicated.⁷⁵ Fasting may play a role in changing bacterial flora, perhaps by enhancing competition and thereby giving dominance to probiotics. Changes in intestinal flora from a vegan diet have been documented.⁷⁶

Fasting contraindications. A two-day water fast is safe for most patients. Certain exclusions are important, such as diabetics, hypoglycemics, and severely nutritionally deficient individuals. The biggest risks to most patients are hypoglycemia and orthostatic hypotension with vertigo, sometimes resulting in fainting. Although these reactions are generally harmless, they can cause a fall. Patients should be warned to take extra care in standing up – i.e., getting out of bed or a hot bath, or getting up from a chair. If faintness or vertigo does not resolve within a few minutes, patients should contact their practitioner.

There is medical literature to suggest that fasting for a prolonged period of time can diminish the body's stores of glutathione, making it more susceptible to aging and disease. Low tissue antioxidant status is found under dietary restriction because fasting lowers glutathione detoxification in the liver.^{77,78} Also, fasting can down regulate phase I detoxification.⁷⁹ Therefore, patients who are fasting should be very careful to avoid any chemical exposure, because lack of dietary protein makes the liver unable to process toxins optimally due to lack of inadequate amino acid precursors that are important to the detoxification pathways. (As an aside,

⁶⁹ Adam O. Anti-inflammatory diet and rheumatic diseases. *European Journal of Clinical Nutrition*, 1995;49:703-717.

⁷⁰ Kjeldsen-Kragh J. Rheumatoid arthritis treated with vegetarian diets. *Am J Clin Nutr*, 1999;70(Suppl.):594S-600S.

⁷¹ Gamlin L, Brostoff J. Food sensitivity and rheumatoid arthritis. *EnviroTox Pharm*. 1997;4:43-49.

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patients who are preparing to undergo surgery might have fewer complications to the anesthetic if they were put on a protein-dense regimen instead of clear fluids.^{80,81})

Oligoantigenic Diet

After a two-day water fast, a simple diet of rice, fruit and vegetables is then followed for five days. This is similar to an oligoantigenic diet, used for allergic, behavioral, and digestive problems.⁸² This simple diet provides enough caloric input to sustain the patient but is very easy on the intestinal environment to allow optimum rest. The rationale for vegetarian fare is twofold: vegetarian diets contain fewer potential food allergens that can cause activation of the gut-associated lymphoid tissue, and enhanced vegetable intake provides more soluble fiber, bioflavonoids, antioxidants, and complex carbohydrates. Some patients do experience fatigue on this program; if it is not ameliorated with rice- or whey-based protein shakes, it will resolve upon resuming normal protein intake (unless, of course, the patient is allergic to the food being reintroduced).

A high vegetable content is recommended because of its ability to modulate liver detoxification in a beneficial way. This is probably due to the effect vegetables have on the CYP450 enzyme system.⁸³ Also vegetables contain a high level of soluble fiber, essential for rebuilding gut integrity. Fiber helps maintain intestinal permeability and fiber could help prevent bacteremia.⁸⁴ Vegetables also provide precursors to stimulate liver detoxification.⁸⁵ The cruciferous family has the widest range of therapeutic benefits.⁸⁶ By choosing organic foods patients have the benefit of higher nutritional value and lower pesticide content.^{87,88} Patients, doctors and government regulatory agencies do not take the health impact of pesticide residues on food supplies seriously.⁸⁹ An Israeli study conclusively related a drop in the incidence of breast cancer among Israeli women to a new law prohibiting the use of pesticides. The estrogenic effects of pesticides accelerate breast cancer and other hormone-sensitive cancers, an effect that is magnified when more than one type of pesticide is present or when combined with the consumption of large quantities of alcohol.

Avoiding Certain Food Groups

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One man's food is another's poison.⁹⁰ Bioactive peptides from foods may act as vasoregulators, growth factors, releasing hormones, or neurotransmitters. Foods have their own reactions that they generate outside of allergy models. As an example tyramine in chocolate causes bouts of headaches in susceptible people because of genetic inability to detoxify this vasoactive amine before it goes out into systemic circulation. This is probably related to genetic predisposition, in patients with migraines, they have a low level of monoamine oxidase (MAO) and phenolsulphotransferase (PST).⁹¹

Partial enzymatic digestion of reactive food protein such as gluten and casein could result in the production of opioid like compounds called exorphins in the gut.⁹² These opioid-like compounds could produce behavioral abnormalities seen in food intolerance.

Sauna and Hydrotherapy

Sauna therapy can support the removal of fat-soluble toxins from the body, and has been shown to provide relief of symptoms for patients with toxicity conditions.^{93,94} Sauna programs need to be carefully tailored to the individual patient and supervised closely, particularly with more compromised patients.

