Discover the Body's Healing Systems and How They Can Work for You!

TOTAL WELLNESS

"The only guide you need to keep yourself and your family healthy."

—from the foreword by Jonathan Wright, M.D.

JOSEPH PIZZORNO, N.D.

Co-author of the Bestselling
ENCYCLOPEDIA OF NATURAL MEDICINE

TOTAL WELLNESS

Improve Your Health by Understanding and Cooperating with Your Body's Natural Healing Systems

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Chapter Five

Decreasing Toxicity

Study this chapter if you suffer from any of the following:

- *Symptoms*
  - Chronic headaches
  - Foul smelling breath or stools
  - Chronic fatigue
  - Feeling of toxicity (dull headaches, chronic hangover as if from too much alcohol)
  - Sensitivity to chemicals
  - Caffeine-containing drinks and foods keep you awake
  - Chronic allergies
  - Unexplained itching
- *Diseases*
  - Acne
  - Anemia
  - Autoimmune disease (e.g., lupus erythematosis, rheumatoid arthritis)
  - Cancer
  - Eczema
  - Gallstones
  - Gilbert's syndrome
  - Inflammatory bowel disease
  - Psoriasis
  - Toxemia of pregnancy
  - Hives or urticaria (an itchy skin rash usually caused by allergic reaction)
  - Liver disease, especially acute or chronic hepatitis

Behaviors that increase risk:

- Using birth control pills or other hormones
- Diet deficient in vitamin C, the B vitamins, magnesium, or zinc
- Using drugs (prescription, over-the-counter, and recreational)
- High levels of exposure to environmental toxins
- Use of broad-spectrum antibiotics, e.g., tetracycline
- Drinking large amounts of grapefruit juice
- Regular consumption of more than one alcoholic drink a day*

*1995 U.S. dietary guidelines define moderate intake as no more than one drink per day for women and two for men; one drink is 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof liquor.

Thumbnail: Quick Support for Your Detoxification Systems

- *To directly neutralize toxins, especially free radials:*
  Beta-carotene: 25 mg per day
  Vitamin C: 2,000 mg per day
  Vitamin E: 600 iu per day
  Chlorophyll: 10 mg per day
- *To decrease the toxic load from the intestines:*
  Lactobacilli supplements (500 mg capsule twice a day between meals)
  Eat fructooligosaccharide-rich foods, such as onions, asparagus, and bananas
  Eat fiber-rich foods and take fiber supplements (40 or more gm of fiber each day)
  Avoid all allergenic foods
- *To improve the liver's detoxification abilities:*
  Regularly consume garlic and onions
  Take *Silybum marianum* (120 mg three times a day)
  Eat brassica family foods (cabbage, broccoli, brussels sprouts)
  Take glutathione (100 mg per day)
- *To detoxify systemically:*
  Do a modified fast (see discussion below)
  Take an extended sauna (see discussion below)

You're being poisoned. Bacteria in your intestines, toxins in the environment, food additives, and incomplete metabolic processes—all put poisons in your body that drain your energy and make you more susceptible to disease or even directly cause disease. Virtually every natural healing system, especially Ayurvedic medicine from India and naturopathic medicine in the U.S., recognizes the profound contribution of toxins to disease. Even conventional medicine is finally becoming aware of this problem and has coined the term *xenobiotic* to describe the toxins that come into our bodies from the environment.

While the concept of "toxicity" may sound quaint and unscientific, a surprising amount of research has documented its validity. The presence in the body of various types of toxic chemicals, heavy metals, partially broken down metabolites, bacterial toxins, and bacterial cell wall components has now been correlated with specific diseases and syndromes. These toxins are a serious threat to our health.

Toxicity is typically recognized in the bowel and liver and systemically throughout the body. In the bowel, the most common type of toxicity is called intestinal dysbiosis, which means that the bowel contains excessive levels of toxin-producing bacteria and inadequate amounts of normal health-promoting

bacteria. Intestinal dysbiosis is typically caused by the use of broad-spectrum antibiotics, eating contaminated foods, not being breast fed, and/or a low fiber diet. The toxic effects of intestinal dysbiosis are diverse, ranging from chronic fatigue to autoimmune disease.

The other primary organ involved with toxicity is the liver. The liver is responsible for eliminating toxins from the blood or absorbed from a toxic bowel, either by disassembling them or by chemically converting them to less toxic forms more easily excreted by the kidneys. Our modern environment seriously overloads our liver, resulting in increased levels of circulating toxins in the blood, which damage most of our body's systems. A toxic liver sends out alarm signals, which manifest as acne, chronic headaches, inflammatory and autoimmune diseases, and chronic fatigue.

Chemicals can damage the body in an insidious and cumulative way. Once the detoxification system becomes overloaded, toxic metabolites accumulate, and we become progressively more sensitive to other chemicals, some of which are not normally toxic. This accumulation of toxins can wreak havoc on our normal metabolic processes.

The conventional medical approach of using drugs to merely alleviate symptoms not only doesn't deal with the underlying cause of the disease but compounds the problem by adding more toxins into the body. Putting drugs that also need to be detoxified into an already overloaded detoxification system increases systemic toxicity (identified as side effects) and can actually increase the individual's chemical sensitivity.

An effective detoxification system is a necessity for everyone. Even a person eating a natural whole-foods diet requires a healthy detoxification system because even healthful fruits and vegetables contain natural toxins that our bodies have, over the aeons, evolved metabolic processes to neutralize. The vast majority of chemicals consumed by humans are natural. According to some researchers, 99% of the pesticides we eat are naturally present in plants to ward off insects and other predators.[1] Even cooking our foods (especially frying), results in the production of toxic chemicals that our bodies must neutralize. If our detoxification systems are overloaded or aren't working properly because critical nutrients are lacking, toxicity results.

Fortunately, we have excellent defense enzymes, most of which the body will produce more of when we need them. Unfortunately, it takes time for the liver to synthesize these enzymes, so the first exposure to a toxin is the worst.

Real-Life Messages About Toxicity and Detoxification

Ted Got Sick Every Summer

Ted worked his way through college by painting houses every summer. At the end of every summer he was always sick, although no specific disease could be found by the doctors he visited. He would become chronically fatigued, he

would have trouble thinking clearly, and he would lose his appetite. Finally, on the recommendation of a friend, he came to see me at the end of one summer. After hearing his story and physically examining him (he was very thin and his liver was tender) I quickly recognized that he was probably suffering from a combination of heavy metal poisoning from the paint he was scraping off houses and solvent toxicity inhaled from the paint as it dried. (Evaporating latex paint also gives off mercury.)

We took a sample of hair from the nape of his head and sent it to a laboratory to analyze it for heavy metals. As I expected, his levels of lead and mercury were greatly elevated. Since such an elevation in head hair lead can sometimes come from direct contamination of the hair from dust in the air rather than through the blood, we repeated the test on his pubic hair since it is protected by clothing. It was also elevated. Unfortunately, at the time, no test was available for measuring solvent damage to the liver.

I put him on a program to chelate the heavy metals out of his body and improve the function of his liver. For the heavy metals, I had him greatly increase his consumption of beans, vitamin-C–rich foods, pectin, and seaweed products. These foods contain compounds that bind to heavy metals, thus helping the body excrete them.

For his liver, I had him drink dandelion tea and supplement his diet with vitamins C and B complex. In addition, he took the herb milk thistle.

After a few months, his symptoms improved, and hair analysis showed that the heavy metals slowly left his body. He continued to paint each summer, and each summer his heavy metal levels would go up. But not as much as they had because he continued the program to help remove these toxins from his body and therefore didn't get as sick.

Ted was so impressed by the results and the better understanding of his body that he developed, that after graduating from the university he enrolled in Bastyr University and eventually graduated as a naturopathic doctor!

An Interesting Case of Pesticide Poisoning

Originally published by detoxification specialist Dr. William Rea, a leading clinician and researcher in environmental medicine, is an interesting case study of a 41-year-old, white, female nurse who developed inexplicable severe spasming of her muscles; spasming of the blood vessels supplying her heart (causing angina) and legs (causing pain and cramping); and low levels of T lymphocytes in her blood. Dr. Rea placed her in an environmental control unit (a special totally clean room with purified air, water, and food) for elimination of all toxins and allergens. This resulted in alleviation of her muscle cramps and artery spasms and her T lymphocytes increased.

She was then experimentally exposed to a pesticide. All her vascular and muscle spasm problems, including angina, returned and her T-lymphocyte count decreased by 19%. Her arterial spasming reaction was so severe, Dr. Rea couldn't even find a pulse in her legs. It took another four days on a pesticide-

free diet, pure water, and a clean atmosphere for her symptoms to resolve and her T cells to return to normal.[2]

The Case That Introduced Me to Naturopathic Medicine

When I first came to Seattle, I got a job working as a research associate in the Department of Rheumatology of the University of Washington School of Medicine. I really enjoyed research and couldn't imagine a much better job than working together with M.D.s and Ph.D.s looking for a cure for rheumatoid arthritis.

Then came an event that changed my life forever. The woman who married my college roommate was cured of her juvenile rheumatoid arthritis by someone called a naturopathic doctor. I was stunned! How could this unknown practitioner "cure" my friend of an incurable disease from which she had suffered for over a decade? I "knew" rheumatoid arthritis was incurable since tens of millions of dollars were being spent nationwide looking for a cure for this disease, which afflicted 3% of the population.

I decided to visit this doctor and ask him what he had done. He offhandedly remarked, "Oh, I just detoxified her liver." Weird! But the more we talked, the more I came to appreciate a different way of thinking about patients and disease. I came to understand that the root cause of many chronic conditions is an overburdened, undernourished liver. What did this naturopathic doctor do for my friend's wife? Read on . . .

How the Detoxification System Works

The body eliminates toxins either by directly neutralizing them or by excreting them in the urine or feces (and to a lesser degree from the lungs and skin). Toxins that the body is unable to eliminate build up in the tissues, typically in our fat stores. The intestines, liver, and kidneys are the primary organs of detoxification (see Table 5-1).

Naturally occurring dietary toxins and contaminants, environmental chemicals (such as tobacco products, drugs, pesticides, food coloring, and food additives), and mutagens (derived from cooking, excess hormones in meat, and invading microbes) pose a serious threat to health. Enzymes in healthful intestinal bacteria and the cells lining the intestine transform many of these chemicals, either into immediately harmless metabolites or into even more toxic substances, which are then shunted to the liver where they are disarmed. About 25% of detoxification occurs within the cells lining the intestine; the remainder occurs in the liver.

The Liver

The liver is a complex organ that plays a key role in most metabolic processes, especially detoxification. To a very large extent, our health and vitality are

Table 5-1 Major Detoxification Systems

Organ	*Method*	*Typical Toxin Neutralized*
Skin	Excretion through sweat	Fat-soluble toxins such as DDT, heavy metals such as lead
Liver	Filtering of the blood	Bacteria and bacterial products, immune complexes
	Bile secretion	Cholesterol, hemoglobin breakdown products, extra calcium
	Phase I detoxification	Many prescription drugs (e.g., amphetamine, digitalis, pentobarbital), many over-the-counter drugs (acetaminophen, ibuprofen), caffeine, histamine, hormones (both internally produced and externally supplied), benzopyrene (carcinogen from charcoal-broiled meat), aniline (the yellow dyes), carbon tetrachloride, insecticides (e.g., Aldrin, Heptachlor), arachidonic acid (from animal fats)
	Phase II detoxification:	
	Glutathione conjugation	Acetaminophen, nicotine from cigarette smoke, organophosphates (insecticides), epoxides (carcinogens)
	Amino acid conjugation	Benzoate (a common food preservative), aspirin
	Methylation	Dopamine (neurotransmitter), epinephrine (hormone from adrenal gland), histamine, thiouracil (cancer drug)
	Sulfation	Estrogen, aniline dyes, coumarin (blood thinner), acetaminophen, methyl-dopa (used for Parkinson's disease)
	Acetylation	Sulfonamides (antibiotics), mescaline
	Glucuronidation	Acetaminophen, morphine, diazepam (sedative, muscle relaxant), digitalis
	Sulfoxidation	Sulfites, garlic compounds
Intestines	Mucosal detoxification	Toxins from bowel bacteria
	Excretion through feces	Fat-soluble toxins excreted in the bile
Kidneys	Excretion through urine	Many toxins after they are made water-soluble by the liver

determined by the health and vitality of our liver. The liver is constantly bombarded with toxic chemicals, both those produced internally and those coming from the environment. The metabolic processes that make our bodies run normally produce a wide range of toxins for which the liver has evolved efficient neutralizing mechanisms. However, the level and type of internally produced

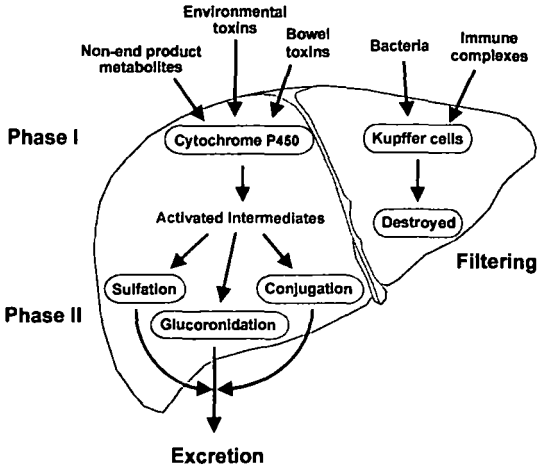

Figure 5-1 The Liver's Detoxification Pathways

toxins increases greatly when metabolic processes go awry, typically as a result of nutritional deficiencies.

Many of the toxic chemicals the liver must detoxify come from our environment: the content of our bowel, the food we eat, the water we drink, and the air we breathe. The polycyclic hydrocarbons (e.g., DDT; dioxin; 2,4,5-T; 2,4-D; PCB; and PCP), which are components of various herbicides and pesticides, are one example. Yet, as mentioned above, even those eating unprocessed organic foods need an effective detoxification system because even organically grown foods contain naturally occurring toxic constituents.

The liver plays several roles in detoxification: It filters the blood to remove large toxins, synthesizes and secretes bile full of cholesterol and other fat-soluble toxins, and enzymatically disassembles unwanted chemicals. This enzymatic process usually occurs in two steps referred to as Phase I and Phase II, with Phase I chemically modifying the chemicals to make them an easier target for one or more of the several Phase II enzyme systems. These processes are summarized in Figure 5-1.

Having an effective detoxification system is absolutely necessary for everyday health and prevention of chronic disease. For example, many diseases—including cancer, the autoimmune disorders (e.g., lupus erythematosis and rheumatoid arthritis), neurological disorders (e.g., Alzheimer's disease, Parkinson's disease), and the impairment of the immune system seen with aging—have been shown to be linked to a poorly functioning liver detoxification system.[3]

Proper functioning of the liver's detoxification systems is especially important for the prevention of cancer. Up to 90% of all cancers are thought to be due to the effects of environmental carcinogens, such as those in cigarette smoke, food, water, and air, combined with deficiencies of the nutrients the

body needs for proper functioning of the detoxification and immune systems. Our levels of exposure to environmental carcinogens varies widely as does the efficiency of our detoxification enzymes. High levels of exposure to carcinogens coupled with sluggish detoxification enzymes significantly increases our susceptibility to cancer.

The link between our detoxification system's effectiveness and our susceptibility to environmental toxins, such as carcinogens, is exemplified in a study of Turin, Italy chemical plant workers who had an unusually high rate of bladder cancer. When the liver detoxification enzyme activity of all the workers was tested, those with the poorest detoxification system were the ones who developed bladder cancer.[4] In other words, all were exposed to the same level of carcinogens, but those with poor liver function were the ones who developed the cancer.

Fortunately, the detoxification efficiency of the liver can be improved with special nutrients and herbs, as I'll discuss later this chapter. Ultimately, your best protection from cancer is to avoid carcinogens and make sure your detoxification system is working well in order to eliminate those you can't avoid before they can hurt you.

Filtering the Blood

Almost two quarts of blood pass through the liver every minute for detoxification. Filtration of toxins is absolutely critical for the blood from the intestines because it is loaded with bacteria, endotoxins (toxins released when bacteria die and are broken down), antigen-antibody complexes (large molecules produced when the immune system latches on to an invader to neutralize it), and various other toxic substances.

This filtration is accomplished by Kupffer cells along with liver cells called hepatocytes. Together, these special cells, *when working properly*, clear 99% of the bacteria and other toxins from the portal blood before it is allowed to reenter the general circulation.[5] The Kupffer cells are macrophages just like those found in the blood, except that they stay in the liver. High-speed motion pictures of the Kupffer cells show them engulfing bacteria in the portal vein in less than 0.01 seconds after contact. A very effective system! Immune complexes and large macro-molecular bacterial products are engulfed and destroyed by the Kupffer cells, while smaller molecules are taken up and transported to the bile by the hepatocytes. It appears that the Kupffer cells don't react to foreign proteins (antigens) in the blood by forming antibodies like some other white cells—they engulf and destroy them instead. This helps prevent us from over-reacting to antigens, such as food particles, absorbed from the gut, which could result in developing food allergies.[6]

When the liver is damaged, this filtration system breaks down. For example, patients with liver disease, especially chronic active hepatitis, have significantly increased levels of antibodies to *E. coli*, *Bacteroides*, and dietary proteins.[7] These

findings suggest that a diseased liver is unable to adequately eliminate the antigens absorbed from the gut, thus allowing them entry into the systemic circulation, where they then provoke an immune system response. When the immune system's alarms are set off constantly, the result is excessive antibody formation and constant inflammation, which disrupts normal metabolic processes and leads to disease.

If the diet is low in antioxidants, the Kupffer cells can be a source of inflammation themselves since, when they come into contact with toxins from the intestines and other sources, they release inflammatory chemicals and free radicals as a side effect of their detoxification processes. These free radicals are used by the Kupffer cells as weapons but must be neutralized by antioxidants after they destroy the toxins or they can damage the liver.

The Bile

The liver's second detoxification process involves the synthesis and secretion of bile. Each day the liver manufactures approximately one quart of bile, which serves as a carrier in which many toxic substances are effectively eliminated from the body. Sent to the intestines, the bile and its toxic load are absorbed by fiber and excreted. However, a diet low in fiber means these toxins are not bound in the feces very well and are reabsorbed. Even worse, bacteria in the intestine often modify these toxins so that they become even more damaging.

The bile is also the major route for excretion of cholesterol and excess calcium. Besides eliminating unwanted toxins, the bile emulsifies fats and fat-soluble vitamins in the intestine, improving their absorption.

