

## Systems Biology, Toxins, Obesity, and Functional Medicine

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Obesity is not a single clinical disorder. Obesity is a complex chronic illness resulting from the interplay among genetics, environment, and lifestyle. Emerging scientific concepts provide a new basis for understanding the multiple causes of obesity as well as the underlying mechanisms involved in weight dysregulation. While most obesity can be effectively treated for compliant patients, using a focused lifestyle intervention based on a whole-foods, low-glycemic-load, phytonutrient-rich diet combined with exercise and stress management, there are patients who do not respond predictably to normally successful interventions. A novel hypothesis linking environmental and internal toxins to disruptions of key mechanisms involved in weight regulation may explain treatment resistance in obesity. The key biological systems involved in obesity (and all diseases) that are altered by toxins are the neuro-endocrine-immune system, and mitochondrial energetics and redox status. Obesity provides an illustrative example of new navigational tools for diagnosis and therapy of chronic illness based on a paradigm that focuses not on disease or symptoms, but on cause and mechanism. This new framework and methodological approach can be applied to any chronic disease and provides an opportunity to integrate fragmentary scientific discoveries into a cohesive whole that creates a new clinical roadmap.

This paper will explore a novel hypothesis that links obesity and toxins; we will discuss how one particular disease and the effect of one underlying cause can create a clinically relevant, holographic view of physiology. Alterations in thyroid metabolism and receptor function, central appetite dysregulation, inflammation's influence on insulin and leptin resistance, impaired mitochondrial oxidative metabolism, and oxidative-stress-mediated effects via nuclear factor kappa B (NFκB) are all mechanisms by which toxins create alterations in metabolism and finely-tuned weight regulatory mechanisms.

These systems are not discrete entities but systems in the true sense of the word – interlocking, interactive, dynamic, overlapping networks of biochemical and physiological informational spheres of functional relationships. Multiple patterns of genetic, physiological, and biochemical dysfunction are linked to obesity, including genetic polymorphisms, inflammation, mitochondrial dysfunction, oxidative stress, neuro-endocrine-immune dysfunction, especially autonomic disturbances involving the hypothalamic-pituitary-adrenal axis, nutritional deficiencies or excesses, and toxins. The nature, causes, and remediation of obesity can be seen through the prism of any one of these patterns. The focus here will be on how toxins mediate their influence through all these mechanisms.

### WEIGHT REGULATION AND TOXINS: UNDERLYING MECHANISMS

The influence of toxins on metabolism occurs through 5 key mechanisms: hormonal regulation, neuro-regulatory mechanisms, immuno-regulatory mechanisms, mitochondrial function, and oxidative stress. Toxins can alter the hormonal regulation of weight, a process that involves insulin, leptin, thyroid, cortisol, adiponectin, resistin, sex hormones, and gut hormones, including ghrelin, peptide YY (PYY), and cholecystokinin (CCK). Toxins alter thyroid hormone metabolism and receptor function leading to lowered metabolic rate. Important neuro-regulatory mechanisms affected by toxins include hypothalamic satiety modulation through effects on peripheral and central inhibitors and stimulators of appetite, including leptin, cortisol, melanocyte stimulating hormone ( $\alpha$ -MSH), and neuropeptide Y (NPY). Stress-induced autonomic dysfunction also alters appetite and weight-control mechanisms. Toxins can influence weight through toxin-mediated increases in inflammatory cytokines (TNF- $\alpha$ , IL-6) on the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors promoting insulin resistance, and on the melanocortin receptor (MCR) system altering central appetite regulation. Counter-regulatory signals triggered by inflammation such as suppressors of cytokine signaling (SOCS) induce leptin resistance. Toxins alter mitochondrial energetics by damaging enzymes involved in fatty acid oxidation and thermogenesis. Oxidative stress influences weight via NFκB-mediated mechanisms of gene transcription that control insulin resistance and inflammation. Other mechanisms may include direct effects of toxins on hepatic control of lipid and glucose metabolism, and on inflammatory cytokines.

### CAN FOREIGN MOLECULES CAUSE OBESITY?

It is clear that ingesting foreign molecules can lead to obesity, including medications. While most drugs are not truly toxins, certain drugs can have toxic effects and cause weight gain—psychotropic medications in particular have been shown to promote weight gain. monoamine oxidase (MAO) inhibitors, lithium, valproate, mirtazapine, clozapine, olanzapine, and some selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine, sertraline, and paroxetine have all been shown to promote weight gain through various mechanisms. Hormones such as megestrol are used to increase appetite in cancer patients. Billions of dollars are pouring into obesity drug research to find the magic molecule that will burn fat or reduce appetite. However, affecting one pathway in a complex cybernetic system will likely fail because of countless counter-regulatory mechanisms. It is clear that medications can affect our weight and may play a role in obesity for some people. But it is important to recognize that, if medications can influence weight, then certainly other foreign chemicals, including environmental toxins, can cause weight gain.

