

## Liver Degenerative Disease

- Liver Function
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- Summary

When compared to other health conditions, it is striking how little attention is given to diseases of the liver, particularly considering the rising level of concern about health and health-related environmental issues. *Hepatoprotection* (or protection of the liver) is a subject that should be of intense interest because the liver plays a critical role in all aspects of metabolism and overall health.

This protocol will present intriguing information about the role of the liver and explain why a well-functioning liver is essential for overall health. Also identified will be environmental hazards that constantly challenge the detoxification capacity of the liver. Research on the effects of alcohol on the liver will be discussed. Additionally, you will learn what you can do to support and optimize the function of your liver and thus optimize your future health and quality of life.

Some beneficial herbs will also be described. In Europe and Asia, herbal liver tonics have been in common use for decades--perhaps even for centuries. The effectiveness of the herbs used in these remedies has been validated during the past several decades through research and clinical studies. These herbs generally contain antioxidants; membrane-stabilizing and bile-enhancing compounds; or substances that prevent depletion of sulfhydryl compounds, such as glutathione.

### WHAT DOES THE LIVER DO?

The liver is located on the right side of the body in the upper abdomen. In the human, it is the second largest organ of the body, weighing about 4 lbs (skin is the largest organ). Even while being exposed to tremendous potential for damage, the liver performs a multitude of essential functions: metabolizing, detoxifying, and regenerating. It does an extraordinary job of keeping us alive and healthy by metabolizing the food we eat, that is, breaking it down into useful parts, and by having detoxifying abilities that protect us from the damaging effects of numerous toxic compounds that we are exposed to on a daily basis. Several times each day, our entire blood supply passes through the liver. At any given time, about a pint of blood is in the liver (or 10% of the total blood volume of an adult) (NIDDK 2000). In addition, the liver has impressive restorative capabilities and is the only organ in the body that is capable of regenerating itself when part of it has been damaged.

The metabolizing functions of the liver are numerous. The liver is intricately involved in carbohydrate, fat, and protein metabolism; in the storage of vitamins and minerals; and in many essential physiological processes. The liver is also involved in several regulatory mechanisms that control blood sugar levels and hormone levels. It synthesizes proteins (such as plasma albumin, fibrinogen, and most globulins) and lipids and lipoproteins (phospholipids, cholesterol), as well as bile acids that are excreted in the detoxification process (NIDDK 2000).

Other important functions of the liver include production of prothrombin and fibrinogen (two blood-clotting factors) and heparin (a mucopolysaccharide sulfuric acid ester that helps prevent blood from clotting within the circulatory system). The liver also processes glucose into glycogen and stores it until the muscles need energy; some glucose is also converted into fat and stored. The released glycogen becomes glucose in the bloodstream.

Additionally, the liver produces and secretes bile (stored in the gallbladder), that is needed to break down and digest fatty acids, and produces blood protein and hundreds of enzymes needed for digestion and other bodily functions. As the liver breaks down proteins, it produces urea, which it synthesizes from carbon dioxide and ammonia. (Urea is the primary solid component of urine, and it is eventually excreted by the kidneys.) Essential trace elements such as iron and copper as well as vitamins A, D, and B12 are also stored in the liver.

The detoxifying function is an essential part of human body metabolism, with the liver playing a key role in the process. Toxic chemicals, of both internal and external origin, constantly bombard the liver. Even our normal everyday metabolic processes produce a wide range of toxins that are neutralized in the liver.

The regenerating capacity of the liver is one of the most intriguing survival mechanisms of the body. The liver is an incredibly resilient organ. Up to 75% of its cells can be surgically removed or destroyed by disease before it ceases to function (AMA 1989). As with some other organs, the liver has been designed with an excess of tissue to protect it from damage or loss of function. The healthy parts of the liver have an amazing capacity to regenerate new, healthy liver tissue to replace damaged liver tissue. We are very fortunate that the liver has a regeneration capacity because our health depends on a well-functioning liver.