Phase I Detoxification

The liver's third role in detoxification involves a two-step enzymatic process for the neutralization of unwanted chemical compounds. These include not only drugs, pesticides, and toxins from the gut, but also normal body chemicals—such as hormones and inflammatory chemicals (e.g., histamine)—which if allowed to build up would be toxic. Phase I enzymes directly neutralize some chemicals, but many others are converted to intermediate forms that are then processed by Phase II enzymes.[8] Unfortunately, these intermediate forms are often much more chemically active and therefore more toxic, so if the Phase II detoxification systems aren't working adequately, these intermediates hang around and are far more damaging.

Phase I detoxification of most xenobiotics (toxins) involves a group of enzymes called mixed function oxidative enzymes, which, collectively, have been named cytochrome P450. Some 50 to 100 enzymes make up the cytochrome P450 system. Each enzyme works best in detoxifying certain types of chemicals, but with considerable overlap in activity among the enzymes. In

other words, they all metabolize the same chemicals, but with differing levels of efficiency. This fail-safe system ensures maximum detoxification.

The activity of the various cytochrome P450 enzymes varies significantly from one individual to another based on genetics, the individual's level of exposure to chemical toxins, and his or her nutritional status. Since the activity of cytochrome P450 varies so much, so does an individual's risk for various diseases. For example, as highlighted in the study of chemical plant workers in Turin, Italy discussed above, those with underactive cytochrome P450 are more susceptible to carcinogens.[9] This variability of cytochrome P450 enzymes is also seen in the variability of people's ability to detoxify the carcinogens found in cigarette smoke and helps to explain why some people can smoke with seemingly impunity, while others develop lung cancer after only a few decades of smoking. Those who develop cancer are typically those who are exposed to a lot of carcinogens and/or those whose cytochrome P450 isn't working very well.

The level of activity of Phase I detoxification varies greatly, even among healthy adults. One way of determining the activity of Phase I is to measure how efficiently a person detoxifies caffeine. Using this test, researchers have found a surprising five-fold difference in the detoxification rates of apparently healthy adults![10]

When cytochrome P450 metabolizes a xenobiotic, it tries to either chemically transform it to a less toxic form, make it water-soluble, or convert it to a more chemically active form. The best result is the first option, i.e., simply neutralizing the toxin. This is what happens to caffeine. Making a toxin water-soluble is also effective because this makes it easier for the kidneys to excrete it in the urine. The final option is to transform the xenobiotic to more chemically reactive forms, which are more easily metabolized by the Phase II enzymes. While ultimately very important for our health, this transformation of xenobiotics into more chemically active toxins can cause several problems.

A significant side effect of all this metabolic activity is the production of free radicals as xenobiotics are transformed. In other words, for each xenobiotic metabolized by Phase I, a free radical is generated. As discussed more fully below, free radicals are extremely damaging. Without adequate free radical defenses, every time the liver neutralizes a toxin, it is damaged by the free radicals produced.

This is how poisonous mushrooms damage the liver: the liver produces so many free radicals while neutralizing the mushroom's poisons that the liver cells are overwhelmed and destroyed in the process. The damage can be so extensive that the majority of the liver is destroyed, which is why people can die from eating poisonous mushrooms. These damaging free radicals are also produced whenever we eat a food to which we are allergic. This powerfully demonstrates the crucial importance of adequate levels of antioxidants to the liver.

The most important antioxidant for neutralizing the free radicals produced as Phase I by-products is the sulfur-containing peptide, glutathione. In the process of neutralizing free radicals, however, glutathione (GSH) is oxidized to

Table 5-2 Nutrients Needed by Phase I Detoxification

Copper	Vitamin C
Magnesium (deficiency substantially increases toxicity of many drugs)[11]	Vitamins B_2, B_3, B_6, B_{12}
Zinc	Folic acid
	Flavanoids

glutathione disulfide (GSSG). Glutathione is required for one of the Phase II detoxification processes, glutathione conjugation. When high levels of toxin exposure produce so many free radicals from Phase I detoxification that all the glutathione is used up, Phase II glutathione conjugation stops working.

Another potential problem occurs because the toxins transformed into "activated intermediates" by Phase I are far more toxic. Some, for example, become carcinogens that can bind to DNA and proteins. Unless quickly removed from the body by Phase II detoxification mechanisms, they can cause widespread problems. Therefore, the rate at which Phase I produces activated intermediates must be balanced by the rate at which Phase II finishes their processing. Unfortunately, some people have a very active Phase I detoxification system but very slow or inactive Phase II enzymes. These people are described as "pathological detoxifiers" because their overactive Phase I results in a build-up of the more harmful intermediate products, which Phase II cannot disarm quickly enough. The end result is that these people suffer severe toxic reactions to environmental poisons.

An imbalance between Phase I and Phase II can also occur when a person is exposed to large amounts of toxins or exposed to lower levels of toxins for a long period of time. In these situations, so many toxins are being neutralized that the critical nutrients needed for Phase II detoxification get used up, which allows the highly toxic activated intermediates to build up.

Recent research shows that cytochrome P450 enzyme systems are found in other parts of the body, especially the brain cells. Inadequate antioxidants and nutrients in the brain result in an increased rate of neuron damage, such as seen in Alzheimer's and Parkinson's disease patients.

As with all enzymes, the cytochrome P450s require several nutrients, listed in Table 5-2, in order to function. A deficiency of any of these means more toxins floating around doing damage.

A considerable amount of research has found that various substances activate cytochrome P450 (see Table 5-3) while other substances inhibit it (see Table 5-4).

Inducers of Phase I detoxification

Cytochrome P450 is induced by some toxins and by some foods and nutrients. Obviously, it is beneficial to improve Phase I detoxification in order to get rid of the toxins as soon as possible. This is best accomplished by providing the

Table 5-3 Substances That Activate Phase I Detoxification

Drugs	Alcohol
	Nicotine in cigarette smoke
	Phenobarbital
	Sulfonamides
	Steroids
Foods	Cabbage, broccoli, and brussels sprouts
	Charcoal-broiled meats (due to their high levels of toxic compounds)
	High-protein diet
	Oranges and tangerines (but *not* grapefruits)
Nutrients	Niacin
	Vitamin B_1 (riboflavin)
	Vitamin C
Herbs	Sassafras (probably due to toxic constituents)
	Caraway and dill seeds
Environmental toxins	Carbon tetrachloride
	Exhaust fumes
	Paint fumes
	Dioxin
	Pesticides

needed nutrients and non-toxic stimulants while avoiding those substances that are toxic. However, stimulation of Phase I is *not* a good idea if your Phase II systems aren't ready to finish the job or if you are a pathological detoxifier.

All of the drugs and environmental toxins listed in Table 5-3 activate P450 to combat their destructive effects, and in so doing, not only use up compounds needed for this detoxification system but contribute significantly to free radical formation and oxidative stress.

Among foods, the brassica family, i.e., cabbage, broccoli, and brussels sprouts, contains chemical constituents that stimulate both Phase I and Phase II detoxification enzymes. One such compound is a combination of vitamin C with a chemical called indole-3-carbinol. It is a very active stimulant of detoxifying enzymes in the gut as well as the liver.[12] The net result is significant protection against several toxins, especially carcinogens. This helps explain the inverse correlation between cancer incidence and brassica vegetable consumption.

Oranges and tangerines (as well as the seeds of caraway and dill) contain limonene, a phytochemical that has been found to prevent and even treat cancer in animal models. Limonene's protective effects are probably due to the fact that it is a strong inducer of both Phase I and Phase II detoxification enzymes that neutralize carcinogens. However, limonene's promotion of regression of breast cancer in rats may also be due to its stimulation of cells to revert to more normal forms by some as yet unknown mechanism.[13]

Table 5-4 Inhibitors of Phase I Detoxification

Drugs	Benzodiazapine antidepressants (e.g., Centrax, Librium, Prozac, Valium, etc.)
	Antihistamines (used for allergies)
	Cimetidine and other stomach-acid secretion blocking drugs (used for stomach ulcers)
	Ketoconazole
	Sulfaphenazole
Foods	Naringenin from grapefruit juice
	Curcumin from the spice turmeric
	Capsaicin from red chili pepper
	Eugenol from clove oil
Other	Aging
	Toxins from inappropriate bacteria in the intestines

Inhibitors of Phase I detoxification

Many substances inhibit cytochrome P450, making toxins more damaging because they remain in the body longer before detoxification. For example, if you are taking drugs or are exposed to elevated levels of toxins, *don't* eat grapefruits or drink grapefruit juice. Grapefruit juice decreases the rate of elimination of drugs, such as cyclosporin (a drug used to suppress the immune system after organ transplants), from the blood.[14] One research study found that after drinking just 8 oz of grapefruit juice a day, six of fourteen healthy adults were found to have a greater than 50% increase in their blood cyclosporin levels compared to when they just drank water! Further research found that a compound in the grapefruit juice, called naringenin, decreased their cytochrome P450 activity by a remarkable 30%. The common inhibitors of Phase I detoxification are listed in Table 5-4.

Curcumin, the compound that gives turmeric its yellow color, is interesting because it inhibits Phase I while stimulating Phase II. This turns out to be useful for preventing cancer. Curcumin has been found to inhibit carcinogens, such as benzopyrene (the carcinogen found in charcoal-broiled meat), from inducing cancer in several animal models. It appears that the curcumin exerts its anticarcinogenic activity by lowering the activation of carcinogens while increasing the detoxification of those that are activated. Curcumin has also been shown to directly inhibit the growth of cancer cells.[15]

Although I've not found any research that has tested this idea clinically, it seems to me that those who smoke should eat lots of curries. This might help because most of the cancer-inducing chemicals in cigarette smoke are only carcinogenic during the period between activation by Phase I and final detoxification by Phase II.

The Phase I detoxification enzymes are less active in old age. (Interestingly, aging has a much smaller effect on Phase II enzymes.) Aging also decreases

blood flow though the liver, further aggravating the problem. Lack of the physical activity necessary for good circulation combined with the poor nutrition commonly seen in the elderly add up to a significant impairment of detoxification capacity, which is typically found in aging individuals. This helps to explain why toxic reactions to drugs are seen so commonly in the elderly—they are unable to eliminate them fast enough, so toxic levels build up.

To ensure Phase I is working well: Eat plenty of brassica family foods (cabbage, broccoli, and brussels sprouts), B-vitamin rich foods (nutritional yeast, whole grains), vitamin-C rich foods (peppers, cabbage, and tomatoes) and citrus foods (oranges and tangerines, but not grapefruits).

Phase II Detoxification

Unlike Phase I detoxification, which essentially involves oxidizing the toxin, Phase II typically involves a process called conjugation, in which various enzymes in the liver attach small chemicals to the xenobiotic. This either neutralizes it or makes it more easily excreted through the urine or bile. Phase II enzymes act on some xenobiotics directly, while others must first be activated by the Phase I enzymes. There are essentially six Phase II detoxification pathways: glutathione conjugation, amino acid conjugation, methylation, sulfation, acetylation, and glucuronidation. Table 5-1 provides examples of toxins neutralized by each of these pathways. The astute reader will notice that some toxins are neutralized through several pathways. This is not uncommon, although usually only one pathway will do the majority of the work.

In order to work, these enzyme systems need nutrients both for their activation and to provide the small molecules they add to the toxins. In addition, they need metabolic energy to function and to synthesize some of the small conjugating molecules. If the liver cell's energy producing plants, the mitochondria, are not functioning properly (which can be caused by a magnesium deficiency or lack of exercise), Phase II detoxification slows down, allowing the build-up of toxic intermediates. Table 5-5 lists the key nutrients needed by each of the six Phase II detoxification systems. Table 5-6 lists the inducers and Table 5-7 the inhibitors of Phase II enzymes.

Table 5-5 Nutrients Needed by Phase II Detoxification Enzymes

Phase II System	*Required Nutrients*
Glutathione conjugation	Glutathione, vitamin B_6
Amino acid conjugation	Glycine
Methylation	S-adenosyl-methionine
Sulfation	Cysteine, methionine, molybdenum
Acetylation	Acetyl-CoA
Glucuronidation	Glucuronic acid

Table 5-6 Inducers of Phase II Detoxification Enzymes[12,16]

Phase II System	*Inducer*
Glutathione conjugation	Brassica family foods (cabbage, broccoli, and brussels sprouts), limonene-containing foods (citrus peel, dill weed oil, and caraway oil)
Amino acid conjugation	Glycine
Methylation	Lipotropic nutrients (choline, methionine, betaine, folic acid, and vitamin B_{12})
Sulfation	Cysteine, methionine, taurine
Acetylation	None found
Glucuronidation	Fish oils, cigarette smoking, birth control pills, phenobarbital, limonene-containing foods

Glutathione conjugation

A primary detoxification route is the conjugation of glutathione (a tripeptide composed of three amino acids—cysteine, glutamic acid, and glycine). The liver enzyme glutathione S-transferase takes sulfur from glutathione and combines (conjugates) it with the toxic substance, making it water-soluble. This water-soluble form, called a mercaptate, is then excreted in the urine. In order to function, glutathione S-transferase needs plenty of glutathione.

Glutathione is also an important antioxidant in the cellular mitochondria, the energy production factories of the cell. Cellular mitochondrial glutathione is our main defense against free radicals produced as a by-product of cellular respiration, i.e., the production of energy in the cells from oxygen and fuel. In addition, glutathione is an important neutralizer of the free radicals produced when the liver neutralizes toxins through the Phase I pathway. Glutathione appears to be especially important in organs exposed to toxins, such as the liver, kidneys, lungs, and intestines. This combination of detoxification and free radical protection results in glutathione being one of the most important

Table 5-7 Inhibitors of Phase II Detoxification Enzymes

Phase II System	*Inhibitor*
Glutathione conjugation	Selenium deficiency, vitamin B_2 deficiency, glutathione deficiency, zinc deficiency
Amino acid conjugation	Low protein diet
Methylation	Folic acid or vitamin B_{12} deficiency
Sulfation	Nonsteroidal anti-inflammatory drugs (e.g., aspirin), tartrazine (yellow food dye), molybdenum deficiency
Acetylation	Vitamin B_2, B_5, or C deficiency
Glucuronidation	Aspirin, probenecid (a drug used to treat gout)

anticarcinogens and antioxidants in our cells, which means that a deficiency is devastating.[17]

When we are exposed to high levels of toxins, glutathione is used up faster than it can be produced or absorbed from the diet. We then become much more susceptible to toxin-induced diseases, such as cancer, especially if our Phase I detoxification system is highly active.[18]

For example, throat cancer is very high in women in northern Iran. These women have been found to consume large amounts of alcohol and foods contaminated with fungal toxins, while their consumption of fruits and vegetables is very low. This results in increased levels of exposure to activated carcinogens since the alcohol activates Phase I detoxification (increasing the production of activated carcinogens from fungal toxins) and the lack of vitamin C and other important micronutrients results in lowered activity of Phase II, which delays the final neutralization of the activated carcinogens. Finally, the lack of antioxidants results in additional damage from the increased levels of free radicals produced by the activated Phase I system.[19]

Similar detoxification problems are seen in those who consume large amounts of alcohol and are exposed to pesticides. The alcohol increases the rate of formation of activated intermediates from the pesticides by Phase I, but the depletion of glutathione means these toxins hang around longer and more free radicals are released, causing more damage, this time to the liver, brain, and nervous system.[20]

Disease states due to glutathione deficiency are not uncommon. A deficiency can be induced either by diseases that increase the need for glutathione, deficiencies of the nutrients needed for synthesis, or diseases that inhibit its formation. For example, people with idiopathic pulmonary fibrosis, adult respiratory distress syndrome, HIV infection, hepatic cirrhosis, cataract formation, and advanced AIDS have been found to have a deficiency of glutathione, probably due to their greatly increased need for glutathione, both as an antioxidant and for detoxification.[21] Smoking increases the rate of utilization of glutathione, both in the detoxification of nicotine and in the neutralization of free radicals produced by the toxins in the smoke.

Glutathione is available through two routes: diet and synthesis. Dietary glutathione (found in fresh fruits and vegetables, cooked fish, and meat) is absorbed well by the intestines and does not appear to be affected by the digestive processes. Besides supporting Phase II detoxification, dietary glutathione appears to also detoxify substances in the intestines before they can be absorbed into the bloodstream. Dietary glutathione whether in foods or from supplements, appears to be efficiently absorbed into the blood.[22]

The body also synthesizes glutathione. Some substances, such as N-acetylcysteine (NAC), glycine, and methionine, help increase the synthesis of glutathione. Supplementation with N-acetylcysteine not only raises liver levels of glutathione, but also mitochondrial levels of this important antioxidant. Supplementation with large oral and large intravenous dosages of NAC has been

used to successfully treat the liver damage caused by drug overdoses, such as happens when large amounts of acetaminophen are taken along with alcohol. N-acetylcysteine has also been shown to help decrease the toxicity of chemotherapeutic drugs used to treat cancer.[23] People with liver disorders, such as cirrhosis, aren't as able to synthesize glutathione, which probably explains why their levels are 30% below normal.[24] A deficiency of vitamin B_6 also results in decreased production of glutathione.

Fresh fruits and vegetables contain 25 to 750 mg of glutathione per pound. Similar quantities are found in cooked meats and fish. However, commercially prepared foods, dairy products (milk has none), most cereals, legumes, and nuts have little glutathione. Among processed foods, frozen foods generally retain their glutathione content. While beer contains moderate amounts of glutathione, it is used up when the body detoxifies the alcohol also in beer. Meat contains a considerable amount of methionine, which the body can convert to glutathione.[25] Longevity has been increased in animals fed cysteine, which increases glutathione synthesis. This is an important observation because studies show that large segments of the elderly have low glutathione levels.[26]

When you are exposed to high levels of xenobiotics, carcinogens, or oxidants, eating glutathione-rich foods and supplementation is especially helpful. Oral supplementation of glutathione for maintenance and antioxidant protection ranges from 100 to 500 mg per day for antioxidant support.[27] Detoxification protocols call for somewhat higher intakes.[28]

To ensure that glutathione conjugation is working well: Eat plenty of glutathione-rich foods (i.e., asparagus, avocado, and walnuts), brassica family foods (cabbage, broccoli, brussels sprouts) and limonene-rich foods (orange peel oil, dill and caraway seeds), which stimulate glutathione conjugation.