Environmental toxins interfere with metabolism, overload hepatic detoxification systems, disrupt central weight-control systems, promote insulin resistance, alter circadian rhythms, activate the stress response, interfere with thyroid function, increase inflammation, damage mitochondria, and lead to obesity. Most researchers have largely ignored the effects of environmental chemicals on metabolism. Still, a few researchers have started connecting the dots linking

toxins with the obesity epidemic. While research linking environmental toxins and impaired detoxification to obesity remains in its infancy, these factors can no longer be overlooked. Detoxification is a central component in long-term effective weight management and creating a healthy metabolism.

#### LIVING IN A SEA OF TOXINS: THE PROBLEM

Why should we worry about toxins unless we work with toxic chemicals or spray pesticides for a living? Isn't exposure minimal? Unfortunately, risks of exposure are substantial, pose significant public health risks, and can no longer be ignored. We live in a sea of toxins. Every single person and animal on the planet contains residues of toxic chemicals or metals in their tissues. Eighty thousand new chemicals have been introduced since the turn of the 20th century and most have never been tested for safety or for synergistic actions. The Centers for Disease Control issued a report on human exposure to environmental chemicals. They assessed human blood or urine levels for 116 chemicals (and there were thousands more for which tests were not conducted) as part of the National Health and Nutrition Examination Survey.<sup>1</sup> While they found high levels of toxins in some, and low levels in many more, the study, in isolation, may not tell the whole story. Why? Because these chemical toxins move quickly from the blood into storage sites—mostly fat tissue, organs, and bones—so the blood or urine levels *underestimate* the total toxic load. Both weight gain (because of stored toxins) and the total toxic load can frustrate attempts at weight loss by impairing two key metabolic organs—the liver and the thyroid, by damaging the mitochondria—the site of energy metabolism, by affecting neuroendocrine signaling, and by increasing inflammation and oxidative stress.

#### FAT AS A STORAGE DEPOT FOR FAT SOLUBLE TOXINS

The Environmental Protection Agency has monitored human exposure to toxic environmental chemicals since 1972 when they began the National Human Adipose Tissue Survey. This study evaluates the levels of various toxins in the fat tissue from cadavers and elective surgeries. Five of what are known to be the most toxic chemicals were found in 100% of all samples (OCDD or octachlorodibenzo-p-dioxin, styrene, 1,4-dichlorobenzene, xylene, and ethylphenol—toxic chemicals from industrial pollution that damage the liver, heart, lungs, and nervous system). Nine more chemicals were found in 91-98% of samples: benzene, toluene, ethylbenzene, DDE (a breakdown product of DDT, the pesticide banned in the US since 1972), three dioxins, and one furan. Polychlorinated biphenyls (PCBs) were found in 83% of the population. A Michigan study found DDT in over 70% of 4 years olds, probably received through breast milk. With the global economy, we may be eating food that was picked a day before in Guatemala, Indonesia, or Asia, where there are not the same restrictions on the use of pesticides as there are in the United States. Many of these chemicals are stored in fat tissue, making animal products concentrated sources. One hundred percent of beef is contaminated with DDT, as is 93% of processed cheese, hot dogs, bologna, turkey, and ice cream.

#### WHERE DO TOXINS COME FROM?

Exposure to toxins comes from two main sources: the environment (external toxins) and the gut (breakdown products of our metabolism, or internal toxins). Both can overload endogenous detoxification mechanisms.

#### External Toxins: The Dangers from Without

The external toxins include chemical toxins and heavy metals. The

#### Testing for Toxins and Detoxification Function

- Genetic testing of detoxification pathways for phase I and phase II SNPs
- Detoxification challenge test (provocations with caffeine, aspirin, acetaminophen)
- Measurement of detoxification enzymes
  - Reduced glutathione
  - Glutathione peroxidase
  - super oxide dismutase (SOD)
- Heavy metals
  - RBC or whole blood
  - Hair analysis
  - Chelation challenge with DMPS or DMSA
- Urinary organic acids
  - Specific compounds measured, including sulfates, pyroglutamate, orotate, and others, can give clues to problems with detoxification pathways.
- Chemical antibodies to various toxins and metals (can occasionally be useful)
- Organophosphates: identified through a 24-hour urine collection test
- Mold and mycotoxin antibodies
- IgG food sensitivity testing
- Celiac testing (IgG and IgA anti-gliadin antibodies, tTG IgA)
- Digestive stool analysis for dysbiosis
- Tests for hidden infections (Lyme, H. pylori, etc.)