## CONDITIONS LEADING TO LIVER DAMAGE

- Cholestasis
- Wilson's Disease
- Autoimmune Hepatitis
- Hepatitis B
- Hepatitis C
- Hemochromatosis
- Steatosis, Steatohepatitis, and Cirrhosis
- Toxic Damage to the Liver

The symptoms that are indicative of reduced liver function or possible liver damage include general malaise; fatigue; digestive disturbances such as constipation; allergies and chemical sensitivities; weight loss; jaundice; edema; and mental confusion. Generalized pruritus (itching), nausea, and vomiting can also result from impaired hepatofunction. The causes of liver damage are numerous and may include congenital defects (malformed or absent bile ducts); obstructed bile ducts (cholestasis); autoimmune disorders; metabolic disorders (hemochromatosis, Wilson's disease); tumors; toxins (drugs, overdoses, poisons); alcohol-related conditions (cirrhosis); bacterial and parasitic infections; and viral infections (hepatitis B and C). This section discusses several chronic disorders and diseases that can lead to degenerative liver damage without proper diagnosis and treatment.

### Cholestasis

Cholestasis is interruption or stagnation of the bile flow in any part of the biliary system, beginning with the liver. Cholestasis has several causes, including obstruction of the bile ducts by the presence of gallstones or a tumor, drug and alcohol use, hepatitis, and existing liver disease (Glanze 1996). In the United States, an important cause of cholestasis and impaired liver function is the consumption of alcohol. Other common causes of cholestasis are viral hepatitis and the side effects of various drugs, particularly steroidal hormones (including estrogen and oral contraceptives).

Cholestasis can cause alterations of liver function tests, indicating cellular damage. In the initial stages of liver dysfunction, standard tests (serum bilirubin, alkaline phosphatase, SGOT, LDH, GGTP, etc.) may not be sensitive enough to be of value for complete, early diagnosis. However, the measurement of serum bile acids is a safe, sensitive test to determine the functional capacity of the liver. Treatment for cholestasis includes surgery so that there will be unobstructed bile flow from the liver. Drug-induced cholestasis will generally disappear if the causative drug is discontinued. There is no specific treatment for cholestasis caused by hepatitis. However, bile flow will improve slowly if inflammation of the liver can be resolved.

### Wilson's Disease

Wilson's disease is an inherited disorder characterized by the liver's inability to metabolize copper, resulting in the accumulation of excessive amounts of copper in the brain, liver, kidney, cornea, and other tissues. The resulting copper accumulation and toxicity result in liver disease and cause brain damage in some patients. Although deposits of copper begin at birth, it may be some time until the symptoms of liver disease become evident. Patients, generally between the ages of 10-40, present symptoms of liver disease; a movement disorder associated with neurological disease; behavioral abnormalities; or often a combination of these. Blood testing will reveal elevated liver enzymes. Symptoms of hepatitis and cirrhosis may be evident. Secondary injury from the accumulation of copper in the body may include kidney damage, neurological disorders, hemolytic anemia, and osteoporosis.

Copper also accumulates in other body organs, particularly the brain, and may result in difficulty with speech, trembling, writing problems, unsteady gait, depression, suicidal impulses, and loss of mental functions. The other body organs may also be damaged by copper overload. Copper can accumulate in the cornea of the eye and cause a characteristic brown pigmentation called Kayser-Fleischer rings. Hemolytic anemia, a low blood count related to damage of red blood cells, may occur in patients with Wilson's disease. There may also be injury to the kidneys from copper overload. Finally, severe bone disease from osteoporosis can occur in patients with Wilson's disease.

If Wilson's disease is left untreated, increasing damage to body organs will occur, especially in the liver and brain. D-penicillamine is a copper chelating agent that is administered to remove excess copper and prevent further accumulations. Trientine may also be used as a copper chelating agent. Both drugs are administered with vitamin B6 (*see the Heavy Metal Toxicity protocol for additional*

*information on chelation*). Foods high in copper content such as shellfish, nuts, chocolate, liver, and mushrooms must be avoided.