Amino acid conjugation

Several amino acids (glycine, taurine, glutamine, arginine, and ornithine) are used to combine with and neutralize xenobiotics. Of these, glycine is the most commonly utilized in Phase II amino acid detoxification. People suffering from hepatitis, alcoholic liver disorders, carcinomas, chronic arthritis, hypothyroidism, toxemia of pregnancy, and excessive chemical exposure are commonly found to have a poorly functioning amino acid conjugation system. For example, using the benzoate clearance test (a measure of the rate at which the body detoxifies benzoate by conjugating it with glycine to form hippuric acid, which is excreted by the kidneys), the rate of clearance is half in those with liver disease compared to healthy adults. This means that in those with liver disease, all the toxins requiring this pathway stay in the body doing damage almost twice as long.[29]

Even in apparently normal adults, a wide variation exists in the activity of the glycine conjugation pathway. This is due not only to genetic variation, but also to the availability of glycine in the liver. Glycine and the other amino

acids used for conjugation become deficient on a low-protein diet and when chronic exposure to toxins results in depletion.

To ensure that amino acid conjugation is working well: Eat adequate amounts of protein-rich foods.

Methylation

Methylation involves conjugating methyl groups to xenobiotics. Most of the methyl groups used for detoxification come from S-adenosylmethionine (SAM). SAM is synthesized from the amino acid methionine. This synthesis requires the nutrients choline, vitamin B_{12}, and folic acid.

SAM is able to inactivate estrogens (through methylation), supporting the use of methionine in conditions of presumed estrogen excess, such as PMS. Its effects in preventing estrogen-induced cholestasis (stagnation of bile in the gall bladder) have been demonstrated in pregnant women and those on oral contraceptives.[30] In addition to its role in promoting estrogen excretion, methionine has been shown to increase the membrane fluidity that is typically decreased by estrogens, thereby restoring several factors that promote bile flow. Methionine also promotes the flow of lipids to and from the liver in humans. Methionine is a major source of numerous sulfur-containing compounds, including the amino acids, cysteine, and taurine.

To ensure that methylation is working adequately: Eat foods rich in choline (lecithin, eggs), folic acid (green leafy vegetables), and vitamin B_{12} (animal products or supplements). (Methionine deficiency is not likely to be a problem because it is widely available in the diet.)

Sulfation

Sulfation is the conjugation of xenobiotics that have been bioactivated by the Phase I system with sulfur-containing compounds. The sulfation system is important for detoxifying several drugs, food additives, and, especially, toxins from intestinal bacteria and the environment.

The enzyme that catalyzes sulfation is called sulfotransferase. Sulfation, like the other Phase II detoxification systems, results in decreased toxicity and increased water solubility of toxins, making it easier for them to be excreted in the urine or sometimes the bile. Sulfation is also used to detoxify some normal body chemicals and is the main way we eliminate steroid hormones (such as estrogen) and thyroid hormones so that they don't build up to damaging levels. Since sulfation is also the primary route for the elimination of neurotransmitters, dysfunction in this system may contribute to the development of some neurological disorders.

The sulfate used for sulfation comes from the amino acid cysteine, through several steps, a crucial one of which is called sulfoxidation. Sulfoxidation (discussed below) requires the trace mineral molybdenum to function properly. Cysteine is available from the diet and can be synthesized from the amino acid methionine.

Many factors influence the activity of sulfate conjugation. For example, the diet needs adequate amounts of methionine and cysteine. A diet low in these amino acids has been shown to reduce the sulfation of acetaminophen—one of the pathways by which the body eliminates this commonly used over-the-counter drug.[31] Sulfation is also reduced by excessive levels of molybdenum (too little molybdenum inhibits sulfoxidation while too much inhibits sulfation) and excessive amounts of vitamin B_6 (over about 100 mg per day).[32] In some cases, sulfation can be increased by supplemental sulfate, extra amounts of sulfur-containing foods in the diet, and the amino acids taurine and glutathione.

To ensure that sulfation is working adequately: Consume adequate amounts of sulfur-containing foods, i.e., egg yolks, red peppers, garlic, onions, broccoli, and brussels sprouts.

Acetylation

Conjugation of xenobiotics with acetyl CoA is the method by which the body eliminates sulfa drugs (commonly used antibiotics for urinary tract infections). This system appears to be especially sensitive to genetic variation, with those having a poor acetylation system being far more susceptible to toxic reactions from such drugs as isoniazid (used to treat tuberculosis), p-aminosalicylic acid (used to treat tuberculosis), and the hallucinogenic mescaline. These slow acetylators suffer neurological damage when they take anti-tuberculosis drugs. While not much is known about how to directly improve activity of this system, it is known that acetylation is dependent on riboflavin (vitamin B_2), pantothenic acid (B_5), and vitamin C.[33]

To ensure that acetylation is working adequately: Eat foods rich in B vitamins (yeast, whole grains) and vitamin C (peppers, cabbage, citrus fruits).

Glucuronidation

Glucuronidation, the combining of glucuronic acid with xenobiotics, requires the enzyme UDP-glucuronyl transferase (UDPGT). Many of the commonly prescribed drugs are detoxified through this important pathway. It also helps to detoxify aspirin, menthol, vanillin (synthetic vanilla), food additives such as benzoates, and some hormones. Glucuronidation appears to work well in most of us and doesn't seem to require special attention, except for those with Gilbert's disease.

A surprising 5 to 7% of us have a genetically weak UDPGT resulting in Gilbert's disease. Those with this genetic weakness are far more susceptible to toxic effects from drugs, environmental toxins, and some normal metabolic products. The main way this condition is recognized is by a slight yellowish tinge to the skin and white of the eye due to inadequate metabolism of bilirubin, a breakdown product of hemoglobin. Gilbert's Syndrome is discussed under How to Treat Common Toxicity Diseases, page 156.

The activity of UDPGT is increased by foods rich in a monoterpene called limonene (citrus peel, dill weed seeds, and caraway seeds). Eating these foods not only improves glucuronidation but has also been shown to protect us from chemical carcinogens. Several studies in animals have shown that limonene not only prevents experimental cancer but even reverses it. One study in rats found a remarkable complete regression of tumors in 90% of the animals after just one to six weeks![34]

To ensure that glucuronidation is working adequately: See Gilbert's Syndrome, page 156.

Sulfoxidation

Sulfoxidation is the process by which the sulfur-containing molecules in drugs (such as chlorpromazine, a tranquilizer) and foods (such as garlic) are metabolized. It is also the process by which the body eliminates sulfite food additives used to preserve foods and drugs. Various sulfites are widely used in potato salad (as a preservative), salad bars (to keep the vegetable looking fresh), dried fruits (sulfites keep dried apricots orange), and in some drugs (such as those used in asthma). Normally, the enzyme sulfite oxidase metabolizes sulfites to safer sulfates, which are then excreted in the urine. Those with a poorly functioning sulfoxidation system, however, have an increased ratio of sulfite to sulfate in their urine.

When the sulfoxidation detoxification pathway isn't working very well, people become sensitive to sulfur-containing drugs and foods containing sulfur or sulfite additives. This is especially important for asthmatics, who can react to these additives with life-threatening attacks. Interestingly, until recently, the inhalers used by asthmatics during attacks actually had sulfite preservatives mixed with the anti-spasmotic drugs!

Dr. Jonathan Wright, one of the leading holistic medical doctors in the country, discovered several years ago that providing molybdenum to asthmatics with an elevated ratio of sulfites to sulfates in their urine resulted in a significant improvement in their condition. Molybdenum helps because sulfite oxidase is dependent upon this trace mineral. Although most nutrition textbooks believe it to be an uncommon deficiency, an Austrian study of 1,750 patients found that 41.5% were molybdenum deficient.[35]

To ensure that sulfoxidation is working adequately: Eat foods rich in molybdenum (dairy products, beans, whole grains).

Example of How a Common Chemical Is Detoxified

Many people freely use acetaminophen for the relief of pain and inflammation. It is clinically effective and, in most circumstances, relatively non-toxic when the liver's detoxification processes are working properly. It is an interesting

example of how the liver detoxifies drugs, since it can be metabolized through several pathways as shown in Figure 5-2. Normally, most acetaminophen is first bioactivated by the Phase I detoxification system. This is followed primarily by Phase II conjugation with glutathione, resulting in a water-soluble mercaptate that is easily excreted via the urine. A small amount of the activated acetaminophen is neutralized directly by Phase II conjugation with either sulfate or glucuronic acid, again for excretion from the kidneys. For most of us, these overlapping detoxification pathways work just fine.

However, if the Phase II glucuronidation pathway isn't working adequately, an activated intermediate builds up and again cycles through at Phase I where it is further bioactivated to a compound called N-acetyl-*p*-benzoquinoneimine (NAPQI). NAPQI is extremely toxic to the liver. The production of NAPQI occurs when liver glutathione reserves are depleted, so Phase II neutralization of the activated intermediates either doesn't occur, or occurs too slowly. As discussed above, liver glutathione reserves are decreased by exposure to high levels of xenobiotics, alcohol, fasting, and poor nutritional status. Glutathione depletion may also be caused by taking large amounts of acetaminophen over long periods of time.[36]

This highlights a crucial concept: Multiple pathways can be used for the detoxification of most xenobiotics. However, for most substances, there is an optimal detoxification process, which eliminates each toxin as rapidly and safely as possible. When the optimal pathway is not working properly, a less effective pathway is used instead. This can result in a toxin staying in the body longer, incomplete detoxification, or production of even more toxic forms. The end result is increased damage and chronic draining of our health and vitality.

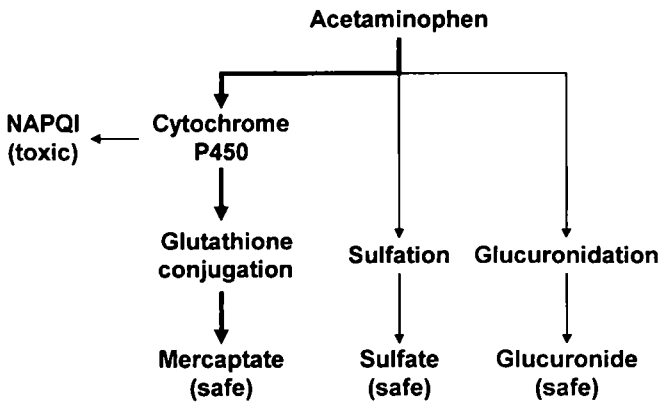

Figure 5-2 The Detoxification of Acetaminophen

How to Recognize Dysfunctional Liver Detoxification Systems

The term "sluggish liver" is an old naturopathic concept indicating an impairment of liver detoxification function. Because of the liver's important role in detoxification, however, even minor impairment of liver function can have profound effects. Liver function can be impaired by excessive exposure to toxins (discussed in the next section), by poor production and excretion of bile, and by inadequate functioning of detoxification enzymes due either to nutritional deficiencies or genetic weakness.

Poor Bile Flow

Once the liver has modified a toxin, it needs to be eliminated from the body as soon as possible. However, when the excretion of bile is inhibited (a condition called cholestasis), toxins stay in the liver longer. Cholestasis has several causes, including obstruction of the bile ducts and impairment of bile flow within the liver. The most common cause of obstruction of the bile ducts is the presence of gallstones. Currently, it is conservatively estimated that 20 million people in the U.S. have gallstones. Nearly 20% of the female and 8% of the male population over the age of 40 are found to have gallstones on biopsy and approximately 500,000 gallbladders are removed because of stones each year in the U.S. The prevalence of gallstones in this country has been linked to the high-fat, low-fiber diet consumed by the majority of Americans.[37]

Impairment of bile flow within the liver can be caused by a variety of agents and conditions, as listed in Table 5-8. These conditions are often associated with alterations of liver function in laboratory tests (serum bilirubin, alkaline phosphatase, SGOT, LDH, GGTP, etc.) signifying cellular damage. However, relying on these tests alone to evaluate liver function is not adequate, since, in the initial or subclinical stages of many problems with liver function, laboratory values remain normal. Among the symptoms people with enzymatic damage may complain of are fatigue, general malaise, digestive disturbances, allergies and chemical sensitivities, premenstrual syndrome, and constipation.

Perhaps the most common cause of cholestasis and impaired liver function is alcohol ingestion. In some especially sensitive individuals, as little as 1 oz of alcohol can produce damage to the liver, which results in fat being deposited within the liver. All active alcoholics demonstrate fatty infiltration of the liver.

Methionine administered as SAM has been shown to be quite beneficial in treating two common causes of stagnation of bile in the liver—estrogen excess (due to either oral contraceptive use or pregnancy) and Gilbert's syndrome.[38]

Poor Enzyme Function

While sophisticated blood tests are necessary to prove a dysfunction of a specific liver detoxification system, several signs and symptoms can give us a good

Table 5-8 Causes of Cholestasis

Presence of gallstones
Alcohol
Endotoxins
Hereditary disorders such as Gilbert's syndrome
Hyperthyroidism or thyroxine supplementation
Viral hepatitis
Pregnancy
Certain chemicals or drugs:
Natural and synthetic steroidal hormones:
Anabolic steroids
Estrogens
Oral contraceptives
Aminosalicylic acid
Chlorothiazide
Erythromycin estolate
Mepazine
Phenylbutazone
Sulphadiazine
Thiouracil

idea of when our liver's detoxification systems are not functioning well or are overloaded. In general, anytime you have a bad reaction to a drug or environmental toxin you can be pretty sure there is a detoxification problem. Table 5-9 lists symptoms that are directly tied to a particular dysfunction.

The strong odor in the urine after eating asparagus (listed in Table 5-9) is an interesting phenomenon because while it is unheard of in China, 100% of the French have been estimated to experience such an odor (about 50% of adults in the U.S. notice this effect). This is an excellent example of genetic variability in liver detoxification function.

Toxins

Toxins bombard us from all directions: the water we drink, the food we eat, and the air we breathe, especially indoors. Even the normal metabolic processes of our bodies regularly produce toxins. As long as the levels of exposure aren't too high, and our detoxification processes are working the way they should, our health continues. Avoidance of toxins is one of the most effective ways to maintain and improve our health. This is true even when our detoxification systems are working well since we waste a lot of needed metabolic energy getting rid of these noxious substances, and their detoxification still causes some damage.

Table 5-9 Recognizing Dysfunctional Liver Detoxification Systems

Symptoms and Diseases	*System Most Likely Dysfunctional*
Adverse reactions to sulfite food additives (such as in commercial potato salad or salad bars)	Sulfoxidation
Alzheimer's disease	Sulfoxidation
Asthma reactions after eating at a restaurant	Sulfoxidation
Caffeine intolerance (even small amounts keep you awake at night)	Phase I
Chronic exposure to toxins	Phase II glutathione conjugation
Eating asparagus results in a strong urine odor	Sulfoxidation
Fasting	Phase II glutathione conjugation
Garlic makes you sick	Sulfoxidation
Gilbert's disease	Phase II glucuronidation
Intestinal toxicity	Phase II sulfation and amino acid conjugation
Liver disease	Phase II amino acid conjugation
Parkinson's disease	Phase I
Premenstrual syndrome	Phase II sulfation
Prostate cancer	Phase II sulfation
Rheumatoid arthritis	Sulfoxidation
Sulfites, such as in commercial potato salad or salad bars, make you feel ill	Sulfoxidation
Toxemia of pregnancy	Phase II amino acid conjugation
Yellow discoloration of eyes and skin, not due to hepatitis	Phase II glucuronidation
Rapid metabolism of caffeine (you can drink two cups of coffee and still sleep well at night)	Overactive Phase I

Table 5-10 lists key external and internal sources of toxins. For most of us, the most consistent source of toxins is an unhealthy intestine, which, technically, is outside of the body. The intestinal mucosa functions just like our skin, keeping the unwanted contents of the intestines out of our blood and tissues.

Intestinal Toxins

Our intestines have paradoxical functions: they are a digestive/absorptive organ as well as a barrier to toxic compounds and undigested food. The intestinal mucosal membranes accomplish their barrier function through a combination of mechanical exclusion and a specialized intestinal immune defense system. Elaborate immunological and mechanical mechanisms exclude potentially toxic constituents of the diet as well as allergenic food proteins, bacterial products, and infectious microbial organisms.[39,40]

Problems with the intestines basically occur in two ways: Excessive amounts of toxins in the intestines produce what is called a "toxic bowel," and

Table 5-10 Primary Causes of Toxicity

Source	*Adverse Effects*
Intestinal dysbiosis, i.e., excessive levels of toxin-producing bacteria combined with inadequate amounts of normal bacteria in the intestines; typically caused by the use of broad-spectrum antibiotics or the ingestion of contaminated foods	Bacterial metabolites form toxins; bacterial cell wall components cross-react with normal tissue proteins, disrupting their normal functioning and suppressing the immune system
Environmental pollutants	Poison enzyme systems, directly damage cells and tissues, displace needed nutrients
Free radicals	Destroy enzyme systems, punch holes in cell membranes, transform DNA to abnormal forms
Liver toxicity	Decreased metabolic control resulting in increased levels of circulating immune complexes

damage to the intestinal barrier allows both normal and toxic bowel constituents to leak into the body, a condition referred to as a "leaky gut."

The intestines contain numerous dietary and bacterial products, many of which are quite toxic if they enter the body. In the past, the gastrointestinal system was thought to be impermeable to bowel contents except for nutrients. We now know this is inaccurate.[41] Toxic bowel constituents can pass into the body, causing a wide range of damaging effects. In fact, many diseases are now known to be associated with, and possibly caused by, excessive gastrointestinal permeability (which is discussed more fully below).

The Toxic Bowel

Toxins from the bowel cause problems in many ways. First, many of them directly damage enzymes and tissues, including the brain and nervous system.[42] Second, when some of these xenobiotic substances are detoxified, they trigger the release of chemicals that cause inflammation. Third, the more toxins the body has to detoxify, the more the detoxification enzymes in the liver are activated, which results in increased free radical production. Finally, endotoxins from the gut bacteria activate the liver's Kupffer cells, causing a release of interleukin 2.

Interleukin 2 decreases the activity of the Phase I detoxification enzymes and depletes Phase II amino acid conjugation in the glutamine pathway. That is, a toxic bowel disrupts both Phase I and Phase II detoxification pathways. In other words, toxic bacteria in the intestines make us more susceptible to environmental and bowel toxins.

The gastrointestinal tract contains a large amount and variety of constituents of varying degrees of toxicity. The toxic constituents come from essentially three sources: food, food additives, and toxic bacteria. Even the average American diet contains significant amounts of toxins from normal constituents of foods and food additives. For example, meat (especially when fried or barbecued) contains heterocyclic compounds, which can be converted to carcinogens by normal gut microflora.[43] Pathogenic bacteria in the intestines directly produce toxins (called endotoxins), convert normal food constituents to toxic forms and, when they die, release their constituents into the bowel, which also can be damaging.