#### Practical Suggestions for Patients

##### Remove Toxins

- Eat organic food and animal products to avoid petrochemical pesticides, herbicides, hormones, and antibiotics.
- Drink filtered water (reverse osmosis or carbon filter).
- HEPA/ULPA filters and ionizers can be helpful in reducing dust, molds, volatile organic compounds, and other sources of indoor air pollution.
- Clean and monitor heating systems for release of carbon monoxide, the most common cause of death by poisoning in America.
- Have houseplants that help filter the air.
- Air out your dry cleaning before wearing it.
- Avoid excess exposure to environmental petrochemicals (garden chemicals, dry cleaning, car exhaust, second-hand smoke).
- Reduce or eliminate the use of toxic household and personal care products (aluminium-containing underarm deodorant, antacids, and pots and pans).
- Remove allergens and dust from your home as much as possible.
- Minimize electromagnetic radiation (EMR) from radios, TVs, and microwave ovens.
- Reduce ionizing radiation (from sun exposure or medical tests such as X-rays).
- Reduce heavy metal exposure (predatory and river fish, water, lead paint, thimerosal-containing products, etc.).

##### Improve Elimination of Toxins

- Have 1-2 bowel movements a day.
- Drink 6-8 glasses of water a day.
- Sweat regularly.
  - Use exercise to help you sweat regularly.
  - Use steam baths or saunas – infrared saunas may be even more beneficial.

Continued, p.58

heavy metals that cause the most ill health are lead, mercury, cadmium, arsenic, nickel, and aluminum. Chemical toxins include volatile organic compounds (VOCs), solvents (cleaning materials, formaldehyde, toluene, benzene), medications, alcohol, pesticides, herbicides, and food additives. Infections (hepatitis C virus) and mold toxins (sick building syndrome) are other common sources of toxins. Our modern refined diet can be considered toxic because it places an extra burden on detoxification systems through excessive consumption of sugar, high-fructose corn syrup (the two most important causes of elevated liver function tests), trans fatty acids, alcohol, caffeine, aspartame, foods made with genetically modified organisms (GMOs), and the various plastics, pathogens, hormones, and antibiotics found in our food supply.

#### Internal Toxins: Danger from Within

Internal toxins include microbial compounds (from bacteria, yeast, or other organisms), and the breakdown products of normal protein metabolism. Bacteria and yeast in the gut produce waste products, metabolic by-products and cellular debris that can interfere with many body functions and lead to increased inflammation and oxidative stress. These include endotoxins, toxic amines, toxic derivatives of bile, and various carcinogenic substances such as putrescine and cadaverine. Lastly, by-products of normal protein metabolism, including urea and ammonia, require detoxification.

#### OBESITY AND TOXICITY: IS THERE A CONNECTION?

##### Effects on Thyroid and Metabolic Rate

Many people reach a plateau during weight loss. After the loss of a few pounds, it is often difficult to shed more weight. What is it that impedes weight loss and interferes with metabolism? A review paper, "Energy balance and pollution by organochlorines and polychlorinated biphenyls,"<sup>22</sup> published in *Obesity Reviews* in 2003 outlines the effects of toxins on metabolic rate and weight regulation via various mechanisms. The authors conclude that pesticides (organochlorines) and PCBs (from industrial pollution) released from the fat tissue, where they are typically stored, during weight loss lower the metabolic rate. The authors go on to conclude that we should lose a little weight to reduce our risk of cardiovascular and degenerative diseases, but not too much because we could poison our metabolism. If there were no way to facilitate endogenous detoxification mechanisms, this would be a sound conclusion; however there are multiple ways to upregulate all phases of detoxification and eliminate both endogenously-liberated and exogenous toxins.

How do the chemical toxins interfere with metabolism? The researchers in the above-mentioned study on the link between chemical toxins and obesity reviewed 63 scientific studies and described many mechanisms. First, people with a higher body mass index (BMI) store more toxins because they have more fat. Those toxins interfere with many normal aspects of metabolism, including causing a reduction in thyroid hormone levels, and increased excretion of thyroid hormones by the liver. Toxins also compete with the thyroid hormones by blocking the thyroid receptors, and by vying for the thyroid transport proteins. Toxins also induce hepatic uridine diphospho-glucuronosyltransferase (UDPGT), which catalyzes glucuronidation of T4 for excretion in bile. T3 concentrations and resting metabolic rate are inversely related to organochlorine levels. Thus, it is clear that organochlorine pesticides and PCBs lower thyroid hormone levels, interfere with their function, and slow the metabolic rate.

##### Toxins Alter Mitochondrial Function, Redox Status, and Cytokine Function

In addition, toxins damage the mitochondria, increase oxidative

Continued from, p.57

- Regular exercise, yoga, or lymphatic massage can improve lymph flow and help flush toxins out of your tissues into your circulation so they can be detoxified.