Because Wilson's disease can be effectively treated, it is extremely important for physicians to learn to recognize and diagnose the disease. Treatment options have evolved rapidly in the last few years, with zinc now being an important choice in most situations (Brewer et al. 1999). Brewer et al. (1999) consider zinc to be so important in the treatment of Wilson's disease that they refer to it as being "the drug of choice."

Wilson's disease requires management by a physician. Self-treating this condition with zinc is not recommended.

### **Autoimmune Hepatitis**

Autoimmune hepatitis is associated with an increase in circulating autoantibodies and gammaglobulin resulting in progressive inflammation of the liver. The symptoms of Type-I autoimmune hepatitis (the most common) are characterized by the presence of antinuclear antibodies and a resemblance to symptoms of systemic lupus erythematosus. The disease occurs most commonly in females during adolescence or early adulthood. Other autoimmune disorders may be present with autoimmune hepatitis including thyroiditis, ulcerative colitis, vitiligo (loss of skin pigmentation), and Sjogren's syndrome (characterized by dry mouth and eyes).

Fatigue, abdominal discomfort, aching joints, itching, jaundice, enlarged liver, and spider angiomas (blood vessels) on the skin are the most common symptoms. More severe complications of liver disease may occur as the disease progresses.

Up to 80% of patients have long-term survival with appropriate treatment. Prednisone and azathioprine are usually administered to treat immunosuppression. The goal of treatment is to control rather than cure the disease.

### **Hepatitis B**

In the United States and Europe, approximately 1.25 million people are chronically infected with the hepatitis B virus (Malik et al. 2000). About 5-10% of those with acute hepatitis B will develop chronic infection. The remainder will recover and develop antibodies to the virus that make them immune from further viral activity (Lammert et al. 2000; Mayerat et al. 1999). At least 1 million chronically infected individuals die each year of complications due to HBV-related diseases, especially liver cancer and cirrhosis. In the entire world, about 5% of the population or 350 million people have chronic hepatitis B (Gumina et al. 2001).

Hepatitis B causes inflammation of the liver resulting from infection with a DNA-type virus. The infection is passed via blood products, as in transfusions or in the sharing of contaminated needles. It may also be acquired by exposure to body fluids in addition to blood, during sexual intercourse, and in transmission from mother to fetus. About 5-10% of volunteer blood donors show evidence of having prior hepatitis B--meaning that they once did have hepatitis B and may or may not still be infectious with the viral agent.

The incidence of hepatitis B is increased in dialysis patients, IV drug users, persons with AIDS, transplant recipients, and patients frequently receiving blood transfusions such as those with leukemia or lymphoma. When acute hepatitis occurs, symptoms include weakness, nausea, vomiting, body aches (myalgias), diarrhea, fever, joint pains (arthralgias), jaundice (yellow discoloration of the skin and whites of the eyes), loss of appetite, weight loss, loss of interest in tobacco products, and sometimes an itching skin rash. The average duration of symptoms of acute hepatitis B is 1-3 months. During the final phase of symptoms, the body begins to build immunity against the hepatitis B infection and does become immune 90% of the time (Lammert et al. 2000). In the other 10%, however, a state of persistent infection occurs for more than 6 months. These persons are designated as having chronic hepatitis B. A liver biopsy is done in those patients having chronic hepatitis B and about one-third of these have chronic active hepatitis and two-thirds have chronic persistent hepatitis. Of these two types, the chronic active hepatitis is more aggressive and has a more rapidly progressing course.

Two forms of therapy are now licensed for use in chronic hepatitis B infection: interferon-alpha and lamivudine (Epivir). A vaccine for hepatitis B now exists and is frequently given to newborns, overseas travelers, and other people at risk to exposure (*refer to the Hepatitis B protocol for more information and specific therapies*).