Intestinal Dysbiosis (Toxic Bacteria)

The gut microflora is large and varied. About 400 species have been isolated, with the number of microorganisms in the colon being estimated at 10^{10} to 10^{11} per gram of fecal material, suggesting that we have more microbial than human cells.[44] The metabolic processes of these bacteria produce many chemicals, some of which are harmful to the body.

Dysbiosis is defined as a disordered microbial ecology that causes disease. This state may exist in the oral cavity, gastrointestinal tract, or vaginal cavity. In dysbiosis, organisms that do not normally cause infection, including bacteria, yeasts, and protozoa, induce disease by producing toxins or altering the nutrition or immune responses of their host. Some of the toxic chemicals they produce are carcinogens while others provoke an allergic response.[45,46] Some of these pathogenic organisms even change dietary constituents and liver excretion products into carcinogens.[47] Unfortunately, many of the microbial metabolic by-products and toxins can pass easily from the intestines into the blood.

Overuse of antibiotics, development of antibiotic-resistant microorganisms, alterations in gut microflora, and the increased incidence of parasites, all contribute to the development of abnormal bacteria in the gut. The overuse of broad-spectrum antibiotics has resulted in increased gastrointestinal yeast, fungus, and anaerobic organisms, some of which have become resistant to antibiotics.

Of particular significance is the research which has shown that these unhealthful intestinal microorganisms produce toxic metabolites that poison our body's enzyme systems. Some of these chemicals are very similar to normal Krebs cycle metabolites. The Krebs cycle is the series of chemical processes in the mitochondria that produce energy for the cells to function. Poisoning these enzymes is devastating to the body because, without adequate energy, cellular processes go awry.

Some of these chemicals also mimic the neurotransmitters that make our brain and nervous system work. The leakage of abnormal forms or inappropriate levels of neurotransmitters into the body can cause significant brain dysfunction and alterations in behavior. Some of these chemicals can even be hallucinogenic. Interestingly, many of these abnormal chemicals have been found in the urine of

Table 5-11 Diseases in Which Intestinal Dysbiosis Is Implicated

Autoimmune joint disease	Inflammatory bowel disease
Chronic fatigue syndrome	Irritable bowel syndrome
Colon and breast cancer	Psoriasis
Cystic acne	Steatorrhea
Eczema	Vitamin B_{12} deficiency

autistic patients. Table 5-11 lists common diseases that have been shown to be associated with, and possibly caused by, intestinal dysbiosis.

For example, patients with psoriasis who have been found to have high levels of circulating endotoxins from bacteria[48] rapidly improve when they take the drug cholestyramine, a strong binder of endotoxin in the gut.[49] In a controlled study of 92 patients, an endotoxin-binding saponin (sarsasaponin) from *Similas officinalis* (sarsaparilla) markedly improved 62% of the patients and resulted in complete clearance in 18%.[50]

The research on intestinal dysbiosis has progressed to the point that correlations are now being seen between specific types of bacteria in the intestines and certain diseases (see Table 5-12). For example, there is a correlation between intestinal infection with *Shigella*, *Salmonella*, *Yersinia*, or *Campylobacter* and Reiter's syndrome, an inflammatory condition of the joints and eye.[51] This suggests that the body reacts to these bacterial proteins by forming antibodies, which then also react with the tissues of the joints.[52] Studies have demonstrated that patients with ankylosing spondylitis, rheumatoid arthritis, and vasculitis have increased intestinal permeability, which may be an important factor in the development of these disorders.[53,54]

The Leaky Gut

The problem with bowel toxins becomes even worse when the intestinal mucosal barrier becomes damaged. Not only does this allow more toxins to enter, but it also allows the entry of viable bacteria, pieces of dead bacteria and yeasts, and dietary proteins.[61] This results in a huge overload for the liver. It also results in food allergies. The term "leaky gut" has been coined to describe this condition.

In the past few years, the association between intestinal inflammation and intestinal leakage and many chronic diseases, including autoimmune diseases, has become well-established. As can be seen from Table 5-13, a leaky gut has been found in diseases as diverse as infection, food allergy, Crohn's disease, eczema, and autoimmune diseases, such as rheumatoid arthritis and ankylosing spondylitis. In some diseases, such as AIDS, the disease appears to cause the increased permeability, while in others such as eczema, increased permeability appears to be a major cause.

Table 5-12 Intestinal Microorganisms Associated with Chronic Diseases[55,56,57,58,59,60]

Microorganism	*Toxic Reaction*	*Disease*
Bacteroides	Separate B_{12} from intrinsic factor	Pernicious anemia
Campylobacter	Cross-reacts with collagen	Reiter's syndrome
Candida albicans	Increase prostaglandin synthesis	Irritable bowel syndrome
Escherichia coli	Cross-reacts with insulin receptors	Diabetes mellitus
	Cross-reacts with nerve acetylcholine receptors	Myasthenia gravis
Klebsiella pneumoniae	Cross-reacts with nerve acetylcholine receptors	Myasthenia gravis
	Cross-reacts with joint tissues	Rheumatoid arthritis
Nisseria meningitidis	Cross-reacts with nerve cell membranes	Meningitis
Proteus vulgaris	Cross-reacts with nerve acetylcholine receptors	Myasthenia gravis
Salmonella	Cross-reacts with collagen	Reiter's syndrome
Shigella	Cross-reacts with collagen	Reiter's syndrome
Yersinia enterocolitica	Cross-reacts with thyroid plasma membrane and collagen	Arthritis, enterocolitis, erythema nodosum, Graves' disease, Hashimoto's disease, Reiter's syndrome, iritis

When the intestines are damaged, from infection, inflammation, or food allergy, leakage into the body of substances that are normally excluded increases dramatically. This is especially a problem in chronic intestinal inflammatory diseases such as Crohn's disease, where the absorption of toxins increases as much as six-fold.[69,70]

The permeability of the gastrointestinal tract can be measured by a procedure called the lactulose/mannitol absorption test.[71] In this test, intestinal leakage is measured by the rate of absorption of lactulose, a molecule so large that it normally does not enter the body in any appreciable amount.

Studies of a wide range of illnesses have demonstrated that increases in intestinal absorption of lactulose correlate well with clinical and pathological conditions, often returning to normal values as the condition improves and worsening as the condition worsens. For example, when Crohn's disease patients are placed on a totally synthetic diet, their previously elevated lactulose/mannitol ratios fall significantly, coinciding with marked clinical improvement.[72] Researchers have consistently reported a correlation between intestinal permeability and bowel inflammation.[73]

In diseases of the small intestine such as gluten-sensitive enteropathy (a severe allergy to wheat, also known as coeliac disease), permeability to large

Table 5-13 Clinical Conditions Associated with Altered Intestinal Permeability[62,63,64,65,66,67,68]

Aging	Inflammatory joint disease
Alcoholism	Intestinal infections
Ankylosing spondylitis	Irritable bowel disease
Asthma	Malabsorption
Chemotherapy	Malnutrition
Coeliac disease	NSAID-induced intestinal damage
Crohn's disease	Psoriasis
Eczema	Reiter's disease
Endotoxemia	Rheumatoid arthritis
Food allergy	Schizophrenia
Giardiasis	Thermal injury (severe burns)
Hives	Trauma
HIV positive	Ulcerative colitis
Infantile colic	Urticaria (hives)
Inflammatory bowel disease	

molecules increases and, paradoxically, permeability to small molecules decreases. This latter effect is due to the destruction of the microvilli, the minuscule folds in the intestines that greatly increase the absorptive surface area of the intestines. While the surface area of a person with a normal intestine is a remarkable 2,000 square feet (about the size of a tennis court), the patient with untreated coeliac disease has an 80% smaller surface area, one that is not very good at discriminating what passes through it.

After exposure to a single oral dose of gluten (the protein in wheat that makes it gluey), the intestinal permeability of people with coeliac disease becomes significantly abnormal. Remarkably, when all gluten is scrupulously avoided, their intestines heal incredibly rapidly and permeability returns almost to normal within one week.

How the Gut Can Be Damaged

Many factors damage the gut: food allergy, drugs (e.g., alcohol), aging, intestinal infections, nonsteroidal anti-inflammatory drugs (e.g., aspirin), chemical toxins ingested with foods, and maldigestion.[74,75] (Maldigestion is covered extensively in Chapter Seven.)

Food Allergy

A very common condition causing, and caused by, a leaky gut, is food allergy. Whether or not a person will develop a food allergy depends on many factors, including heredity, gut permeability, an overly sensitive immune response, poor digestive function, and excessive exposure to a limited number of foods. While

Grains and the Immature Digestive Tract

A case I saw in the teaching clinic when I was a young medical student at the National College of Naturopathic Medicine had a huge impact on my clinical thinking. Charlotte brought her four-year-old son Michael into the clinic and laid him on my examining table. While his older brothers bounced around the examining room, Michael lay listlessly on the table—very uncharacteristic of a young child! Michael had suffered from diarrhea and debility for three years. His mother had taken him to countless doctors, specialists, and hospitals and spent thousands of dollars, yet his diarrhea and debility continued. I saw a passive child with dark circles under his eyes, a sallow complexion, a protruding belly, bowed legs, and what looked like a ricketic rosary (lumps at the ends of his ribs).

I, and this child, had the great fortune of having Dr. John Bastyr supervising in clinic that shift. (Dr. Bastyr, who died recently at the age of 83, was a wonderful healer and physician who inspired several generations of naturopathic doctors-to-be. He had such a powerful impact on us that when we decided to start a new naturopathic school in 1978, we named it in his honor to provide a guiding spirit for the institution.)

After examining Michael and asking his mother about his diet, Dr. Bastyr quickly recognized the cause of his problems: food allergies. Michael's mother had introduced grains into his diet before his digestive system had matured enough to digest them properly. He told Charlotte to stop feeding her son grains, not just wheat, but also rye, barley, oats, corn, and rice. In addition, he told her to feed her son only equal amounts of carrot juice and raw goat's milk (one of Dr. Bastyr's famous concoctions) for one week and then to bring him back for re-evaluation.

One week later, Michael had dramatically improved. His diarrhea had stopped, and he was bouncing off the walls, just like his brothers. Unfortunately, over the next year, Charlotte would, despite my admonitions to the contrary, try feeding him grains, and each time he would again develop diarrhea.

- *The message:* Food allergies can cause serious chronic damage to the body, yet don't turn up on conventional medical evaluation.

conventional medical texts assert that only about 1% of the population has food allergies, nutritionally oriented physicians will tell you that half of all patients they test are allergic to at least one food, some many more. Chronic inflammatory skin diseases, such as eczema, also appear to be associated with food allergy and a leaky gut. Patients with atopic dermatitis and/or urticaria demonstrate increased permeability when given an oral challenge of the food(s) that provoke their symptoms.[76]

Most people are unaware that they are sensitive to foods because most only think of allergies as an immediate reaction, like hives or asthma attacks. Far more common are what are called "masked" or "delayed" reactions, which occur hours, or even days, after the food is ingested. This delay makes it very difficult to connect the eating of a specific food with the reaction. Immediate reactions are mediated by IgE type antibodies while IgG and IgM antibodies mediate the delayed reactions. Unfortunately, most conventional allergists believe food allergies are only mediated by IgE and ignore delayed food reactions. Patients who have had their chronic, "incurable" diseases cured by avoiding the foods that they are allergic to know otherwise.

There are two basic ways of detecting food allergies: laboratory methods, which attempt to measure antibodies in the blood to various foods, and experiential clinical tests, where a person eats a suspected food according to a special protocol and watches for reactions.

Laboratory procedures for diagnosing food allergy

Table 5-14 summarizes the strengths and weaknesses of the currently available laboratory procedures. These procedures require the assistance of a physician.

Experiential tests for food allergy

Many physicians, including myself, believe that the oral food challenge is the best method (the "gold standard") for diagnosing food intolerance. I use the term "intolerance" rather than allergy because some people have a reaction to a food that is not mediated by antibodies and, technically, a reaction is not an allergy unless there are antibodies involved. The food challenge is an accurate and useful procedure when used appropriately. As might be expected, there are a wide variety of protocols among the physicians using this method.

There are two broad categories of food provocation challenge testing: (1) elimination diet (meaning only a few, relatively low allergenic foods are eaten) followed by food reintroduction and (2) pure water fast followed by food challenge. Food challenge may be performed in an open, single-blind, or double-blind manner.

Please note: Food challenge testing should *not* be used by those with symptoms that are potentially life-threatening (such as the airway constriction found in asthma or severe anaphylaxis).

The typical procedure is pretty straightforward:

1. For four days either eat no food of any kind (except liberal amounts of water) or only a few foods or a synthetic hypoallergenic formula (such as UltraClear).
2. On the fifth day, begin eating one new food each day, alternating between the suspected foods and foods that are usually safe. My recommended order is wheat, carrots, corn, cabbage, milk, pears, cheese, avocado, peanuts, apples, soy, grapes, tomatoes, cucumbers, and beef.

Table 5-14 Laboratory Food Allergy Tests

Procedure	*Advantages*	*Disadvantages*
RAST	Convenient Good for inhalants Office kits available	Low sensitivity Expensive Detects IgE only
RASP	Convenient Good sensitivity	Expensive Not widely available Detects IgE and only some IgG
FICA	Patient convenience Good sensitivity Detects IgG	Expensive Not widely available Little research
Cytotoxic	Convenient Moderate cost Many foods easily tested	Poor reproducibility Limited availability
ELISA/ACT	Patient convenience Good sensitivity Detects both immediate and delayed reactions	Expensive Not widely available Little research
Skin prick	Widely available Good for inhalants	Poor sensitivity for food allergens Inconvenient
Provocation	Good for chemicals Office procedure Facilitates therapy	Expensive Time-consuming
EAV Acupuncture	Inexpensive Easily applied	No scientific basis Little research
Kinesiologic	Inexpensive Easily applied	No scientific basis Little research

3. Very carefully keep track of symptoms, not only on the day the food is introduced but also the next morning. Fortunately, most people react within an hour, but some people react as much as two or three days later, making detection more complicated.
4. Continue until all foods in the diet have been tested.

The first four days are considered the cleansing period, with the gastrointestinal tract being cleared of previously ingested foods, thus decreasing food sensitivity reactions. On the fifth or sixth day, symptoms due to food allergy usually start to disappear (if the allergic food was eliminated) and the person generally feels better.[77]

During the first two to three weeks after stopping a food, a person will actually become even more sensitive, or hyper-reactive, to the offending foods. This explains why the reintroduction of foods may produce more severe or

more easily recognizable symptoms. Foods are usually reintroduced in the order of probability, with a person's favorite food, especially a food they crave, being the most likely suspect. While it is beyond the scope of this book to fully explain why this happens, the short answer is that due to physiological adaptation the person usually becomes addicted to the foods causing the most trouble. When I bring up the idea of food allergy to a patient, very often he or she will say "Well I know it can't be 'x' as I always feel better when I eat it." Virtually always, 'x' is their worst food allergen!

In order for this procedure to work, great care must be exercised in keeping track of symptoms and ensuring that only pure foods are eaten. Many of the foods we eat contain food additives that are at times the real culprits and sometimes other foods are hidden in the food being tested. For example, various corn, wheat, and dairy products are often added to other foods, without their presence being listed on labels. Keeping a careful daily-symptom diary, noting when various foods were introduced, is absolutely necessary for the recognition of reactions.

Challenge testing is great for those wanting to take more control of their health, those with limited financial resources, and those with less severe health problems. Another advantage is the dramatic increase in symptoms you feel after eating the food to which you are allergic. It makes it much easier to avoid the offending foods when you have such a direct experience with how damaging they can be to your health. A disadvantage is that it is time-consuming and requires considerable discipline. The fewer the allergenic foods, the greater the ease of establishing a diagnosis with an elimination diet.

In general, better results can be achieved by eliminating all foods and just drinking water for four days. However, you are much more likely to experience "withdrawal" symptoms and a feeling of toxicity, which will usually subside by the fourth or fifth day. This method is only advisable for those who are physically and mentally capable of the more rigorous water fast.

Alcohol

Drinking more than moderate amounts of alcohol damages the mucous membranes of the intestinal tract—the more you drink, the worse the damage. Alcoholics' intestinal permeability is elevated and this dysfunction persists for up to two weeks after they stop drinking.[78] Their increased permeability may account for some of widespread damage commonly found in alcoholics. The leaky gut also exposes the liver to more toxins from the bowel, which aggravates alcohol-induced liver disease.

Aging

In rats and other laboratory animals, aging results in a diminished capacity to prevent larger molecules from penetrating the intestinal mucosa, possibly allowing antigenic or mutagenic compounds to reach the systemic circulation.[79]

Intestinal Infections

Many intestinal infections cause increased permeability.[80] Studies show that the body's responses to these infections result in increased passage of microorganisms and endotoxins into the systemic circulation.[81] Several researchers believe that this breach of the mucosal barrier is an important aspect in both the acute and chronic systemic effects of intestinal infection.

Severe Burns

Researchers have found that intestinal permeability increases in human beings after a major burn.[82] This occurs even in the absence of infection of the burned areas. In addition, increasing evidence shows that the gut barrier's failure to function may play a role in initiating the multiple-organ-failure syndrome that occurs after major trauma. Loss of blood supply to the intestines due to the trauma probably explains the mucosal changes.

Non-Steroidal Anti-Inflammatory Drugs

Numerous studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) disrupt the intestinal barrier function and cause increased permeability.[83] This is of particular importance in arthritic patients treated with NSAIDs because the increased permeability probably contributes to the progression of their disease; a sad example of relieving the symptoms at the cost of aggravating the underlying disease. The most common NSAIDs are listed in Table 5-15.

Constipation

Constipation significantly increases the toxicity of the body because the longer toxins stay in the bowel, the more time they have to damage the intestinal mucosa and leak into the body. Constipation has several causes, the most important being a low-fiber diet and food allergies.

Transit time, the time taken for passage of material from the mouth to the anus, is greatly reduced on a high-fiber diet. Cultures consuming a high-fiber diet (100 to 170 gm per day) usually have a transit time of 30 hours and a fecal

Table 5-15 Common Non-Steroidal Anti-Inflammatory Drugs

Acetaminophen (e.g., Tylenol)	Meclofenamate (e.g., Baprosyn)
Aspirin	Phenylbutazone
Fenoprofen (e.g., Nalfon)	Piroxicam (e.g., Feldene)
Ibuprofen (e.g., Advil, Motrin, Nuprin)	Sulindac (e.g., Clinoril)
Indomethacin (e.g., Indocin, Indometh)	Tolmetin (e.g., Tolectin)

weight of 500 gm (a little over a pound). In contrast, Europeans and Americans, who typically eat a low-fiber diet (20 gm per day) have a transit time of greater than 48 hours and a fecal weight of only 100 gm.[84]

The dietary fiber supplements I recommend most frequently are psyllium seed and oat bran.