##### Increase Fiber Intake

- Eat more beans, whole grains, vegetables, fruits, nuts, and seeds.

##### Feed Your Gut with Healthy Bacteria

- Taking probiotics such as lactobacillus and bifidobacter species helps normalize gut flora and reduce endotoxins (toxins produced by imbalances in gut bacteria).

##### Foods and Phytochemicals that Boost Detoxification

- Try to eat at least one cup of cruciferous vegetables daily.
- Eat a few cloves of garlic every day or take a garlic supplement.
- Try decaffeinated green tea in the morning.
- Try fresh vegetable juices including carrots, celery, cilantro, beets, parsley, and ginger.
- Try prepared herbal detoxification teas containing a mixture of burdock root, dandelion root, ginger root, licorice root, sarsaparilla root, cardamom seed, cinnamon bark and other herbs.
- Eat high-quality, sulfur-containing proteins – eggs, whey protein, garlic, onions.
- Consume citrus peels, caraway, and dill oil (they contain limonene).
- Consume bioflavonoids in grapes, berries, and citrus fruits.
- Eat cruciferous vegetables (cabbage, broccoli, collards, kale, Brussels sprouts).
- Consume dandelion greens to help liver detoxification, improve the flow of bile, and increase urine flow.
- Eat celery to increase the flow of urine and aid in detoxification.
- Consume cilantro, which may help remove heavy metals.
- Consume rosemary, which has carnosol, a potent booster of detoxification enzymes.
- Consume curcuminoids (turmeric and curry) for their antioxidant and anti-inflammatory action.
- Consume burdock root for aid in detoxification.
- Consume chlorophyll in dark green leafy vegetables and in wheat grass.
- Take pycnogenol (found in grape seeds) in supplement form for support of detoxification and circulation.

##### Supplements for Detoxification

###### The Basics

- Take a high potency multi-vitamin and mineral formula.
- Take extra-buffered vitamin C 1000-4000 mg a day with mineral ascorbates in powder, capsule, or tablets during periods of increased detoxification. (This can cause loose stools. If it does, just reduce the dose or stop.)
- Take milk thistle (silymarin) 70 to 210 mg a day.
- Supplement with essential fatty acids (omega-3 fatty acids), 1000-2000 mg a day.

###### Additional Supplements (use under medical supervision)

- N-acetylcysteine 500 to 1000 mg a day
- Amino acids (taurine 500 mg twice a day, glycine 500 mg twice a day)
- Alpha-lipoic acid 100 mg to 600 mg a day
- Carnitine 1000 to 2000 mg a day in divided doses
- Bioflavonoids (citrus, pine bark, grape seed, green tea)

stress, and reduce their ability to burn fat and calories by inhibiting thermogenesis through effects on fatty acid oxidation. Organochlorines alter skeletal muscle oxidative enzyme activities. Enzymes of electron transport are inhibited by toxins, specifically 3-hydroxyacyl-CoA dehydrogenase (HADH) and cyclooxygenase (COX), both markers of fatty acid metabolism. Toxins also lead to decreased capacity for fatty acid utilization in skeletal muscle.

Oxidative stress is both a cause and effect of obesity. Toxins increase oxidative stress and affect redox signaling. Redox signaling influences gene transcription and signaling pathways controlling insulin resistance, cytokine modulation, and mitochondrial function. Activation of NF $\kappa$ B (a gene transcription factor) is mediated by redox balance and is a final common pathway for obesity and many other chronic illnesses.<sup>3</sup> All of these actions cause both weight gain and resistance to weight loss.

Toxins may also influence metabolism and obesity through cytokine-mediated mechanisms. Toxins activate neutrophils.<sup>4</sup> Increases in tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 6 (IL-6) induced by toxins promote insulin resistance via effects on PPAR and NF $\kappa$ B.<sup>5</sup> Leptin resistance is also triggered by inflammation via SOCS.<sup>6</sup>

#### Detoxification Enzyme Polymorphisms and Obesity

The effect of toxins on an individual is determined, in part, by the polymorphisms of phase I and phase II detoxification enzymes. Highly prevalent single nucleotide polymorphisms (SNPs) of glutathione transferase enzymes predispose to increased toxic loads. Detoxification of heavy metals is an important task for the body. It depends on specific proteins and enzymes that bind the metals and transport them out of the cells. In one recent study, mice bred without the protein (metallothionein) that is necessary for heavy metal detoxification gained more weight over their lifetime than mice that could eliminate the metals. They were more sensitive to the effects of toxic metals and oxidative stress.