### **Hepatitis C**

Hepatitis C can be transmitted by blood and blood product transfusion. Up to 170 million persons are infected worldwide. In the United States, more than 4 million people are infected with HCV. Most liver transplants in the United States are a result of hepatitis C. Hepatitis C has a frightening tendency to result in chronic hepatitis, resulting in cirrhosis (15-20% of those infected) or hepatocellular carcinoma (primary liver cancer) (Ou 2002).

The hepatitis C virus (HCV) is an RNA virus, spherical and enveloped in a lipid (fatty) outer envelope, which can be transmitted by narcotics use, transfusion of blood products, and exposure of medical personnel to infected patients. In some cases, the reason one contracts hepatitis C cannot be determined. The hepatitis C virus inflicts most of its damage by latching onto molecules of iron

and generating free-radical damage to liver cells. These free radicals can induce liver inflammation, cirrhosis, and primary liver cancer via oxidative attacks on liver cells.

Successful eradication of the hepatitis C virus from the body often requires that iron levels in the liver and blood be at very low levels. In many cases, high stores of iron in the liver preclude successful therapy against the hepatitis C virus. It is desirable to reduce iron levels in the body before initiating treatment with conventional (interferon and ribavirin) therapy. Despite substantial scientific evidence, few physicians implement iron-depletion therapy when treating hepatitis C. This partially accounts for the high failure rate to eradicate the virus.

In patients with hepatitis C, particularly those who are HIV-positive, a systemic depletion of glutathione is present, especially in the liver. This depletion may be a factor underlying the resistance to interferon therapy. This finding represents a biological basis for taking supplements that boost cellular glutathione levels. Glutathione is a critical factor in protecting liver cells against free-radical damage.

Standard therapy for hepatitis C has consisted of ribavirin combined with interferon. However, a combination therapy of peginterferon alpha-2b and ribavirin is currently the standard of care (*refer to the Hepatitis C protocol for more information and specific therapies*).

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# Liver Degenerative Disease

## Hemochromatosis

Hemochromatosis is a hereditary disorder in which too much iron is absorbed from the diet resulting in free-radical damage to the liver, heart, and pancreas. It is estimated that over 1 million Americans suffer from the disease. If diagnosed early, hemochromatosis can be controlled by phlebotomy (giving blood) until stored iron levels are reduced. High levels of antioxidants and herbal detoxifiers are usually recommended to neutralize free radicals generated by excess iron. Chelation therapy is an alternative treatment in which a synthetic amino acid is administered intravenously to bind and extract unwanted metals from the body. People with hemochromatosis must avoid iron-fortified foods, cast-iron cookware, and red meat. Symptoms may not appear until middle age, after multiple organ damage has occurred. Due to blood loss from menstruation and pregnancy, the disease is less prevalent in women than men (*refer to the Hemochromatosis protocol for more information and specific therapies*).

## Steatosis, Steatohepatitis, and Cirrhosis

Steatosis (or fatty liver) is a common finding in biopsy of the human liver. Fatty liver is a condition in which fat accumulates within the liver cells (hepatocytes) without causing any specific symptoms. (Fatty liver is defined as either more than 5% of cells containing fat droplets or total lipid exceeding 5% of liver weight.)

Fatty liver is usually a long-standing chronic condition, occurring in association with a wide range of diseases--exposure to poisonous and toxic substances, taking certain drugs, and drug abuse (injecting recreational drugs) (Glanz 1996)--although in clinical practice, the majority of cases are the result of excessive use of alcohol, diabetes, and obesity. Less common are occurrences of acute fatty liver during pregnancy or as a response to the administration of tetracyclines, acetaminophen, prescription drugs, and toxins.