Hydrotherapy has been employed for hundreds of years because of its ability to stimulate circulation. It used to be the mainstay of traditional naturopathic medicine for the treatment of chronic degenerative disease. One medical study on the effectiveness of hydrotherapy for detoxification proved it to be effective in the treatment of lead poisoning.⁹⁵ This study showed the increase in lead excretion by two hundred and fifty percent. Cold water application in winter swimmers has shown an increase in the level of reduced glutathione in red blood cells.⁹⁶ There is a study showing that after wet sheet pack hydrotherapy, there was a statistically increased level of cognitive functioning.⁹⁷ Other research has shown its usefulness in symptomatic relief of many conditions, including rheumatoid arthritis,⁹⁸ osteoarthritis,^{99,100} chronic heart failure,¹⁰¹ management of spasticity,¹⁰² and other similar conditions.

⁹⁰ Roberts, P.R., and G.P. Zaloga. "Dietary Bioactive Peptides," *New Horizons* 2, 2 (1994): 237-43.

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Theoretically, application of alternating hot and cold water to the body stimulates regulation of sympathetic tone in the extracellular matrix, and generates a “pumping” action that stimulates circulation of blood and lymph. The extracellular matrix is now understood to influence cellular development, movement, reproduction, and shape, as well as biochemical function. Dr. Alfred Pischinger, professor of histology and embryology at the University of Vienna, saw the importance of the extracellular matrix. In 1991, he wrote that the extracellular matrix is the support system for the cell and the foundation substance in which all cells are embedded. The extracellular matrix is made up of collagens and polysaccharides that form proteoglycans. These two molecules form a water-filled, gel-like “ground substance” in which the connective tissue fibers are embedded. The condition of the space around a cell is as important to health as what occurs within the cell and in the membrane that encloses it.

Instruct the patient to do the hydrotherapy at home or institute a hydrotherapy option as part of your clinical practice.

Supplements

There is a complex set of variables involved in choosing the appropriate supplements for detox patients. Supplement programs should be adapted to the individual patient’s need, using the following general strategies:

- Antioxidants for cellular protection
- Amino acids for phase II detoxification
- Cholagogues (bile stimulants)
- Bile binding
- Replacing probiotic bacteria
- Repairing intestinal permeability
- Vitamins, minerals, and nutritional co-factors
- Cathartics
- Antiparasitics

Glutathione

Glutathione is primary detoxification chemical in the body.¹⁰³ A sick liver does not produce adequate levels of it thereby accelerating damage and disease.¹⁰⁴ Glutathione protects cells against free radicals,¹⁰⁵ drugs and environmental pollutants and enhances immune function.

¹⁰⁰ Foley A, Halbert J, Hewitt T, Crotty M. Does hydrotherapy improve strength and physical function in patients with osteoarthritis – a randomized controlled trial comparing a gym based and a hydrotherapy based strengthening programme. *Ann Rheum Dis.* 2003;62:1162-1167.

¹⁰¹ Michalsen A, Ludtke R, Buhning M, et al. Thermal hydrotherapy improves quality of life and hemodynamic function in patients with chronic heart failure. *Am Heart J.* 2003;146(4):E11.

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Small decreases in mitochondrial glutathione results in cell death. Oral supplementation appears inadequate. In patients who appear to need glutathione, based on history or lab analysis, give a 500 mg IV several times a week to once a month. Vitamin C orally and IV is also an effective way to recycle glutathione but in patients with poor liver function, prefer glutathione direct.¹⁰⁶

Lipoic Acid

Lipoic acid has powerful antioxidant abilities extend to both the oxidized and reduced form.¹⁰⁷ It helps the functions of other antioxidants like vitamin C, E, co-enzyme Q10 and glutathione to “recharge” themselves to their active forms. It has the ability to protect organs like the brain and liver from free radical damage.¹⁰⁸ Like other liver-protecting agents, lipoic acid has proven effective in treating poisoning from mycotoxins, mercury, lead, carbon tetrachloride, and aniline dyes.¹⁰⁹¹¹⁰ It has also been used to treat liver disease, alcohol-induced cirrhosis, viral hepatitis, AIDS, glaucoma and complications of diabetes.

The recommended dosage of lipoic acid is 600 mg twice daily.

Milk Thistle

Milk thistle has a group of bioflavonoids collectively known as silymarin. Silymarin is really an antitoxin. No drug can protect your liver the way silymarin can because of its strong action against free radicals and its ability to enhance glutathione production by more than 35 percent, thus increasing liver detoxification. Its effectiveness has been measured by lower enzyme markers on liver function tests, which reflect nonspecific liver cell inflammation.¹¹¹

Silymarin has been used successfully in the treatment of the following:

- Neurological complications caused by diabetes
- Fatty liver disease in diabetic patients
- Nausea caused by high levels of hormones naturally produced during pregnancy
- Chronic alcoholic liver diseases
- Toxic exposure to industrial chemicals
- Acute viral hepatitis
- Cirrhosis of the liver
- Immune system and liver protection

The recommended dosage of silymarin is 200 mg three times daily.

Curcumin

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¹⁰⁷ Marangon K, et al. Comparison of the effect of alpha-lipoic acid and alpha-tocopherol supplementation on measures of oxidative stress. *Free Radic Biol Med.* 1999;27(9-10):1114-21.