#### Toxins Impair Central Appetite Regulation

Toxins have many effects. Besides directly lowering thyroid hormone levels, metabolic rate, and fat burning (fatty acid oxidation), they can damage the mechanisms by which hormonal and neuro-regulatory signals control our appetite and behavior. These signals are finely choreographed and sensitive to environmental inputs. To briefly review, the hypothalamic appetite-control system is centered in the arcuate nucleus. It receives peripheral feedback from leptin, insulin, PYY, and adiponectin. Central inhibition of food intake is regulated by pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART). Central stimulation of intake is modulated by neuropeptide Y and agouti-related peptide (AgRP).<sup>8</sup> The melanocortin system and its receptors, MC3R and MC4R, play a crucial role in appetite control. Specifically,  $\alpha$ -MSH binds to MCR, suppresses appetite, stimulates the thyroid axis, and increases energy expenditure, brown fat temperature, and sympathetic activity. It is inhibited by TNF- $\alpha$ . Other downstream control sites also exist in the related areas of the brain. Reward centers also play a role and are targets for new drug research including the endocannabinoid and serotonin receptors.<sup>9</sup>

Leptin resistance is found in obesity. Leptin's inhibitory effect on appetite is impaired by toxins, leading to leptin resistance and increased hunger. Hyperleptinemia increases mitochondrial reactive oxygen species monocyte chemoattractant protein-1 (ROS MCP-1). Leptin induces inflammation in a feed-forward cycle. Toxins may inhibit satiety effects of leptin, leading to increasing hyperleptinemia.

Researchers treated rats with a neurotoxin that damaged another

critical appetite control system (the melanocortin system).<sup>10</sup> The toxin lowered levels of alpha-melanocortin-stimulating hormone ( $\alpha$ -MSH), which acts as a brake on appetite.<sup>11</sup> This pathway may be a missing link in understanding the effects of toxins on obesity through the interaction of  $\alpha$ -MSH<sup>12</sup> and TNF- $\alpha$ <sup>13</sup> and PPAR.  $\alpha$ -MSH is a central and peripheral inhibitor of TNF- $\alpha$ , IL-1, and IL-6 via inhibition of NF $\kappa$ B and cytokine-mediated gene transcription. TNF- $\alpha$  downregulates genes that are required for normal insulin action, has a direct inhibitory effect on insulin signaling, and induces elevated free fatty acids via stimulation of lipolysis. A key effect of TNF- $\alpha$  is the negative regulation of PPAR $\gamma$ , an important insulin-sensitizing nuclear receptor. Neurotoxins also may directly inhibit  $\alpha$ -MSH, leading to hyperphagia and increased body weight.<sup>14,15</sup>

Human studies complement research from animal studies. One study examined prenatal and breast milk exposure to PCBs and DDE (a by-product of DDT).<sup>16</sup> Researchers followed 594 children who had their prenatal and breast milk exposures to PCBs and DDE measured. At puberty, children with the highest exposures were larger, and girls were an average of 12 pounds heavier. In a second study, a group of researchers from Laval University in Quebec found that, during weight loss, those who released the most organochlorines from their fat stores had the slowest metabolism after weight loss.<sup>17</sup> Their explanation for the decreased thermogenesis, after taking into account all other possible factors, was the exposure to pesticides. In yet another study, the rise of toxins during weight loss in men inhibited normal mitochondrial function and reduced their ability to burn calories, retarding further weight loss.<sup>18</sup> Weight loss seems to prevent further weight loss, and one of the key mechanisms may be the release of internally-stored toxins that occurs during weight loss.

#### Hormone Disrupters: Hormonal Chaos

The dance of hormones is critical for balancing your metabolism. Environmental chemicals and heavy metals are well known hormone disrupters. A Tufts University professor, Sheldon Krinsky, in his book *Hormonal Chaos, the Scientific and Social Origins of the Environmental Endocrine Hypothesis*, has extensively reviewed the research in this field. Low levels of these toxins, levels far below what are considered acceptable by the Environmental Protection Agency, interfere with our normal hormone balance, including sex hormones, which may lead to early puberty in girls and an increase in hormonal disorders. Toxins can affect many of the major weight-control hormones including thyroid, estrogens, testosterone, cortisol, insulin, growth hormone, and leptin. Toxins interfere with our stress response (our autonomic nervous system), and alter the normal circadian rhythms<sup>19</sup> that control our eating behavior. These connections were explored at a conference co-sponsored by the National Institute of Environmental Health Sciences and Duke University entitled, *Obesity: Developmental Origins and Environmental Influences*.<sup>20</sup> While we still have much to learn about this connection, we can no longer ignore the effect of environmental toxins on weight. It is certainly not the only factor in our obesity epidemic, or in any one person's struggle with weight, but it must be considered in the evaluation and treatment of obesity.