Our understanding of the fatty liver condition has advanced considerably. At one time, fatty liver was believed to be a benign, reversible condition. However, clinical studies now demonstrate that fatty liver, whether from alcoholic or nonalcoholic origin, can lead to inflammation, cell death, and fibrosis (steatohepatitis), perhaps even progression to cirrhosis. Cirrhosis is the *irreversible* end result of fibrous scarring, a response by the liver to a variety of long-standing inflammatory, toxic, metabolic, and congestive damage processes (*refer to the Liver Cirrhosis protocol for more information and specific therapies*).

As stated earlier, in the Western world, alcohol is a common cause of fatty liver and is the second most common cause of cirrhosis. However, there are considerable inter-individual differences in the degree of liver damage produced by excessive alcohol intake. There seems to be no correlation between the incidence and severity of fatty liver and either the amount, type, or duration of alcohol abuse. In some individuals, it is unclear why fatty liver, whatever its etiology, never progresses to steatohepatitis and cirrhosis.

Obesity is among the causes for *nonalcoholic* steatohepatitis (NASH) and is considered to be the most common cause. There is evidence to suggest that liver disease can actually be considered to be a complication of obesity. However, no major prospective longitudinal studies of NASH have been carried out. Generally, it seems that the risk of progression to cirrhosis is low for nonobese individuals, but significant among obese individuals. Unfortunately, there is also no predictable correlation between symptoms (or lack of them), abnormality of liver function tests, and severity of liver tissue damage.

As early as 1985, a study of 50 unselected, obese subjects who were admitted to a hospital for weight reduction found that 10% had normal livers, 48% had fatty livers, 26% had steatohepatitis, 8% had fibrosis, and 8% had cirrhosis (Brailon et al. 1985). Obesity was defined as being 21-130% above ideal body weight.

Interestingly, among patients with fatty liver related to obesity, it has been observed that rapid weight loss caused by dieting and intestinal bypass surgery actually increased the risk for developing steatohepatitis. The resulting increase in the concentration of fatty acids and/or ketones within the liver severely augmented the generation of free radicals (Day et al. 1994).

A study by Yang et al. (1997) indicated that obesity also increases susceptibility to endotoxin-mediated liver injury. Endotoxins are cell wall components produced by intestinal Gram-negative bacteria that are thought to play a role in liver injury induced by alcohol and other hepatotoxins. Under normal conditions, endotoxins are absorbed into the portal venous circulation and detoxified by the liver. Hepatic dysfunction interferes with this clearing mechanism and amplifies the negative activities of endotoxin, such as lipid peroxidation, reduced P-450 function, and impairment of the immune system.

Berson et al. (1998) summarized well insights from research on the mechanisms of steatohepatitis:

Its development requires a double hit, the first producing steatosis, the second a source of oxidative stress capable of initiating significant lipid peroxidation. This concept provides a rationale for both the treatment and prevention of disease

progression in steatosis of alcoholic and non-alcoholic causes. Management strategies should ideally be directed at reducing the severity of steatosis and at avoiding and removing the triggers of inflammation and fibrosis. Specific treatment modalities for at-risk individuals might include sensible weight reduction, cessation of exposure to toxins and treatment with antioxidants and inhibitors of peroxisomal  $\beta$ -oxidation.

## Toxic Damage to the Liver

It is the *external* environment that contributes most to the load of toxins that the liver has to detoxify. Today, the burden on the liver is heavier than ever before in history. Additionally, nutritional deficiencies and imbalances from unhealthy eating habits add to the production of toxins, as do alcohol and many prescription drugs, further increasing stress on the liver and requiring a strong detoxification capacity. Surprisingly, even unprocessed organic foods can have naturally occurring toxic components that require an effective detoxification system.

Toxic chemicals are found in the food we eat, in the water we drink, and in the air we breathe, both outdoors and indoors. In a study by the Environmental Protection Agency (EPA), chemicals such as p-xylene, tetrachloroethylene, ethylbenzene, and benzene were documented as "everywhere present" in the air (Wallace et al. 1989). Listed as "often present" were chloroform, carbon tetrachloride, styrene, and p-dichlorobenzene. A customary trip to a gas station or a dry cleaner (as well as smoking) results in elevated levels of inhaled toxins.