Besides a low-fiber diet, allergy to cow's milk may be a significant cause of chronic constipation. A group of researchers in Italy studied 27 children under three years of age who suffered from chronic constipation. No changes were made in their diet, other than substituting soy milk for cow's milk. The results were quite impressive, with 21 showing a significant improvement, i.e., an increased number of stools per day, softer stools, and elimination or decrease in intestinal discomfort and anal and perianal fissures. The children improved within three days but their symptoms returned rapidly when cow's milk was reintroduced.[85]

Other Sources of Toxins

Free Radicals

Our life depends on the easy availability of oxygen, which is required for many critical metabolic processes. For example, our mitochondria, the cells' energy-producing factories, use oxygen to convert fuel (from food) to energy, and white blood cells use oxygen to destroy invading microbes. However, oxygen is such a powerful reactant that it creates free radicals, which do considerable damage when not properly controlled. This results in damage to our enzyme systems, cell membranes, and DNA. Free radical attack and cumulative oxidative damage are associated with more than 100 degenerative conditions, the most common of which are summarized in Table 5-16.

Ischemia (loss of blood supply), reperfusion (re-establishment of blood supply after ischemia), burns, trauma, cold, exercising to excess, toxins, inflammation, radiation, and infection—all release free radicals. But being implicated does not necessarily mean that they are the initiating factor. Sometimes the free radicals are just a consequence of tissue injury. However, if not immediately quenched, they keep the damage going. Once an initial event generates free radicals, a cascade ensues, producing ever more free radicals, which continue to snowball unless held in check by antioxidant defenses.[86]

In addition to free radicals, the body generates other powerful oxidizing agents, including hydrogen peroxide (H_2O_2), lipid peroxide (ROOH), hypochlorite (OCl^-—the same powerful oxidizer found in commercial bleach), chloramines (RNHCl), and several other highly reactive oxidizing chemicals. All of these various oxidizing molecules are referred to here by the term *free radicals*.

Targets of free radicals include polyunsaturated fatty acids in membranes, serum lipoproteins, proteins, and even DNA. The products may be lipid peroxides

Table 5-16 Conditions Mediated by Free Radical Damage[87,88,89,90,91,92,93,94]

Alcohol-induced damage	Liver cirrhosis
Atherosclerosis	Myocardial infarction
Autoimmune diseases (rheumatoid arthritis and others)	Nephrotoxicity
	Nutrient deficiencies
Cancer	Obstructive lung disease
Contact dermatitis	Parkinson's disease
Diabetic cataracts	Premature aging
Drug toxicity	Premature retinopathy
Emphysema	Senile dementia and neurologic degeneration
Hypertensive cerebrovascular injury	Stroke
Immune deficiency of aging	Thermal injury
Inflammatory bowel disease	Viral infections, including AIDS
Iron overload disease	

(oxidized fats implicated in cardiovascular disease), protein carbonyls (oxidized proteins that are carcinogenic), or altered purines (DNA components). The consequences are often subtle, such as damage to cell membrane receptor proteins, which alters cellular regulatory mechanisms so that enzymes required for ATP production are inactivated, leading to low energy.

Production of Free Radicals

As listed in Table 5-17, free radicals are produced by external sources, such as radiation and environmental pollution, as well as normal internal metabolic and defense processes. These add up to a surprisingly heavy load of free radicals.

Inflammation represents a major source of oxidants, especially during a chronic disease process. Infection, immune complexes, bacterial toxins, toxic exposure, ischemia (low blood supply), trauma—all activate phagocytes, the immune cells that surround and destroy undesirable cells and substances. This triggers the local production and release of highly reactive free radicals to destroy damaged tissues, viruses, bacteria, and toxic chemicals. While many toxins can be neutralized this way, unfortunately, some are converted to even more reactive forms.[97] As discussed in more detail in Chapter Six, inflammation also activates the arachidonic acid cascade, which produces the inflammatory prostaglandins and leukotrienes, which contribute to the free radical load. The continuous production of free radicals by activated phagocytes during chronic (even undetected low level) inflammation will eventually deplete antioxidant defenses, thus allowing free radicals to damage cells.

The term "oxidative stress" refers to an increase in the ratio of pro-oxidants to antioxidants. The oxidative overload is due to excessive free radical production or inadequate antioxidant defenses. Increased oxidative stress results in chronic tissue injury and progressive damage to metabolic processes. The body's ability to protect itself from oxidative stress is affected by the degree of exposure

Table 5-17 The Production of Free Radicals[95,96]

Source	*Mechanism*
Air pollution	Ozone and nitrogen oxides are strong oxidants.
Radiation	Cosmic rays and radiation produce free radicals when they impact body tissues.
Energy production	Up to 2% of oxygen molecules passing through mitochondria end up as superoxides instead of energy. This generates about 10 gm of superoxide per day.
Fatty acid oxidation	Cells contain little organs that oxidize fatty acids as part of metabolizing fat with the side effect of producing hydrogen peroxide. Drugs such as clofibrate increase the activity of these organelles.
Metabolism of DNA, RNA, and ATP	The metabolism of DNA, RNA, and ATP relies on the enzyme xanthine oxidase, which produces superoxide.
Metabolite and xenobiotic detoxification	Phase I detoxification generates free radicals. Metabolism of drugs, such as penicillamine and phenylbutazone, and environmental poisons, such as paraquat and alloxan, produce free radicals. These oxidative products account for the liver damage caused by many pesticides and drugs.
Inflammatory response	Iron and copper are released from storage sites during inflammation and injury. These ions catalyze the spontaneous production of free radicals.
Immune response	White cells produce free radicals as part of their defensive mechanism.

to pollutants, the level of dietary consumption of antioxidants, one's age and genetic factors. When free radical production exceeds the ability of the neutralizing systems, progressive cellular damage occurs. When this damage is severe or long lasting, a downward spiral from health to chronic disease results.

Americans consume relatively low amounts of the antioxidant nutrients: vitamins C and E, beta-carotene, zinc, selenium, copper, and manganese. This is probably because fewer than 10% eat the recommended five daily servings of fruits and vegetables.[98,99]

Food Additives

Irregularities in the detoxification system may make individuals especially sensitive to natural compounds in foods and to synthetic food additives. Symptoms include chronic urticaria (hives), angioedema, asthma, rhinitis, nasal polyps, headaches, upper abdominal pain, and mood changes. Offending additives include benzoates, tartrazine and other synthetic colors, and acetylacetic acid.[100]

Drugs

Virtually all drugs need to be detoxified by the liver. Adverse side effects are experienced by 15 to 30% of those taking medications (both over-the-counter and prescription), and drug reactions account for 20 to 30% of hospital admissions. Often the side effects people experience are from the damage these foreign chemicals cause to the liver. This damage can be caused directly by the drugs, or indirectly as a result of the liver's detoxification of the drug or the effect of the drug on the metabolism of other drugs. This is one reason why the mixing of prescription drugs can cause so many problems and is widely discouraged.

Benzodiazepines

Benzodiazepines (e.g., Centrax, Librium, Prozac, Valium, etc.) are drugs widely prescribed to relieve the symptoms of anxiety and insomnia. While modestly clinically effective, they cause significant problems for the elderly, where their use is associated with the development of neurological damage in the brain. This may in part be due to benzodiazepines' suppression of Phase I detoxification enzymes, both in the liver and in the brain. This results in slower metabolism of some neurotransmitters that the body needs to regularly eliminate lest they reach toxic levels.

The combination of bacterial toxins from the intestine, poor liver detoxification processes, and the addition of drugs such as benzodiazepines that further aggravate the toxicity problem appears to result in greatly increased risk of brain and nervous system dysfunction, called by some "brain toxicity."

Acetaminophen

Although normally relatively safe, combining acetaminophen with either alcohol or fasting can damage your liver. The danger appears to start at about three drinks per day.[101] This toxicity reaction can also happen in those with very poor nutrition and by taking large amounts over long periods of time.

Heavy Metals

All metals in our environment are toxic at some level of exposure. Even metals that are required nutrients, such as iron, are toxic at high levels, while some, such as lead, are toxic at any level of exposure.

Aluminum

More and more research is showing that aluminum poses a serious health problem for humans. We now know that aluminum catalyzes free radical damage to the nervous tissue in the brain. This is especially a problem for those with Alzheimer's disease, because their ability to transport and detoxify aluminum appears to be impaired.[102] However, a high exposure to aluminum is probably a problem for everyone. For example, miners given aluminum powder as

prophylaxis against silicotic lung disease between 1944 and 1979 were found during a later study to perform less well on cognitive state examinations as compared to non-exposed miners, with their level of impairment directly related to the duration of the aluminum exposure.[103]

As might be expected, those who work with aluminum experience problems also. When 25 workers from an aluminum smelting plant were evaluated for neurologic symptomatology, 88% reported frequent loss of balance, 84% reported memory loss, 84% had signs of coordination loss, 75% showed mild or greater impairment on memory tests, and 89% were depressed according to the Minnesota Multiphasic Personality Inventory. The researchers also found a correlation with the degree of exposure and coordination loss.[104]

Those on dialysis for kidney failure are commonly poisoned by aluminum. A side effect of the chemicals used for the procedure is the leakage of aluminum salts into the body tissues. When the aluminum builds to a toxic level, these people develop a condition known as dialysis encephalopathy. This manifests as dementia, speech disorders, jerking muscles, seizures, and psychotic episodes. Before symptoms occur, their EEGs (a measure of electrical activity in the brain) become abnormal as the aluminum starts to disrupt brain neurochemistry.[105]

Mercury

Mercury is highly toxic, especially to the nerves. The saying "mad as a hatter" came from stories of hatters in England in the nineteenth century. The hatters used a mercury compound to help stiffen the cloth used to make hats. Unfortunately, they absorbed some of the mercury and developed such mental dysfunction they became psychotic.

The tendency of mercury to concentrate in the nervous tissue is well-documented and the role of mercury-containing tooth fillings as a chronic source is cause for serious concern. Autopsy samples of the central nervous system (especially the olfactory [smelling] region and the pituitary gland) and kidney cortex have revealed a high concentration of mercury in those having amalgam fillings when compared to amalgam-free cadavers.[106] The association between amalgam load and the accumulation of mercury in tissues is thought to be caused by swallowing and inhalation of mercury vapor released from amalgam fillings. Because the vaporization rate is low, blood and urine mercury levels (the indicators used by the dental and amalgam representatives to claim that amalgams are safe) remain low and are a poor diagnostic indicator of body burden.[107] Although the exposure is low, it is constant and cumulative and our nervous system is especially sensitive.

Even in those without overt disease, research suggests that the mere presence of mercury amalgams in the teeth has an impact on mental symptoms. In one study, 50 university students with amalgam fillings were compared to 51 with no dental fillings. The amalgam group was found to have 201% higher mercury levels in the urine and 26% higher in the hair. Health questionnaires

showed an increase in the number of subjective physical and mental complaints. Removal of their fillings resulted in a significant improvement in their symptoms.[108] Many dentists are now aware of this problem and are replacing amalgam fillings with safer plastic and ceramic alternatives.

Lead

Lead, the oldest known environmental pollutant, continues to be a serious problem for our society. While changing gasoline from leaded to unleaded certainly has helped, lead continues to contaminate our environment: the typical person has 100 to 1,000 times as much lead in his or her body as our prehistoric ancestors. No level of lead exposure has been shown to be safe.

Research over the past decade has substantially increased our understanding of lead toxicity, and we now recognize that levels previously considered safe are not. Subclinical toxicity can cause inhibition of enzymes, kidney damage, hypertension, sperm malformation, slowing of nerve conduction, and central nervous system dysfunction. All these effects have occurred in apparently healthy workers at levels of exposure to airborne lead below OSHA's (Occupational Safety and Health Administration) supposedly safe exposure levels.[109]

Common sources of lead in the environment include leaded paint, water, copper-leaded pipes, leaded gasoline, batteries, and lead smelters. Another very significant source is cigarettes, with smokers having twice the body load of nonsmokers.[110] Two of the many toxic effects of lead of particular importance are the blockage of hemoglobin formation (hence the anemia and chronic tiredness) and the inhibition of glutathione regeneration resulting in increased susceptibility to environmental chemical toxins. Children and those on a calcium-deficient diet are the most susceptible to lead.

Fortunately, treatment with chelating agents can be used to reduce blood and tissues levels of toxic heavy metals. In a recent animal study, the combined use of prescription drugs EDTA and meso 2,3-dimercaptosuccinic acid was more beneficial in reducing blood and liver lead compared to treatment with these drugs alone.[111] However, as these drugs cause lead to be excreted through the kidneys, care must be exercised that the rate isn't too fast which could damage the kidneys.

Recognizing heavy metal overload

While acute poisoning or high levels of heavy metal toxicity are easy to recognize, chronic low level exposure can be difficult to recognize since the symptoms can be subtle and pervasive. Table 5-18 lists the common signs and symptoms of heavy metal toxicity. As can be seen, many of the common discomforts of life can be caused by heavy metals, making diagnosis from symptoms alone difficult and unreliable.

A simple and inexpensive test, hair analysis, can easily warn us of exposure. Unfortunately, hair analysis has developed a controversial reputation because some misguided practitioners have inappropriately used this procedure to evaluate nutritional status. The research is clear: With a few exceptions

Table 5-18 Signs and Symptoms of Heavy Metal Toxicity[112]

Toxic Metal	*Symptoms*
Aluminum	Colic, dementia, esophagitis, gastroenteritis, liver dysfunction, loss of appetite, loss of balance, kidney damage, muscle pain, psychosis, shortness of breath, weakness
Cadmium	Anemia, dry and scaly skin, emphysema, fatigue, hair loss, hypertension, joint soreness, kidney stones, liver dysfunction, loss of appetite, osteoporosis, pain in back and legs, yellow teeth
Lead	Abdominal pain, anemia, anxiety, bone pain, confusion, depression, difficult concentration, dizziness, drowsiness, fatigue, headaches, hypertension, incoordination, indigestion, irritability, loss of appetite, memory impairment, muscle pain, restlessness, tremors
Mercury	Anemia, colitis, depression, dermatitis, dizziness, drowsiness, emotional instability, fatigue, headaches, hearing loss, hypertension, incoordination, insomnia, irritability, loss of appetite, loss of balance, kidney dysfunction, memory impairment, metallic taste, numbness, psychosis, inflamed gums, strange sensations in hands, tremors, vision impairment, weakness
Nickel	Apathy, blue color of lips, diarrhea, fever, headaches, insomnia, nausea and vomiting, shortness of breath, very rapid heart rate

(chromium, manganese, and selenium), hair analysis is not a reliable tool for measuring mineral status and is absolutely worthless for measuring vitamin status.[113] It is, however, very useful and reliable for detecting heavy metal exposure and is sensitive enough to detect exposure before it is bad enough to cause significant clinical symptoms. Hair analysis is useful for recognizing exposure to mercury, lead, iron, and arsenic.[114,115]

Helicobacter Pylori

Helicobacter pylori infection is associated with stomach cancer and other health problems (see Table 5-19). It is estimated that 50% of the population over the age of 60 in the U.S. is infected with *H. pylori*.[116] For most of those infected, their mucosal resistance factors are working just fine and they are asymptomatic. For others though, it contributes to both peptic ulcer disease and the risk of gastric adenocarcinoma.

Some research is helping us understand why some people develop stomach ulcers and stomach cancer while others effectively resist *H. pylori*. One research group found that while users and non-users of nonsteroidal anti-inflammatory agents (NSAIDs) had the same incidence of *H. pylori*, those taking NSAIDs had a four-fold increased risk of ulcers. In other words, aspirin and other NSAIDs inhibited the stomach's ability to protect itself from *H. pylori*.[118] Coffee consumption also appears to help the *H. pylori* cause trouble.[119]

Table 5-19 Effects of *Helicobacter Pylori* Infection[117]

Change Induced by H. pylori	*Effect*
Hyperproliferation of gastric mucosa	Greater opportunity for mutagen integration and fixation Greater susceptibility to carcinogen formation and activity
Altered pH	Impairs digestion
Genetic changes in host mucosal tissue	Impairs normal repair process
Denaturation or oxidation of mucosal cell ascorbic acid, setting the stage for vitamin C deficiency	Enhanced formation of nitrosamines which are carcinogenic
Enhanced mutagenic/carcinogenic insult	Increased risk of cancer
Atrophic gastritis, with loss of parietal cells and hypochlorhydria	Hyperproliferation of nitrosamine-forming bacteria in small bowel and release of toxic substances Alteration of GI flora, affecting steroid deconjugation and, therefore, the metabolism and activity of estrogenic hormones

H. pylori infection also causes destruction of vitamin C. In a study of 19 patients with *H. pylori*, their gastric juice ascorbic acid concentrations were 75% lower than uninfected controls. These patients also had a significant increase in inflammation in the stomach and intestines. Eradicating the *H. pylori* resulted in an increase in gastric juice ascorbic acid concentration. In other words, the infection uses up vitamin C. This is especially important because vitamin C neutralizes nitrosamines, carcinogens thought to be the primary cause of stomach cancer.[120]

Also of interest is the research that shows that a 5 to 10% per volume solution of manuka honey completely inhibits *H. pylori in vitro* after 72 hours of incubation.[121] Human studies are now needed to determine if this will be clinically useful.

Silicone Implants

Silicone (polydimethylsiloxane) is used for body implants for the breast, penis, and muscle enhancement and in replacement joints. Unfortunately, a growing body of evidence shows that silicone molecules leach from the implants and are picked up by macrophages. This results in their transport throughout the body where they combine with normal proteins to form abnormal proteins that activate an autoimmune reaction. These then initiate an inflammatory response, which continues unabated due to continued stimulation. The

silicone particles also suppress natural killer cell activity, which returns to normal after removal of the implant.[122] Unfortunately, the body has no detoxification system for these man-made molecules.