#### Fatty Liver: Cause or Effect in Weight Gain

Non-alcoholic steatohepatitis (fatty liver) is the most common liver disease in America, affecting 20% of the population. The major cause is not medication, a virus, or pollution. It is the most abundant toxin in our diet: *sugar*. Increases in sugar or refined carbohydrate consumption increase insulin and insulin resistance, which leads to

the accumulation of fat in the hepatocytes. Increased fat inside the hepatocytes is produced from sugar, refined flour products, and high fructose corn syrup. The sugar is turned into intracellular triglycerides. Excess sugar calories also increase oxidative stress and further damage the mitochondria. Damaged mitochondria can't effectively burn fat or calories, which leads to a slower metabolism and more weight gain. A fatty liver further impairs detoxification. A fatty liver is also an inflamed liver; it is called non-alcoholic steatohepatitis (NASH), a form of hepatitis caused by insulin resistance. A fatty liver produces more inflammatory cytokines, free radicals, and leads to more mitochondrial damage. Fatty liver impairs optimal hepatic detoxification of endogenous and exogenous toxins.

#### OPTIMIZING DETOXIFICATION: A NOVEL STRATEGY FOR THE MANAGEMENT OF OBESITY

While still a hypothesis, the emerging evidence forms a plausible link between toxins and obesity. To review, toxins alter metabolism, interfere with key weight-control mechanisms, disrupt endocrine function, damage the mitochondria, increase inflammation and oxidative stress, lower thyroid hormones, and alter circadian rhythms and the autonomic nervous system. Using a comprehensive approach to obesity, including the assessment and treatment of toxin-mediated effects, it is necessary to address this multi-faceted disorder affecting two-thirds of Americans. Simple lifestyle choices, as well as medical detoxification, can reduce exposure to toxins and enhance mobilization and elimination of stored and external toxins.

#### Amino Acids, Nutrients, and Phytonutrients in Detoxification

The detoxification system relies on the right balance of protein, fats, fiber, vitamins, minerals, and phytochemicals to be effective. All these play a role in facilitating the elimination of toxins. For example, adequate protein is required to supply the amino acids used by the liver to provide glycine, cysteine, and glutamine to synthesize glutathione, as well as amino acids critical for many phase II detoxification pathways including methylation, acetylation, glucuronidation, and glycation. Glutathione is the most critical antioxidant and detoxifier in the body, and one that is easily depleted in the face of chronic exposure to toxins. Many phytochemicals enhance detoxification pathways.<sup>21</sup> These include many pigmented plant foods such as cruciferous vegetables (broccoli, kale, collards, Brussel sprouts, cauliflower), green tea, watercress, dandelion greens, cilantro, artichokes, garlic, ginger, rosemary, turmeric, citrus peels, and even cocoa. Polyphenols found in berries, green tea, and cocoa enhance the genetic expression of  $\gamma$  glutamylcysteine synthetase, which increases intracellular glutathione concentration.

#### Hyperthermic Therapy

*“Regular use of a sauna or steam bath may impart a similar stress on the cardiovascular system [as exercise], and its regular use may be as effective a means of cardiovascular conditioning and burning calories as regular exercise.”*

W. Dean. Effect of sweating. *JAMA*. 1981;246:623.

Heat therapy is an underutilized treatment in medicine. It helps balance the autonomic nervous system, reduce stress, lower blood glucose, increase caloric expenditure, and enhance excretion of pesticides and heavy metals through the skin. Sauna therapy is an established treatment for chemical poisoning. While more research is needed, a review paper on “thermal therapy” suggests many promising effects including a reduction of inflammation and oxidative

stress,<sup>22</sup> as well as weight loss.<sup>23</sup> In a 2-week study of 25 obese adults, body weight and body fat were reduced after sauna therapy for 15 minutes at 60 degrees Celsius daily, for two weeks, in a far-infrared sauna. One case report described an obese patient who couldn't exercise because of knee arthritis and who lost 17.5 kg, decreasing body fat from 46% to 35% after 10 weeks of sauna therapy. Sauna therapy has many benefits, including increasing autonomic balance through increases in heart rate variability, reduction in cardiac arrhythmias, and reduction of oxidative stress, as well as mobilization and excretion of toxins.

#### Practical Implications in Obesity: Elimination of Toxins and Maximizing Detoxification

In the face of the toxic environment of the 21st century, and with the reality that all living species contain increasing levels of environmental toxins with widespread biologic effects, it is clear that both new research to elucidate the mechanisms by which toxins affect health and novel clinical strategies for detoxification are needed. What follows is an overview of a comprehensive clinical approach to identifying and eliminating toxins (in the broadest sense of factors that affect weight and metabolism), as well as maximizing endogenous detoxification mechanisms.