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¹⁰⁹ Rogers SA. Lipoic acid as a potential first agent for protection from mycotoxins and treatment of mycotoxicosis. *Arch Environ Health.* 2003;58(8):528-32.

¹¹⁰ Patrick L. “Mercury Toxicity and Antioxidants: Part I: Role of Glutathione and alpha-Lipoic Acid in the Treatment of Mercury Toxicity.” *Alt Med Rev* 7(6), 456-471.

¹¹¹ Salmi HA, Sarna S. Effect of silymarin on chemical, functional, and morphological alterations of the liver. A double-blind controlled study. *Scand J Gastroenterol* 1982;17:517-521;

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Turmeric and its active bioflavonoid curcumin has been used by Indian and Chinese herbalists for thousands of years. It is known to protect the liver and promote bile flow and act as a powerful anti-inflammatory.¹¹²¹¹³ ¹¹⁴ Curcumin's ability to fight inflammation also makes it helpful as an antioxidant, scavenging free radicals and protecting DNA from oxidant breakage and lipid peroxidation.¹¹⁵

The recommended dosage of 500 mg three times a day

Green Tea

Catechin is found in green tea. Green tea contains several polyphenol catechins but the strongest is EGCG.¹¹⁶ Studies have shown that drinking green tea offers smokers some protection from cardiovascular disease. Its ability to activate detoxification enzymes in the liver has also been shown to provide a defense against cancer. Catechin has a special affinity for the liver, so it can be used effectively in the treatment of liver diseases, hepatitis, and alcohol-related liver syndromes. It also offers protection from bacterial toxins in the intestines and from arthritis and scleroderma.

The recommended dosage of green tea is 5 cups a day

NAC

NAC is the primary precursor to glutathione. Studies have shown that NAC affects concentrations of glutathione in the blood, helping to provide adequate levels so that the chemicals produced during detoxification don't damage other tissues.¹¹⁷ Studies have shown it to be effective in managing HIV and hepatitis C.¹¹⁸¹¹⁹¹²⁰

The recommended dosage of NAC is 500 mg three times daily between meals.

Probiotics

Antibiotics, steroids, and birth control pills commonly upset the normal bacterial equilibrium in the intestines. Poor diet and chronic constipation are also contributing factors. Reseeding the intestines with favorable bacteria creates an optimum, balanced environment, protecting the

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¹¹⁴ Iqbal, M., et al., Dietary supplementation of curcumin enhances antioxidant and phase II metabolizing enzymes in ddY male mice: possible role in protection against chemical carcinogenesis and toxicity. *Pharmacol Toxicol*, 2003. 92(1):33-8.

¹¹⁵ Kiso Y, Suzuki Y, Watanabe N, et al. Anti hepatotoxic principles of *Curcuma longa* rhizomes. *J Med Plant Res*. 1983;49:185-187.

¹¹⁶ Leung LK, et al (2001) Theaflavins in black tea and catechins in green tea are equally effective antioxidants. *J Nutr* 131(9); 2248-51.

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¹¹⁸ De Rosa, S.C., et al., N-acetylcysteine replenishes glutathione in HIV infection. *Eur J Clin Invest*, 2000. 30(10): p. 915-29.

¹¹⁹ Kinscherf R; Fischbach T; Mihm S; et al. Effect of glutathione depletion and oral N-acetyl-cysteine treatment on CD4+ and CD8+ cells. *FASEB J* 8:448-451; 1994.

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intestines and the rest of the body from dangerous bacterial insurgents.¹²¹ An investigation in monkeys demonstrated a marked increase in the proportion of mercury-resistant bacteria in the floras of the intestine and oral cavity soon after installation of dental amalgam tooth fillings, which increased until after the amalgam was removed.¹²²

Additional tips:

- No supplements during the water fasting except for vitamin C.
- Structuring supplement recommendations for twice-a-day dosing improves compliance.
- Ensure that there is some sort of protein shake for the patient to use, if needed.

Chelation

After determining the offending heavy metals, select a chelating substance that fits the patient and the problem(s). Time the chelation as a “post” detoxification strategy, patients can only handle so much healing before it makes them sick.

Post Detox Recommendations

After the seven-day program, it is best to continue the hydrotherapy and/or saunas and the supplement strategies for at least a month. The patient should slowly re-introduce foods, starting with foods least likely to irritate the intestinal mucosa. Since the diet is relatively low in essential amino acids, the introduction of eggs, fish, or lean meat on a daily basis helps to restore proper protein balance. After several days of this regimen, begin adding foods that seem prudent for the individual patient; last, introduce known allergens like dairy products, wheat, and soy foods (one at a time and allowing a day or two between each new food to determine any reactions). Detoxification therapy can take months in chronically ill patients so patience is a critical ingredient to the care of our poisoned population.

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¹²² Summers, A.O., et al. “Mercury Released from Dental ‘Silver’ Fillings Provokes an Increase in Mercury and Antibiotic Resistant Bacteria in Primates Oral and Intestinal Flora,” Agents and Chemotherapy 37 (1993): 825–34.