Pesticides and Herbicides

Farmers have an increased incidence of certain types of cancers, particularly those of the stomach, connective tissue, skin, brain, prostate, and lymphatic and blood-forming system. Herbicide exposure may be the cause. A large study of over 69,000 Saskatchewan farmers, ages 35 or older, found a strong correlation between the use of herbicides and the incidence of non-Hodgkin's lymphoma. Mortality from non-Hodgkin's lymphoma rose in proportion to the number of acres sprayed with herbicides. The association was specific in that the incidence of non-Hodgkin's lymphoma was not correlated to education, income, ethnicity, fuel expenditure, use of fertilizers, or insecticides.[123]

Another disconcerting study looked at the association between various childhood cancers and the home and yard use of pesticides. They found significant association between the use of pest strips and leukemias, brain tumors, and lymphomas. Yard pesticides were associated with soft tissue sarcomas while house insect extermination was associated with lymphoma.[124]

How to Recognize When Your Detoxification Systems Are Overloaded or Aren't Working Adequately

Many of the daily discomforts we suffer, as well as several diseases, are the result of unrecognized toxicity, either due to excessive exposure or inadequate detoxification. Table 5-20 shows a list of common symptoms that indicate the build up of toxins.

Supporting the Detoxification Systems

No mater how good our food or how pure an environment we live in, we will always be exposed to toxins. They naturally occur in foods, are produced as a normal by-product of metabolism, and are even secreted by health-promoting bacteria in the intestines as unwanted chemicals. The bottom line is that we need our detoxification systems to work well.

Enhancing the Liver's Detoxification Functions

The liver has remarkable regenerative and detoxification properties, if given the chance. Optimizing liver function focuses on protecting the liver from toxins, increasing the excretion of toxins from the liver, normalizing the liver's detoxification systems, and protecting the liver from the build-up of fat. Liver-protecting substances include many nutritional and herbal compounds that

Table 5-20 Signs and Symptoms of Toxicity

Acne, especially cystic acne	Foul-smelling stools
Autoimmune disease	Generalized pruritis (itching)
Bad breath	Intolerance of garlic
Chronic degenerative disease with unknown cause	Irritable bowel syndrome
	Liver disease
Chronic fatigue	Nausea and vomiting during pregnancy
Chronic fatigue syndrome	Premature development of "age spots"
Chronic headaches	Psoriasis
Colon and breast cancer	Sensitivity to chemicals
Eczema	Toxic headache

prevent the damage to the liver associated with detoxifying harmful chemicals. Lipotropic factors are, by definition, substances that hasten the removal or decrease the deposit of fat in the liver. Choleretics are agents that stimulate bile secretion by the liver, while cholagogues are agents that stimulate gallbladder contraction in order to improve the excretion of bile into the intestines.

Protecting the Liver from Virus- and Toxin-Induced Damage

As noted above, whenever the liver metabolizes toxins, free radicals are produced. In order to prevent damage to the liver, these must be neutralized as soon as possible. Following is a discussion of a few of the free radical quenchers that are especially important for the liver. A more complete discussion of free radical quenching nutrients, enzyme systems, and herbs are discussed later this chapter.

Nutrients

The nutritional antioxidants—i.e., vitamins C and E, bioflavonoids, carotenoids, glutathione, and selenium—are essential for protecting the liver from the free radicals produced during the neutralization of toxins. The protective effects of these antioxidant nutrients can be substantially augmented by increasing the diversity and magnitude of other antioxidants such as coenzyme Q and catechin.[125] Also of particular value are several flavonoids from herbs, which have the surprising property of being concentrated in the liver, just where they are most needed and most effective.

Phospholipids (a kind of fat found in cell membranes) are of special value because they protect the liver from chronic exposure to organic solvents. This appears to be due to the incorporation of phospholipids into cellular membranes, resulting in improved membrane fluidity, activation of membrane-dependent enzyme processes, and regeneration of damaged liver cells.[126] The phospholipids that protect the liver include phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine. These important nutrients are found in egg yolks and lecithin and can be obtained from dietary supplements.

Silybum marianum (Milk thistle)

Silybum is possibly the most potent liver protective agent known. It is so effective in protecting the liver that in experiments with mice, if silybum is given within a few minutes of ingestion of the deadly *Amanita phalloides* mushroom, death is not only prevented, but little liver damage is found! It works by preventing free radical damage (several time stronger than vitamin E) and by stimulating protein synthesis and production of new liver cells. The constituents that provide this protection are a mixture of three flavanolignins collectively referred to as silymarin.[127] The concentration of silymarin is highest in the fruit, but it is also found in the seeds and leaves.

The clinical efficacy of silybum has been well-documented in large clinical studies. For example, in one multicenter trial, 2,637 patients with various liver disorders (56.1% fatty infiltration of the liver, 19.3% hepatitis and cirrhosis, and 22.6% no clear diagnosis) were given an average of four tables (140 mg of silymarin per tablet) of standardized milk thistle extract daily. After eight weeks, 63% of the patients reported a complete disappearance of their symptoms (nausea, pruritis, abdominal distention, lack of appetite, and fatigue). Laboratory evaluation confirmed the subjective results with the level of liver enzymes in the blood (a measure of liver damage) decreasing by an average of 40%. Those with liver enlargement also had their liver decrease in size. Only 0.8% complained of side effects (stomach upset, nausea, and light diarrhea) and stopped their herbal medication.[128]

Other clinical trials have shown that silymarin is effective in treating cirrhosis, chronic hepatitis, fatty infiltration of the liver (chemical and alcohol induced), and inflammation of the bile duct.[129] The therapeutic effect of silymarin in all of these disorders has been confirmed by histological (biopsy), clinical, and laboratory data.

Silymarin protects the liver from such diverse toxic chemicals as alcohol, carbon tetrachloride, amanita mushroom toxin, galactosamine, and praseodymium nitrate.[130,131] Silybum is also particularly helpful for those having to take drugs for various reasons. For example, many of the psychotropic drugs used for patients with psychiatric disorders cause significant damage to the liver. In one study of 60 patients receiving long-term drug treatment with phenothiazines and butyrophenones, 90 days of treatment with 800 mg per day of silymarin resulted in significantly reduced levels of liver damage. The silymarin did not interfere with the clinical efficacy of the psychotrophic drugs.[132]

- *Dosage:* 120 mg silymarin three times a day

Catechin

Catechin is a flavonoid extracted from the herbs *Acacia catechu* (black catechu) and *Uncaria gambier* (pale catechu, gambier). It is widely used in Europe for treatment of liver disease. In the laboratory, catechin has been shown to

directly inactivate endotoxins and quench free radicals produced by bacterial endotoxins.[133] Supplementation has been shown to be effective in treating a variety of liver diseases, including chemical damage (such as from carbon tetrachloride poisoning), alcoholism, bacterial toxin damage (such as those secreted by gram-negative bacteria in the intestines), autoimmune hepatitis, viral hepatitis, and cirrhosis.[134] However, clinical trials have shown inconsistent results in chronic hepatitis with it appearing to be effective in treating hepatitis B and C, but not acute hepatitis A. It has also been shown to protect against some chemical carcinogens in experimental mice models.[135]

Catechin, however, is one nutrient that must be used with caution because some people will develop hemolytic anemia after high dosages or long periods of use.[136] The major dietary source of catechin is green tea.

- *Dosage:* 250 mg catechin twice a day or 2 cups of green tea a day

Protecting the Liver from Fat Buildup

The first step in protecting the liver from fat infiltration is dietary: Decrease the consumption of saturated fats (which increase the risk of developing fatty infiltration and the build-up of bile in the liver and gallbladder) and increase dietary fiber, particularly the water-soluble fibers (which promote increased bile secretion). Alcohol consumption must also be limited because excessive consumption stimulates the build-up of fat in the liver.

The next step is to ensure adequate consumption of lipotropic factors, because these nutrients are required by the liver to metabolize toxins, other metabolites, and fatty acids. Lipotropic factors appear to be especially indicated in women taking oral contraceptive agents, women who are pregnant, and anyone exposed to toxic compounds, especially organic solvents and polycyclic hydrocarbons, such as pesticides and herbicides, since these put an additional load on the lipotropic-dependent metabolic processes of the liver.

Compounds commonly employed as lipotropic agents include choline, methionine, betaine, folic acid, carnitine, and vitamin B_{12}. One of the best supplements for protecting the liver from toxins, especially alcohol, is carnitine.

Carnitine is a vitamin-like compound that we get from our diet (mainly from meat) or synthesize from the amino acids lysine and methionine, with the help of vitamin C, iron, niacin, and vitamin B_6. Since carnitine normally facilitates the conversion of fatty acids to energy, a high level of carnitine in the liver is needed to handle the increased fatty acid load produced by alcohol consumption, a high-fat diet, and/or chemical exposure. Carnitine supplementation is one of the few therapies that significantly inhibits alcohol-induced fatty liver disease. Chronic ethanol consumption, chemical exposure, and heavy exercise result in a deficiency of carnitine.[137] By supplementing L-carnitine, this functional deficiency state is reversed, leading to normalization of fatty acid transport and alleviation of fatty acid infiltration within the liver.

A Very Sick Boat Builder

Seattle claims to have one of the highest per capita rates of boat ownership in the world. As might be expected, there are many boat builders in the area. Jack was a wooden boat builder in Port Townsend, Washington. Although a young man, he was becoming progressively debilitated, a problem that he noted was far worse in the winter. He had become so weak, he was having problems getting out of bed in the morning to do his work. At the urging of friends, he took the two-hour trip to Seattle to seek my advice. As usual, he had seen several medical doctors, and none could provide an effective therapy for his ailments because they could find no recognizable disease. By the time he came to see me, he was very weak, felt like he had the flu all the time, and was desperate because he had a wife and young children to support. A bit of detective work quickly pinpointed the cause of his problems.

Wooden boat builders are exposed to several very toxic chemicals, especially solvents in varnishes and heavy metals in special paints used to keep barnacles from growing on the bottom of the boat. While this was not much of a problem for him in the summer, in the winter he would close all the doors and windows in his workshop to keep the heat in. As might be expected, this also kept the toxins in, despite the vents. Since his workshop had been approved by OSHA, he assumed the chemicals he worked with weren't a problem. Not only was he not using a mask, he wasn't even wearing gloves most of the time, and his living space was right next-door and smelled of solvents!

On examination, I found that he had an enlarged and very sensitive liver. His hands were discolored as was his complexion, which appeared waxen. I immediately put him on an intensive detoxification program. First, we eliminated all toxin exposure: He stopped working for one week, moved his family several blocks away from his workshop, added a heater, opened all doors and windows in the workshop, and began using both gloves and a chemical mask.

Next, we stimulated his detoxification processes. For one week Jack went on a modified fast, consuming only raw and cooked fruits and vegetables. To this he added large dosages of vitamin C and B-complex. Finally, he took two herbs for detoxification, *Chionanthus virginicus* (fringe tree) and *Chelidonium majus* (tetterwort). These herbs have been traditionally used by naturopathic doctors for detoxification of the liver. They are both powerful cholagogues, meaning that they help eliminate bile from the liver while stimulating its detoxification actions. (Since I've not been able to find any modern research supporting the clinical use of these herbs, I now use others, such as *Silybum marianum*, which have more documentation.)

Jack had a good constitution and responded rapidly to the therapy. Within a few weeks he was back to his normal energetic self. By improving the ventilation in his workshop and having him rigorously limit contact exposure, he was able to continue building his beautiful wooden boats.

- *The message:* The chemical solvents in our home and work environments progressively damage our health in direct proportion to exposure.

One toxin that is particularly damaging to carnitine metabolism is valproate, one of the primary anti-epileptic drugs given to children. Supplementation with carnitine reverses most of the toxicity commonly seen with this drug.[138] Another problem is the common food additive sodium benzoate, which is added to many foods and drinks as a preservative (look at the label). It also causes trouble by interfering with the synthesis of carnitine.[139]

- *Dosage:* 250 mg carnitine, 500 mg choline, B-complex (with an average of 25 mg of each of the B vitamins)—all twice a day

Increasing the Flow of Bile

One of the best ways to detoxify and protect the liver is to get toxins out of it as soon as possible. This is done by increasing the excretion of bile from the liver, because that's where the liver puts the toxins. Several herbs do this quite effectively. However, they are most effective for those on a high-fiber diet since there isn't much point in excreting bile into the intestine unless there is fiber there for it to bind to for elimination from the body.

Taraxacum officinale (Dandelion root)

While many consider the common dandelion to be an unwanted weed, herbalists all over the world have revered this valuable liver remedy for centuries.[140] Dandelion is regarded as one of the finest liver remedies, both as food and medicine. Studies in humans and laboratory animals have shown that dandelion enhances the flow of bile, improving such conditions as liver congestion, bile duct inflammation, hepatitis, gallstones, and jaundice.[141] Dandelion's action on increasing bile flow is two-fold. It causes an increase in bile production and flow to the gallbladder (choleretic effect) and stimulates the gallbladder to contract and release the stored bile (cholagogue effect) into the intestine. Dandelion's beneficial effect on a wide variety of conditions is probably closely related to its ability to increase the elimination of toxins from the liver.

- *Dosage:* 4 gm of dried root or 4 to 8 ml fluid extract of *Taraxicum officinale* three times a day

Cynara scolymus (Artichoke leaves)

Artichoke leaf extracts increase the excretion of bile from the liver. Clinical research comparing artichoke to placebo has demonstrated significantly more bile excretion for two to three hours after administration of a standardized extract containing 0.06% cynarin (a constituent of artichoke leaves).[142] This effect is so potent, that artichoke extracts are now used as cholesterol lowering agents, since cholesterol is eliminated from the body through the bile. In one study of 30 patients, 500 mg per day of cynarin lowered blood cholesterol by 20% and triglycerides by 15%.[143]

- *Dosage:* 500 mg *Cynara scolymus* extract (15% cynarin) per day

Curcuma longa (Turmeric)

The common spice turmeric contains the yellow pigment curcumin, which has demonstrated protective effects similar to those of silymarin and cynarin, i.e., it increases the flow of bile from the liver and decreases blood cholesterol levels.[144] It is especially effective in lowering cholesterol levels as demonstrated in experiments with rats fed large amounts of cholesterol, where it decreased blood levels a remarkable 50%.[145]

- *Dosage:* Use turmeric liberally as a spice; 300 mg curcumin three times a day

Promoting Liver Regeneration

The oral administration of liquid liver extracts has been used in the treatment of many chronic liver diseases since 1896. Numerous scientific investigations into the therapeutic efficacy of liver extracts have demonstrated that they possess a lipotropic effect, promote liver cell regeneration, and prevent scarring (fibrosis).[146] Clinical studies have demonstrated efficacy in the treatment of chronic liver disease, including chronic active hepatitis.[147] However, as valuable as this extract is, those with gout should probably avoid liver extracts since their high concentration of DNA and RDA may raise blood uric acid levels. This is not a problem for the average person.

- *Dosage:* 500 mg liver extract three times a day

While milk thistle (*Silybum marianum*, discussed above) is best known for its liver protective effects, possibly of even greater value is its use in stimulating regeneration of the liver. Its flavonoid complex silymarin stimulates liver protein synthesis. The result is an increase in the production of new liver cells to replace the damaged old ones.[148]

- *Dosage:* 120 mg silymarin three times a day

Increasing Phase II Detoxification

Sulfur compounds

Supplementing with the amino acid L-cysteine, inorganic sulfate, or taurine helps increase liver sulfation.[149] Since the sulfation system backs up the glutathione system for some toxins, if a person is exposed to such high levels of xenobiotics that all the glutathione is used up, their sulfate stores can also be used up. Garlic and onions are good dietary sources of sulfur compounds.

Glycine

Glycine has been used as an aid for many toxic conditions. As long ago as the 1960s, pioneer nutrition researcher Roger Williams, Ph.D., recommended it for alcoholics and others exposed to high levels of chemical toxins. It works through several mechanisms to support Phase II detoxification.

It is used in direct conjugation of xenobiotics and for the synthesis of glutathione, and indirectly aids in the production of glucuronic acid, which is used in glucuronidation.

Brassica family foods

Brassica family foods (cabbage, cauliflower, and especially brussels sprouts) contain several compounds that greatly improve the functioning of liver detoxification.[150,151] The flavonoids and carbinols contained in these foods increase the activity of the Phase II glutathione-S-transferase detoxification system. These foods are especially valuable in the prevention of cancer.[152]

Vitamin C

Vitamin C is a cofactor in both Phase I and Phase II detoxification processes.[153] Exposure to xenobiotics causes up-regulation of the specific enzymes that detoxify these substances. Because humans lack the ability to produce their own vitamin C, exposure to toxins increases the need for vitamin C. Unfortunately, both smoking and exposure to cigarette smoke deplete the body's vitamin C stores.[154]

Glutathione

Glutathione, utilized in the liver in Phase II conjugation, is available in the diet and synthesized from the amino acids glycine, cysteine, and glutamic acid. Glutathione intercepts toxic compounds by combining with them to form a water-soluble conjugate, which is discharged harmlessly in body wastes. Glutathione is also a component of glutathione S-transferase, a liver enzyme important in alcohol detoxification.[155] *Silybum marianum* not only prevents the depletion of glutathione caused by alcohol and other liver toxins, but has been found to even increase the levels of glutathione in the liver by 35% over controls. This is extremely useful when exposure to toxic substances is high.

Controlling Toxins

We need to decrease our exposure to toxins, and when present, eliminate them from our body as rapidly and safely as possible. This entails a bit of detective work to determine what we are being exposed to. However, this can be difficult, so I recommend concentrating on those that most commonly affect the most people. In general, we need to control four major sources of toxins: bowel toxins, free radicals, heavy metals, and environmental poisons.

Since the intestines are a major consistent source of toxins for most of us, improving the health of the intestines is one of the most effective actions we can take to improve our health. Even though we may be exposed to other sources of toxins, decreasing the load on the liver from the intestines allows the liver to more effectively eliminate the other toxins, whether from the environment or faulty metabolic processes. This entails both decreasing the

amount of toxins in the intestines and healing the damaged intestines so they are a better barrier to the toxins they contain.

The other highly effective action we can take is to optimize our free radical defenses, since so many of the damaging effects of toxins are mediated through free-radical damage.

Supporting Intestinal Health

Reestablishing a healthy intestine is critical for health because a leaky gut full of poisonous bacteria and toxic metabolites contributes to many chronic diseases. In addition, an unhealthy intestine can result in malabsorption and malnutrition, leading to a wide range of metabolic dysfunctions. Healing the intestines can rapidly relieve symptoms and gradually improve health and vitality.

Healing the damaged intestinal mucosa requires a comprehensive approach that includes eliminating all factors that injure the intestine (such as toxic bacteria), reestablishing the normal bowel flora, removing toxins from the intestines, improving digestion (see Chapter Seven), decreasing inflammation, and promoting the metabolism and repair of the intestinal-lining cells.