A broad-based and comprehensive strategy for addressing the obesity epidemic is needed,<sup>24</sup> including the implications of new research linking toxins and obesity. Toxins have their impact through effects on endocrine function, the immune system and cytokines; central neuro-regulatory systems; and mitochondrial and oxidative stress. Strategies for treatment of obesity need to be inclusive of research on meal timing, meal composition, glycemic load,<sup>25</sup> phytonutrient content, reducing inflammation, balancing autonomic function by reducing stress,<sup>26</sup> improving sleep habits and duration, as well as treatments aimed at enhancing mitochondrial function and balancing redox status. In addition, minimizing exposure to toxins and enhancing detoxification can be an integral part of obesity management, especially in treatment-resistant patients.

A comprehensive detoxification strategy<sup>27</sup> should include the identification and removal of infections, limiting endogenous toxicity by improving digestive function, enhancing blood and lymphatic circulation, facilitating phase I and II detoxification pathways, and addressing the toxic effects of stress.

The first step is a thorough clinical evaluation for a history of toxic exposures, including amalgams, fish, mold, occupational exposures, and pollution or chemical contamination of water, air, or food. The toxic effects of occult infections, allergens, and medications also need to be considered.

Reduction of dietary toxins or chemicals can be helpful in reducing overall toxic load; these may include *trans* fatty acids, processed foods and suspect additives (aspartame, high fructose corn syrup), sugar and refined flours, salt, caffeine, charbroiled meats, and alcohol. Identifying and eliminating common food allergens such as gluten, dairy, eggs, soy, corn, and yeast may be helpful in reducing the effects of inflammatory cytokines on weight regulation. Minimizing unnecessary medications such as acetaminophen and non-steroidal anti-inflammatory or acid-blocking medications can prevent depletion of hepatic glutathione and reduce altered gut function. Recommendations to eat organic food, drink filtered water, and use an air filter can further limit overall toxic exposures. Common household or environmental exposures can be limited by considering the causes of sick building syndrome (mediated through the effects of mycotoxins), garden chemicals, household cleaners, dry cleaning sol-

vents, second-hand smoke, plastics and phthalates in food and water containers, toxic molds common in basements and bathrooms, and UV radiation, which can be limited by sunscreen and sun glasses. Heavy metal exposure is also common, including mercury from fish, amalgams, water, latex paint, vaccines, and contact lens solutions; lead from old paint, blinds, and canned foods; and aluminum common in deodorants, antacids, and baking powder. Addressing occult infections is also important; consider *H. pylori*, chlamydia, viruses, Lyme disease, chronic fungal sinusitis, periodontal disease and infected root canals, as well as intestinal dysbiosis from yeast, parasites, and bacteria. Psychosocial stressors can exacerbate the effects of other toxins and affect central and peripheral appetite control mechanisms.

Optimizing digestive function is important through the elimination of common food allergens and medications, re-inoculation with beneficial flora (probiotics), and the use of specific nutrients for gut repair, including essential fatty acids, zinc, and glutamine. Regular elimination is critical to excrete toxins through the bile and can be facilitated by fiber, magnesium, vitamin C, and charcoal. Enhancing blood and lymphatic circulation can be accomplished through aerobic exercise, yoga, massage and body work, sauna and heat therapy, as well as skin exfoliation and brushing. Facilitation of endogenous detoxification systems can be accomplished through diet and strategic supplementation, including the use of specific nutrients, amino acids, and herbs. Useful strategies include a high-potency multi-vitamin and mineral (enzyme cofactors), buffered vitamin C, and regular intake of phytonutrient-rich foods that facilitate phase I and II detoxification (Brassicacae, alliums, lemon peel, green tea, watercress, cocoa, pomegranate, cilantro, and artichoke). Detoxifying herbs include milk thistle, green tea, and dandelion. Additional supplements that can be helpful include N-acetyl cysteine,  $\alpha$ -lipoic acid, amino acids, and bioflavonoids. Probiotics, omega-3 fatty acids, and adequate monounsaturated oils are important. Adequate fluid intake to facilitate renal toxin excretion is also important. Finally, an increased intake of plant foods can alkalize the urine, which helps facilitate toxin excretion.

## SUMMARY

By recognizing the role of toxins in obesity and altered function of the neuro-endocrine-immune and mitochondrial and redox systems, and by creating a comprehensive strategy for both the reduction of exposure to and elimination of toxins, as well as the development of effective clinical strategies, treatment resistance in obesity may be more successfully addressed. Further research is needed to explore the clinical relevance and the mechanisms that underlie this hypothesis and to examine clinical detoxification methods. Through the prism of functional medicine, a context and road map exist for tackling many treatment-resistant and complex chronic diseases, including obesity.

## References

- Centers for Disease Control and Prevention. Second National Report on Human Exposure to Environmental Chemicals, NCEH Publication No. 03-0022. Atlanta, GA: Centers for Disease Control. Available at: <http://www.cdc.gov/exposurereport/2nd/>
- Pelletier C, Imbeault P, Tremblay A. Energy balance and pollution by organochlorines and polychlorinated biphenyls. *Obes Rev*. 2003;4(1):17-24.
- Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocrine Reviews* 23(5):599-622.
- Girard D. Activation of human polymorphonuclear neutrophils by environmental contaminants. *Rev Environ Health* 2003;18(2):75-89.
- Sonnenberg GE, Krakower GR, Kissebah AH. A novel pathway to the manifestations of metabolic syndrome. *Obes Res*. 2004;12(2):180-186.
- Wang Z, Zhou YT, Kakuma T, et al. Leptin resistance of adipocytes in obesity: role of suppressors of cytokine signaling. *Biochem Biophys Res Commun*. 2000;277 (1):20-26.
- Beattie JH, Wood AM, Newman AM, Bremner I, et al. Obesity and hyperleptinemia in metallothionein (-I and -II) null mice. *Proc Natl Acad Sci U S A*. 1998;95(1):358-363.
- Goto M, Arima H, Watanabe M, et al. Ghrelin increases neuropeptide y and agouti-related peptide gene expression in the arcuate nucleus in rat hypothalamic organotypic cultures. *Endocrinol*. 2006.;147(11):5102-5109.
- Wynne K, Stanley S, McGowan B, Bloom S. Appetite control. *J Endocrinol*. 2005;184(2):291-318.
- Dube MG, Pu S, Kalra SP, et al. Melanocortin signaling is decreased during neurotoxin-induced transient hyperphagia and increased body-weight gain. *Peptides*. 2000;21(6):793-801.
- Shoemaker RC, House DE. A time-series study of sick building syndrome: chronic, biotoxin-associated illness from exposure to water-damaged buildings. *Neurotoxicol Teratol*. 2005;27(1):29-46.
- Catania A, Delgado R, Airaghi L, et al. alpha-MSH in systemic inflammation. Central and peripheral actions. *Ann N Y Acad Sci*. 1999;885:183-187.
- Moller DE. Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. *Trends Endocrinol Metab*. 2000;11(6):212-217.
- Dube MG, Pu S, Kalra SP, et al. Melanocortin signaling is decreased during neurotoxin-induced transient hyperphagia and increased body-weight gain. *Peptides*. 2000;21(6):793-801.
- Shoemaker RC, House DE. A time-series study of sick building syndrome: chronic, biotoxin-associated illness from exposure to water-damaged buildings. *Neurotoxicol Teratol*. 2005;27(1):29-46.
- Gladen BC, Ragan NB, Rogan WJ. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. *J Pediatr*. 2000;136(4):490-496.
- Tremblay A, Pelletier C, Doucet E, et al. Thermogenesis and weight loss in obese individuals: a primary association with organochlorine pollution. *Int J Obes Relat Metab Disord*. 2004;28(7):936-939.
- Imbeault P, Tremblay A, Simoneau JA, et al. Weight loss-induced rise in plasma pollutant is associated with reduced skeletal muscle oxidative capacity. *Am J Physiol Endocrinol Metab*. 2002;282(3):E574-E579.
- Nicolau GY. Pesticide effects upon the circadian time structure in the thyroid, adrenal and testis in rats. *Endocrinologie*. 1982;20(2):73-90.
- Duke University Integrated Toxicology Program, National Institute of Environmental Health Sciences/NIH/DHHS, Obesity: Developmental Origins and Environmental Influences. Available at: <http://www.niehs.nih.gov/multimedia/qt/dert/obesity/agenda.htm>.
- Moskaug JO, Carlsen H, Myhrstad MD, et al. Polyphenols and glutathione synthesis regulation. *Am J Clin Nutr*. 2005;81(1 Suppl):277S-283S.
- Masuda A, Miyata M, Kihara T, et al. Repeated sauna therapy reduces urinary 8-epi-prostaglandin F(2alpha). *Jpn Heart J*. 2004;45(2):297-303.
- Biro S, Masuda A, Kihara T, Tei C. Clinical implications of thermal therapy in lifestyle-related diseases. *Exp Biol Med* (Maywood). 2003;228(10):1245-1249.
- Hyman M. *Ultrametabolism*. New York: Scribner; 2006.
- Hyman MA. Systems biology: the gut-brain-fat cell connection and obesity. *Altern Ther Health Med*. 2006;12(1):10-16.
- Hyman MA. Refrigerator rights--the missing link in health, disease, and obesity. *Altern Ther Health Med*. 2005;11(4):10-12.
- Lyon M, Bland J, Jones DS. Chapter 31: Clinical approaches to detoxification and biotransformation. In: Jones, DS (Ed). *Textbook of Functional Medicine*. Gig Harbor, WA: Institute for Functional Medicine; 2006.