Eliminating Toxic Bacteria and Yeasts

Toxic bacteria in the bowel both directly damage the intestinal lining cells and release toxins that can be absorbed into the body. Most bowel pathogens can be eliminated by the use of two herbs: goldenseal and garlic.

Hydrastis canadensis (Goldenseal)

Goldenseal is a useful herb for all kinds of infections, including those of the intestines. It is especially of value when toxic bacteria are overgrowing the gut. The alkaloid berberine that is found in *Hydrastis canadensis*, works in two ways: First, it kills abnormal bacteria and second, it inhibits the activity of the bacterial enzymes that damage the intestinal cells. By inhibiting these damaging microbial enzymes (called decarboxylase enzymes) it blocks the production of vasoactive amines such as histamine, tyramine, putrescine, and cadaverine, all of which contribute to increased intestinal permeability.[156] Unlike antibiotics which decimate healthy as well as toxic bacteria, *Hydrastis* has the remarkable property of leaving the lactobacilli we need for intestinal health alone.

- *Dosage:* 2 gm of goldenseal root three times per day for two weeks

Allium sativum (Garlic)

Garlic is very useful for eliminating toxic microorganisms, especially yeasts, from the intestine. It directly inhibits several toxic intestinal microorganisms, such as *Staphylococcus*, *Streptococcus*, *Bacillus*, *Brucella*, *Salmonella enteritidis*, *Candida albicans*, *Mycobacteria*, *Cryptococcus neoformans* and *Vibrio* species, even at low concentrations.[157,158,159,160] The most effective extracts of garlic

for antimicrobial activity are those that are high in allicin—the aged extracts, while effective for lowering cholesterol, are not effective for killing off pathogens. One caveat: Those with a poorly functioning sulfoxidation enzyme system (see discussion above) need to limit their garlic consumption since they have trouble metabolizing its sulfur-containing compounds.

- *Dosage:* Eat freely as part of a regular healthful diet and take ½ a clove (or equivalent in garlic extract) three times a day

Reseeding the Intestines with Health-Promoting Bacteria

Fundamental to correction of gastrointestinal dysfunction is re-establishment of the appropriate microbial flora of the intestine. The health-inducing bacteria are especially important because they suppress the growth of toxic bacteria. Reseeding the intestines is done through the use of probiotics and prebiotics. Probiotics are the intestinal bacteria found in the healthy intestines. Prebiotics are indigestible substances that help the healthful bacteria grow. Prebiotics also help by increasing the production of secretory IgA in the intestines, which also helps protect against bacteria and food allergens.[161]

Probiotics

The primary beneficial organisms used to reseed the intestines are *Lactobacilli* and *Bifidobacteria*. They play many important roles, a crucial one of which is inhibiting the growth of toxic bacteria, viruses, fungi, yeasts, and parasites.[162] These health-promoting intestinal bacteria also aid in digestion, synthesize vitamins (folic acid and other B vitamins), reduce blood ammonia levels, lower cholesterol levels, neutralize carcinogens, and stimulate the immune system.[163]

As important as these bacteria are to reestablishing the health of the bowel, finding effective products is difficult. One problem is that most of the traditional sources, i.e., fermented products such as yogurt, miso, and some cheeses, no longer contain *lactobacilli* because commercial production has switched to other bacteria that work better for mass production. Unfortunately, the bacterial strains they use have little value for human health. The other problem is that most of the *lactobacilli* products on the market are either the wrong strain or contain so few live bacteria that they have little effect. Two forms I've found to be clinically effective are Eugalin Forte (available in health food stores) and HMF (available from InterPlexus in Kent, Washington 1-800-875-0511).

- *Dosage: Lactobacilli*-containing dairy products and 2 (250 mg each) capsules of *Lactobacilli* + *Bifidobacteria* twice a day between meals

Prebiotics

An important part of reseeding the intestines is to ensure that the food the health-promoting bacteria need to live on is easily available. One of the best ways to do this is with oligosaccharides, especially fructooligosaccharides.

Fructooligosaccharides are short-chain carbohydrates composed of three to ten molecules of sugars, at least two of which are fructose. This molecule is essentially indigestible by humans. However, the good intestinal bacteria, *Bifidobacteria* and *Lactobacilli*, preferentially utilize fructooligosaccharides to grow and multiply. In contrast, toxic bacteria are unable to use these short-chain carbohydrates.[164] Fructooligosaccharides also help by inhibiting the attachment of toxic and parasitic bacteria to the gastrointestinal mucosa.[165] Foods rich in fructooligosaccharides include onions, asparagus, bananas, and maple syrup.

In addition to containing fructooligosaccharides, bananas help heal the damaged intestinal mucosa because they contain water-soluble polysaccharides, pectin, and valuable phospholipids.

- *Dosage:* 1 gm of fructooligosaccharides or two bananas per day

Removing Toxins from the Intestines

Not only do we need to remove toxins from the intestines to help promote health, but we should also try to keep them from accumulating in the first place. A high-fiber diet is one of the most effective ways to keep toxins from accumulating. Fiber consumption is most easily increased by eating a whole-foods diet. However, fiber supplementation also works. Increasing fiber intake (via whole, unprocessed grains, vegetables, and fruits) aids digestion, decreases the amount of time toxins stay in the intestine, and decreases toxin absorption from the gut. Fiber increases the excretion of bacterial breakdown products as well as the protein putrefaction metabolites found in the gut.[166]

Dietary fiber also helps to maintain healthful colonic bacterial flora. A low-fiber intake is associated with an overgrowth of endotoxin-producing bacteria and a lower percentage of *Lactobacilli* and other healthful bacteria.[167] A high-fiber diet provides short-chain fatty acids, which are metabolized by healthful bacteria to provide some of the fuel used by the intestinal mucosal cells.

Pectin (a fiber found in fruit and also available as a supplement) increases the secretion of digestive enzymes (trypsin, chymotrypsin, lipase, and amylase), prevents absorption of toxic molecules in the bowel, and decreases transit time, thus decreasing the opportunity for absorption of toxins.[168]

Protecting the Intestines and Stimulating Repair

The most common non-bacterial causes of intestinal damage are non-steroidal anti-inflammatory drugs (NSAIDs); ingestion of allergenic foods; consumption of alcohol, chemicals, and drugs; trauma; and endotoxemia. The first step in protecting our intestines is to control what we put in our mouth!

Glutathione Just like in the liver, glutathione is useful in the intestine for helping stimulate cell regeneration and protecting against further damage since

it works both as a free radical quencher and as a direct neutralizer of some toxins. When the antioxidant properties of glutathione are being used, extra selenium is needed to help convert it back to its healthy form.[169]

- *Dosage:* 100 mg glutathione twice a day

Quercetin Cromolyn sodium is a prescription drug that inhibits the release of inflammatory chemicals from sensitized mast cells. It has been used in many clinical trials to reduce the intestinal damage caused by ingestion of food allergens.[170] Quercetin is a natural bioflavonoid with similar metabolic and clinical effects. Quercetin and other bioflavonoids have been shown to inhibit the release of inflammatory chemicals from mast cells, scavenge free radicals, and inhibit irritability of the muscles of the intestines.[171] Naturopathic doctors use quercetin to help control food allergies and heal the damaged intestinal mucosa in chronic inflammatory bowel disease. It's also useful in the treatment of such conditions as acute and chronic diarrhea and stomach ulcers.

- *Dosage:* 500 mg of quercetin 15 to 20 minutes before meals

Anti-Oxidants A significant portion of the intestinal mucosal damage is due to free radicals produced by the inflammatory reaction to food allergens and intestinal toxins. The problem with free radicals is further aggregated when the blood supply to the intestines is inadequate.[172] Administration of free radical scavengers helps neutralize these toxic chemicals. Some common natural antioxidants are: vitamin E, beta-carotene, ascorbic acid, zinc, selenium, and superoxide dismutase.

Avoiding allergenic foods

Researchers have observed that intestinal permeability increases even after ingestion of an amount of an allergenic food that is not large enough to cause a clinical reaction.[173] In other words, eating any amount of a food allergen appears to damage the intestines, but overt clinical symptoms don't appear until the leakage gets bad enough. Apparently people with food allergies have intestines that are especially sensitive to food allergens. For example, a number of studies have shown that people with food allergies have increased permeability even while fasting and that the permeability further increased after ingestion of an offending allergen. Fortunately, the intestines heal quickly (within a few days) when the offending food is removed.

Digestive aids

A poor digestive function causes many problems: malnutrition, food allergies, and an increased risk of intestinal infections. Most people with food allergies have an inadequate digestive system. Poor digestion (as discussed in Chapter Seven) means large molecules are in the intestine where they don't belong. Digestive aids—such as fungal enzymes, HCl, pepsin, and pancreatin—help to

lessen the allergic damage done to the intestines when allergenic foods are eaten by ensuring that the food molecules are broken down the way they should be. As might be expected, patients with low stomach acid have increased gastrointestinal permeability and an increased delivery of bacterial toxins to the liver. Interestingly, maldigestion does not cause as much trouble with fat and carbohydrate absorption as it does with protein and trace mineral absorption.[174] This means people can absorb enough calories to be fat, but not enough nutrients to be healthy and energetic.

When our digestion is functioning properly, the enzymes released by the pancreas digest food constituents (specifically the short-chain fatty acid carboxylic acid) into acetate, propionate and butyrate, all essential nutrients for the intestinal mucosal cells. However, when the digestion is not working properly, bacterial fermentation occurs instead. This results in the production of isobutyrate, valarate, and isovalarate, which are not utilizable by the intestinal mucosa.[175] Butyric acid is manufactured in the lower intestines as a by-product of bacterial fermentation of fiber. It is the main energy source for lower intestinal epithelial cells and is important for the repair and regeneration of damaged cells.[176]

Glutamine

Glutamine (the most abundant amino acid in the blood) is one of the principle fuels used by the intestinal lining cells, accounting for 35% of their energy production. While readily available in the diet and synthesized in the body, supplementation improves the energy metabolism of the gastrointestinal mucosa, thus stimulating regeneration.[177] Glutamine prevents intestinal mucosal damage and has been shown to decrease bacterial leakage across the intestines after they are damaged, presumably by stimulating repair.[178]

Glutamine supplementation is of particular value for healing the serious, even life-threatening, intestinal damage caused by abdominal irradiation.[179] Glutamine is also important any time there are intense demands for cellular repair, such as after major surgery and severe burns. During these times, glutamine levels drop precipitously and blood flow to the intestines is reduced. This adds up to a significant problem for the intestinal cells and is why intestinal degeneration is seen in those with severe trauma, such as burns over large areas of their body. Glutamine supplementation is also of value for enhancing repair of the damage seen in chronic intestinal diseases such as Crohn's disease and colitis.[180]

- *Dosage:* 500 mg glutamine three times a day

Fasting The intestinal mucosa appears to heal during fasting as indicated by the decrease in intestinal permeability seen in patients who fast. Fasting patients with rheumatoid arthritis decrease their intestinal leakage after only four days. After seven to ten days their joint tenderness, pain and stiffness is reduced as is their sedimentation rate and level of acute phase reacting plasma

proteins (both measures of inflammation in the body). However, returning to the same diet results in a return of symptoms and intestinal leakage after only one week.[181] Predictably, the researchers interpreted this to mean fasts were of no long-term value for arthritis. A better interpretation is that they started eating their food allergens again and reestablished the pathology in their intestines and subsequently their joints. Although described as a fast, they were actually on diluted fruit and vegetable juice (2–3 liters per day). Very long fasts, such as over three weeks can result in damage to the intestines and digestive processes and should never be attempted without the guidance of a practitioner highly experienced in supervising fasts. Interestingly, one of the reasons long-term fasting can be a problem is that it causes depletion of glutamine.

Neutralizing Free Radicals

Considering the serious and widespread damage that free radicals cause, it is not surprising that the body utilizes many mechanisms to neutralize them. Most of these processes use antioxidants, i.e., substances that neutralize free radicals. Antioxidants can be either nutrients or enzyme systems, which either directly attack oxidants or regenerate antioxidant nutrients. Table 5-21 lists the antioxidant defenses that protect against free radicals.

Nutrient Antioxidants

A healthful diet provides a wide range of substances, primarily of plant origin, that act as antioxidants. Some have been classified as required vitamins while others appear to be important but have not (yet) been recognized as required.

Table 5-21 Antioxidant Defenses

Nutrient Antioxidants	Vitamin E Vitamin C Carotenoids Xanthophylls Flavonoids
Antioxidant Enzymes	Superoxide dismutases (require copper, zinc, manganese) Catalases (require iron) Glutathione peroxidases (require selenium)
Antioxidants Made by the Body	Glutathione Coenzyme Q_{10} Melatonin
Herbal Antioxidants	*Silybum marianum* (Milk thistle) Picnogenols Livotrit

This is probably due to the current bias of the RDAs toward only classifying substances as vitamins if a deficiency results in a specific disease. Unfortunately, this ignores the role of those nutrients whose primary role is to promote health and prevent or ameliorate disease. As might be expected. a diet of whole, unrefined foods, especially those of vegetable origin, contains the highest levels of these important nutrients.

Vitamin E

One of the most important and well-known antioxidants is vitamin E (tocopherol). It actually includes eight fat-soluble compounds, of which alpha-tocopherol is the best known. Vitamin E is a very important antioxidant for the heart, blood lipids, and cell membranes. Vitamin E also inhibits the formation of nitrosamines (highly carcinogenic and inflammatory substances), and decreases inappropriate blood clot formation.[182,183] These protective actions help to ensure proper functioning of the many biological processes needed for health.

The current RDA for vitamin E is 15 iu (10 mg alpha tocopherol equivalents, or TE) for men and 12 iu (8 mg TE) for women, which isn't sufficient. This amount is designed to prevent myopathy and neuropathy, but is far too low to maintain optimal health. Several studies have shown that supposedly healthy people eating diets supplying the RDA of vitamin E have less oxidative damage when supplemented with vitamin E at a modest 150 iu per day.[184] The real daily requirement varies according to the amount of oxidative stress a person experiences. Living in a polluted city, consuming large amounts of polyunsaturated fatty acids (such as fish oils), and heavy exercise—all increase the need for vitamin E and other antioxidants. And even though too low, the RDA still isn't met by the typical U.S. diet.

Because the best sources of vitamin E—unrefined vegetable oils, wheat germ, liver, and eggs—are high-fat foods, it is difficult to provide high levels of vitamin E in the diet without supplementation. Synthetic vitamin E contains a mixture of d and l isomers (meaning they are mirror images of each other). Only the d form is active in the body. Combining vitamin E with acetate, succinate, or palmitate makes it more chemically stable. Whether this makes it more clinically useful has yet to be determined.

Vitamin E itself becomes a free radical after its neutralizes a more toxic free radical. Fortunately, the vitamin E radical does not readily attack lipids and proteins and will decompose. It can also be converted back to the normal antioxidant vitamin E by vitamin C, glutathione, and coenzyme Q_{10}.[185,186]

Topical applications of vitamin E are also very effective. For example, rubbing vitamin E on your skin will greatly decrease the redness, inflammation and skin sensitivity from sunburn, a very visible demonstration of its anti-inflammatory properties.[187]

- *Dosage:* 600 iu mixed tocopherols a day

Vitamin C

Vitamin C is a prominent, water-soluble antioxidant present in body fluids and the cells. It is a very efficient antioxidant and can neutralize a wide range of free radicals including superoxide, singlet oxygen, hypochlorite, and sulfur radicals.[188] Vitamin C protects lipids and cell membranes from oxidative damage by neutralizing peroxyl and hydroxyl radicals. This helps to reduce the risk of cataracts and retinal damage, increase immune function, and decrease heavy metal toxicity.[189,190,191]

Supplementing with vitamin C reduces the gastrointestinal production of fecal mutagens—potent cancer-causing chemicals.[192] This, along with vitamin C's immune potentiation, probably explains why increased vitamin C intake is correlated with a reduced risk of cancer of the cervix, stomach, colon, and lung.[193] Vitamin C supplementation also reduces oxidation of fats in the blood, important for protection from atherosclerosis.[55]

Several research studies have demonstrated that vitamin C supplementation protects cells from radiation-induced transformation to cancerous forms. Vitamin C apparently accomplishes this by quenching the free radicals produced by the irradiation before they can interact with the cell's DNA and other important components. This protective effect has been demonstrated in cells in the laboratory as well as in cells in irradiated animals.[194,195] If you are planning to get a diagnostic x-ray, take your vitamin C first!

Vitamin C works with glutathione and lipoic acid to regenerate vitamin E. Like vitamin E, vitamin C is also converted to a free radical when it neutralizes oxidants. Fortunately, also like the vitamin E radical, the vitamin C radical (dehydroascorbate) is relatively stable, has little tendency to attack cells, and can be converted back to vitamin C.

- *Dosage:* 500 mg vitamin C twice a day

Carotenoids

Carotenoids represent over 500 different plant pigments and are divided into carotenes and xanthophylls (oxygenated carotenes). Beta-carotene is the most abundant carotenoid in nature and is the major carotenoid in the liver, adrenal gland, kidney, ovary, and fat tissues. However, it represents only 25 to 33% of the carotenoids in plasma, possibly because xanthophylls make up 90% of the carotenoids in green leafy vegetables, a major source of dietary carotenoids for humans. Lycopene, a red pigment from tomatoes, is prevalent in the testes, prostate, and human plasma.[196]

In general, carotenoids are versatile antioxidants and lycopene, lutein, and zeaxanthin are all effective quenchers of free radicals, although they do not form vitamin A, as does beta-carotene.[197] Beta-carotene is especially effective at low oxygen levels such as that found in tissues.[198]

The antioxidant effects of carotenoids result in significant health benefits as listed in Table 5-22.The correlation of carotenoid consumption with cancer

Table 5-22 Health Effects of Carotenoids[201,202,203]

Decreased blood lipid oxidation
Protection against coronary artery disease
Decreased risk of age-related macular degeneration, the most common cause of old age blindness
Decreased incidence of some forms of cancer

prevention has received considerable research interest, with 29 of 31 studies showing significant protection.[199] However, a highly publicized study of Finnish men with a long history of heavy cigarette smoking and alcohol use failed to find a reduced risk with beta-carotene supplementation.[200] This unexpected result has several possible explanations: the researchers were using synthetic beta-carotene, which is different from the natural; these people's diet and lifestyle were so bad that the antioxidants might have little effect; and, while high levels of beta-carotene in the blood are certainly associated with a lower incidence of cancer, it may only be a marker for another as yet unrecognized nutrient.

- *Dosage:* 25 mg mixed natural carotenoids a day

Flavonoids

One of the largest classes of dietary antioxidants is the flavonoids. They are found mainly in fruits, vegetables, legumes, and tea. About 5,000 flavonoids have been reported, with quercetin and kaempferol being among the most abundant. Flavonoids directly neutralize free radicals, potentiate the effects of vitamin C (as vitamin C potentiates the action of flavonoids), and protect other easily oxidizable substances.[204] Flavonoids are especially effective antioxidants, several times as powerful as vitamins E and C. Unfortunately, the typical U.S. diet contains only about 23 mg a day.

- *Dosage:* 500 mg mixed flavonoids a day

Table 5-23 Antioxidant Effects of Various Flavonoids[205,206,207,208,209]

Flavonoid	*Effect*
Rutin, myricetin, and quercetin	Scavenge superoxide and block LDL oxidation
Anthocyanidins (from blueberries and grapes)	Protect collagen from superoxides
Many flavonoids	Bind metals, limiting their ability to catalyze free radical formation
Most flavonoids	Decrease risk of some forms of cancer and cardiovascular disease

Antioxidant Enzymes

Oxidant detoxification enzyme systems occur throughout our cells, tissues, and fluids. Three types detoxify free radicals: superoxide dismutase, catalase, and glutathione peroxidase. These enzymes work together to neutralize oxidants through several steps.

Superoxide dismutase

Superoxide dismutase (SOD) very rapidly converts free radicals into hydrogen peroxide (H_2O_2) before they can damage tissues. Because hydrogen peroxide itself is highly reactive, SOD operates in conjunction with catalase and glutathione peroxidase, which break it down further to water. Several different types of superoxide dismutase exist. The form in the mitochondria requires the trace mineral manganese, while the form in the cell requires copper and zinc. That's why these trace mineral nutrients are often classified as antioxidants, although it is actually the enzyme that they activate that does the antioxidant work. During acute inflammation, the manganese form of SOD increases as part of the body's process to ensure the inflammatory processes do not get out of control.[210]

SOD is a useful therapeutic agent. However, as a supplement it is not very well-absorbed (about 10%) into the body because it is damaged by the digestive processes.[211] Special forms of SOD have now been synthesized to improve its absorption and utilization by the body. In one of these, it is bound up in a liposome (a little ball of fat). Liposomal SOD has been successfully used to treat patients with Crohn's disease.[212] Administering SOD bound to polyethylene glycol together with catalase has been shown to reduce the damage from experimental trauma in animals.[213]

- *Dosage:* 10 mg of manganese, 5 mg of copper, 25 mg zinc per day

Catalase

Catalase is an iron-dependent enzyme that occurs widely in cells. Its primary function is to neutralize hydrogen peroxide. Animal studies with catalase, usually in conjunction with SOD, suggest it provides protection against ischemic (low blood supply) injury to the retina, free radical damage to the intestine, and the free radicals produced by radiation.[214,215,216]

A zinc-dependent version of catalase appears to be especially important for protecting the macula (the part of the eye responsible for acute vision). When compared to matched controls, catalase activity in eyes with signs of macular degeneration is reduced by 32%. Supplementation of zinc in patients with macular degeneration has shown reduced vision loss.[217]

- *Dosage:* 10 mg of iron and 10 mg of zinc per day

Glutathione Peroxidase

This family of enzymes disposes of peroxides, such as hydrogen peroxide. Glutathione peroxidase requires the trace mineral selenium for activation, which

is why selenium is sometimes referred to as an antioxidant nutrient. Glutathione peroxidase exists in several forms, and more is synthesized when needed. For example, in animal models, exhaustive exercise causes oxidative stress leading to increased levels of SOD, glutathione peroxidase, and glutathione transferase. On the other hand, prior supplementation with vitamin E and selenium reduced free radical production and lesser amounts of detoxification enzymes were produced.[218]

- *Dosage:* 150 μg selenium per day

Antioxidants Made by the Body

The body makes several special compounds that provide antioxidant support, especially in the mitochondria and the cells.

Glutathione (GSH)

Glutathione occurs in high concentrations in most cells, where it is used by the antioxidant enzyme glutathione peroxidase. It also works together with vitamin C to regenerate vitamin E. In addition, glutathione directly neutralizes several free radicals (singlet oxygen, hydroxyl radicals, and superoxide radicals). This neutralization results in the oxidation of glutathione (GSSG), which is converted back to the normal form by reductase enzymes.[219] In a healthy person, the ratio of normal to oxidized glutathione (GSH/GSSG) is greater than 100 to 1. However, when a person is exposed to high levels of free radicals (oxidative stress), this ratio is decreased. AIDS patients have substantially depressed levels of glutathione in their cells, apparently due to the chronic inflammation they suffer.

- *Dosage:* 100 mg glutathione twice a day

Coenzyme Q_{10} (Ubiquinone)

Ubiquinone are fat-soluble antioxidants. The most common form in humans is ubiquinone-10 or coenzyme Q_{10} (CoQ_{10}). CoQ_{10} protects lipids, especially the very delicate membranes within the cells, against oxidation.[220] It is especially effective in protecting the heart cells from toxic chemicals.[221] In addition, CoQ_{10} can regenerate vitamin E.[222] CoQ_{10} synthesis in the body requires vitamins B_2, B_6, B_{12} and folate, and synthesis is limited in people with low intake of these nutrients. CoQ_{10} deficiencies commonly occur in older persons, being 65% lower in 80 year olds compared to 20 year olds.[223] Because CoQ_{10} is not well-absorbed, increasing plasma CoQ_{10} levels through diet (liver, heart, and germs of grains are rich sources) or supplementation can be difficult.

- *Dosage:* 10 mg of coenzyme Q_{10} per day (people with AIDS have even more trouble absorbing coenzyme Q_{10}, so we recommend 100 mg in our teaching clinic)

Melatonin

Melatonin is best known for its role in setting the circadian rhythms and in helping initiate the sleep process. However, equally important, it is a potent and efficient free-radical scavenger. The central nervous system consumes 20% of the oxygen used daily and generates free radicals at a high rate. Normally present in high concentrations in the nervous system, melatonin appears to play a pivotal part in preventing oxidative damage to the nerves and brain.[224] Aged animals and humans are melatonin-deficient and more sensitive to oxidative stress. Melatonin supplementation and treatments aimed at preserving the endogenous rhythm of melatonin formation appear to retard the rate of aging and the time of onset of age-related diseases.[225]

- *Dosage:* Start with 1 mg half an hour before going to bed. Increase the dose until effective, but no more than 5 mg.

Herbal Antioxidants

Herbs have been used since antiquity by natural medicine practitioners around the world. Interestingly, modern research suggests that many of their medicinal properties are due to the antioxidants they contain, especially their flavonoid constituents. In fact, some of the most potent antioxidants currently known, such as the flavonoid silymarin from milk thistle, are found in traditional herbal medicines. Another example is the antioxidant activity of procyanidolic oligomers from grape seed skins which is a remarkable 50 times that of vitamin C and vitamin E. Another valuable aspect of these botanical medicines is their tendency to concentrate their antioxidants in specific organs. For example, silymarin from *Silybum marianum* concentrates in the liver, which may explain why it is such an effective protective agent for the liver. This tendency of herbal constituents to concentrate in specific organs has led to the concept of organ specificity of herbs. Table 5-24 lists the antioxidant activity and tissue predilection of several herbs as well as the conditions they help alleviate. All dosages are for the standardized extracts.

How to Decide Which Antioxidant to Use

The extreme diversity of free radicals and the mechanisms and sites for oxidant damage means that no single antioxidant could possibly provide all the protection we need. Also, in general, antioxidants and antioxidant enzyme systems appear to work best synergistically. As might be expected, animal studies indicate that a diversity of antioxidants provides more antioxidant protection than a single nutrient.[226]

Table 5-25 provides my recommended intake of antioxidants for maximum protection from free radicals (based on a comprehensive chapter written by Dr. Robert Ronzio for *A Textbook of Natural Medicine*). Adequate amounts of a broad spectrum of antioxidants are essential to promote optimal health and to minimize the effects of aging, degenerative disease, and toxin exposure.

Table 5-24 Antioxidant Herbs

Herb	*Antioxidant Constituents*	*Target Tissue*	*Conditions*	*Daily Dosage*
Crataegus oxyacantha (hawthorn berry)	Anthocyanidins and proanthocyanidins (also known as procyanidins)	Heart	Congestive heart failure, atherosclerosis, hypertension	100–250 mg
Ginkgo biloba	Ginkgoflavonoglycosides	Brain	Dementia, Alzheimer's disease, cerebral ischemia	120 mg
Vaccinum myrtillus (blueberry)	Anthocyanidins	Retina of eye	Macular degeneration, myopia, glaucoma, cataracts	150 mg
Vitex vinifera (grape seed skins) and pine bark	Procyanidolic oligomers (also known as pycnogenols)	Blood vessels	Varicose veins, diabetic retinopathy, atherosclerosis	50 mg

Removing Heavy Metals

Acute poisoning or the accumulation of high levels of heavy metals requires the immediate expert care of a physician skilled in environmental medicine. Such situations are extremely dangerous and typically require intravenous administration of chelating drugs. Fortunately, such situations are rare. Lower levels of exposure can be effectively treated with nutrition (See Table 5-26), when the heavy metal toxin has been identified and the source of contamination controlled.

Detoxification

Detoxification, simply defined as the removal of toxins from the body, is accomplished by stimulating the body tissues to release toxins and then neutralizing or excreting them as rapidly as possible. Eating a wholesome diet, adopting a healthful lifestyle, and following the advice above for improving the detoxification function of the liver and healing and detoxifying the intestines will result in progressive elimination of toxins over time. However, some may want to accelerate the process. The fastest way is through fasting.

However, before fasting, the routes of elimination from the body must be open and fully functional. There is no point in stirring up toxins if there is no way to eliminate them or if they are released faster than the body can cope with them. This is why the best detoxification results are found when the liver's detoxification enzyme systems are working at their best and the bowel is healthy enough to ensure that toxins excreted into it are quickly removed from

Table 5-25 Recommended Daily Dosages of Antioxidants

Nutrient	*Daily Dosage*	*Potential Toxicity*
Mixed tocopherols	600 iu	No significant toxicity for natural tocopherols has been reported. Mild, reversible side effects have been noted at intakes greater than 1,000 mg per day.
Mixed carotenoids	25 mg	Generally, no adverse side effects have been noted other than hypercarotenemia (skin turning yellow) at levels above 30 mg per day.
Vitamin C	2,000 mg	There are generally no adverse effects with long-term consumption of up to several grams of vitamin C daily.
Vitamin A	5,000 iu	Toxicity with chronic consumption of 25,000 retinol equivalents per day can occur rarely. Levels above 100,000 iu per day commonly causes problems.
Copper	5 mg	High copper content in drinking water has been associated with a significantly elevated incidence of atherosclerosis.
Manganese	10 mg	Large amounts may raise blood pressure and chronic overdose may cause neurologic disorders.
Selenium	150 μg	Excessive selenium can be toxic.
Zinc	25 mg	High levels (>75 mg per day) block copper assimilation and are immunosuppressive.
Ginkgo biloba	120 mg	None known
Vaccinum myrtillus	50 mg	None known

the body. Also, great caution should be exercised by those who have high levels of toxins. For example, when patients suffering from significant contamination with fat-soluble toxins, such as DDT, fast, so much DDT is released into circulation that it can reach blood levels toxic to the nervous system.[235]

Fasting

Fasting is a potent and very rapid method for eliminating toxins from our bodies. However, I'm of two minds on fasting and no longer support fasts of over two weeks. For centuries, fasting has been used around the world as an effective therapeutic tool. However, recent research tells us that the toxins released by fasting quickly use up the nutrients in the liver needed for Phase II detoxification. This results in increased toxicity *while* toxins are being released. This problem can be alleviated by using products that support the liver while engaging in a more modest fast.

Although our culture fears fasting and assumes death is imminent after only a few days, as long as water is available, the average adult can actually go

Table 5-26 Nutrients to Chelate Heavy Metals Out of the Body[227,228,229,230,231,232,233,234]

Heavy Metal	*Nutrient Chelate*	*Dosage*
Arsenic	N-acetylcysteine (NAC)	1 gm per day
Cadmium	Garlic	1 clove (or equivalent) three times a day
	Selenium	250 µg per day
	Zinc	50 mg per day
Gold	Garlic	1 clove (or equivalent) three times a day
Lead	Garlic	1 clove (or equivalent) three times a day
	Onion	3 oz three times a day
	Pectin	3 gm per day
	Methionine	100 mg per day
	Selenium	250 µg per day
	Thiamin (B_1)	100 mg per day
	Zinc	200 mg per day(this dosage should only be used under the supervision of a physician)
Mercury	Garlic	1 clove (or equivalent) three times a day
	Selenium	250 µg per day
	Vitamin E	1,000 iu per day
Silver	Selenium	250 µg per day

without any food for quite a long period of time. As can be seen in Table 5-27, the body has several sources of energy reserve, with protein and fat providing the most. Under extreme circumstances, the average adult can actually survive without food for over two months. This is obviously not recommended! I have supervised water fasts as long as 30 days, although I no longer believe such a long time is healthful. The longest water fast I have done myself was ten days.

What happens during a fast

During fasting, the body's metabolic processes change in several ways, according to the length of the fast. The physiology of fasting is a highly ordered series of events that conserve body energy reserves while maintaining the basic metabolic rate (which decreases by about 1% per day during fasting, until it stabilizes at about 75% of normal).[236] It has been suggested that humans, like other species, have evolved as a survival mechanism special biochemical pathways to subsist for long periods of time without food.[237] Some believe this has also evolved as an important part of the self-healing process.

The body's response to the lack of energy input can be divided into three stages: early fasting, fasting, and starvation. Maintaining adequate energy resources for metabolism during fasting involves several adaptations, which change as the body moves from one stage to the next.

Normally, glucose, fatty acids, and amino acids are the major energy fuels of the body. The initial physiological response to the lack of food is the breakdown of glycogen by the liver to produce glucose for release into the bloodstream.

Table 5-27 Energy Reserve Utilization

Energy Source	*Reserve (These estimates are based on 100% utilization of each fuel)*
Glucose	1 hour
Food in the digestive tract	4 to 8 hours
Glycogen	12 hours
Amino acids	48 hours
Protein	3 weeks (if protein were the only fuel used for gluconeogenesis) 24 weeks (obligatory loss only)
Triglycerides	8 weeks

Glucose is especially needed by the red blood cells and the brain, which consumes about 65% of the total circulating glucose.[238] Together they consume 100 to 180 gm of glucose per day. Early in fasting, the liver is the sole source of glucose for the bloodstream. However, liver glycogen stores can only supply enough glucose for a few hours. (Although muscle actually contains more glycogen than the liver, it lacks the needed enzymes to convert glycogen to glucose for release into the bloodstream.[239]) The liver then begins converting amino acids to glucose, a process called gluconeogenesis. Interestingly, later in fasting, the glycogen reserves are restored.

Since liver's amino acid stores are also limited, amino acids from other tissues, primarily the muscles, are accessed. As the fast proceeds, the kidneys become progressively more important in the maintenance of blood glucose levels, and eventually the renal cortex synthesizes more glucose from amino acids than does the liver. If the body continued to require its normal 100 to 180 gm of glucose a day for the brain, gluconeogenesis during fasting would quickly use up much body protein, and death would ensue within three to four weeks. During the early stages of fasting, the body converts 60 to 84 gm of protein to glucose per day.

After two to three days, the body converts to using the fat stores as the primary source of energy.[240] At this stage, the liver produces energy from the fatty acids released by the breakdown of triglycerides (the storage form of fat) in the fat cells. The brain also changes its metabolic processes and begins to use fatty acids for energy (technically described as oxidation of beta-hydroxybutyrate) instead of sugar. However, there is still a need for approximately 80 gm of glucose a day for the brain, red cells, muscles, and other tissues. This requirement increases significantly during exercise. Some of the needed glucose is synthesized from glycerol, which is released when the fat cells give up fatty acids. The rest of the glucose requirement is met by the catabolism of 18 to 24 gm of protein a day. These metabolic changes result in the elevation of ketones in the blood, which appear in the urine by the third day.

An average 154-pound male has the fat stores to maintain basic caloric requirements for two to three months of fasting. Starvation occurs when the

body's fat reserves are depleted and significant protein catabolism again becomes necessary for energy production. The body's protein stores are adequate for only a few weeks, after which essential proteins are utilized and death occurs.

Why fasting can be beneficial

Unfortunately, most of the fasting research has been focused on understanding how the body maintains energy levels and determining whether it was effective in treating various diseases. However, some tantalizing research suggests the mechanisms by which fasting helps to promote health. Obviously, it is very effective in removing toxins from the fat (and other) stores, because fat-soluble toxins are rapidly released during fasting. However, probably its most useful effects for detoxification are immune system enhancement, removal of immune complexes from the blood, and removal of food allergens from the intestines.

Changes in the immune system during fasting include: increased macrophage activity, increased cell-mediated immunity (T lymphocytes and lymphokines), decreased complement factors, decreased antigen-antibody complexes, increased immunoglobulin levels, increased neutrophil bactericidal activity, depressed lymphocyte blastogenesis, heightened monocyte killing and bactericidal function, and enhanced natural killer cell activity.[241,242] The net effect appears to be an increase in the toxin scavenging activity of the white cells combined with elimination of immune complexes, which can cause widespread inflammatory damage in the body.

The leaky gut syndrome may help to explain why fasting leads to improvement of chronic inflammatory diseases such as rheumatoid arthritis. Fasting reduces gut permeability by allowing the damaged intestines to heal when the offending foods are removed.[243]

Chronic food restriction has been well-documented as increasing longevity and decreasing cancer in animals. This is probably partially due to an increased rate of detoxification. For example, in rat research, it was found that food restriction increased the detoxification of the polycyclic aromatic hydrocarbons (benzopyrene), which are carcinogenic. This detoxification process may be important in the protective action of reduced food intake.[244] Table 5-28 lists diseases that have been alleviated by fasting. Note, however, that some of this research is very old and has not been verified by more recent rigorous standards.

Table 5-28 Diseases Alleviated by Fasting

Arthritis[245,246]	Leaky gut[252]
Autoimmune disease[247]	Obesity[253,254]
Atherosclerosis[248]	Pancreatitis[255]
Diabetes[249,250]	PCB and DDT contamination[256] (extreme caution must be exercised)
Epilepsy[251]	