The Food and Drug Administration (FDA) has found an alarming level of chlorinated pesticides in food. Dichlorodiphenyldichloroethylene (DDE) was found in 63% or more of 42 food samples, even though the use of dichlorodiphenyltrichloroethane (DDT) and DDE has been banned in the United States since 1972. DDE is a breakdown product of DDT. Unfortunately, carried by the winds, toxic chemicals used anywhere in the world can move easily around the globe. There is enough evidence of a connection between chemical exposure and chronic health problems for us to be aware that herbicides, pesticides, household chemicals, food additives, etc. pose serious health concerns.

So what happens when the liver's detoxification system is overloaded? The answer is simple. When the liver does not function properly, toxins that we are exposed to accumulate in the body. These toxins affect us in numerous ways, and have damaging effects on many body functions, particularly the immune system, causing chronic health problems. It is not surprising that an overburdened and undernourished liver can be a root cause of many chronic diseases.

Cancers are also thought to be a result of the effects of environmental carcinogens (e.g., cigarette smoke, chemical fumes, toxic exhaust, and airborne particulates), particularly if combined with deficiencies of nutrients required for optimal functioning of the detoxification and immune systems. In a study of chemical plant workers in Turin, Italy, Vineis et al. (1985) analyzed the association of bladder cancer according to occupation (i.e., textiles, leather, printing, dyestuffs, tire and rubber goods production). Highest risks were for the leather, dyestuffs, and tire production industries. An association was found for cancer and the aromatic amines, with the risk being estimated at 10% for those occupations consistently associated with bladder cancer. Vineis et al. (1984) also found that there was a multiplicative effect of relative risks for persons in high-risk occupations who also smoked cigarettes.

## HOW THE LIVER DETOXIFIES

The liver has three main *detoxification* pathways:

- *Filtering* the blood to remove large toxins.
- *Enzymatically* breaking down unwanted chemicals. This usually occurs in two steps, with Phase I modifying the chemicals to make them an easier target for the Phase II enzyme systems.
- *Synthesizing and secreting* bile for excretion of fat-soluble toxins and cholesterol.

*Filtering* the blood is an essential detoxifying function of the liver. As noted earlier, our total blood supply passes through the liver several times a day and at any given time, about a pint of blood is in the liver undergoing detoxification. Blood detoxification is critical because the blood is loaded with bacteria, endotoxins, antigen-antibody complexes, and other toxic substances from the intestines. A healthy liver clears almost 100% of bacteria and toxins from the blood before the blood enters the general circulation.

The second essential detoxifying role of the liver involves a two-step *enzymatic process* for the neutralization of unwanted chemical compounds, such as drugs, pesticides, and enterotoxins from the intestines. Even normal body compounds such as hormones are eliminated in this way. Phase I enzymes directly neutralize some of these chemicals, but many others are converted to intermediate forms that are then processed by Phase II enzymes. These intermediate forms are often much more chemically active and therefore more toxic than the original substances. Therefore, if the Phase II detoxification system is not working properly, the intermediates linger and cause damage.

Phase I detoxification involves a group of 50-100 enzymes that has been named the cytochrome P450 system. These enzymes play a central role in the detoxification of both exogenous (beginning outside the body, such as drugs and pesticides) and endogenous (coming from inside the body, such as hormones) compounds and in the synthesis of steroid hormones and bile acids.

A side effect of this metabolic activity is the production of free radicals that are highly reactive molecules that will bind to cellular components and cause damage. The most important antioxidant for neutralizing these free radicals is glutathione, which is needed for Phase I and Phase II detoxification. When exposure to high levels of toxin produces so many free radicals from Phase I detoxification that glutathione is depleted, Phase II processes that are dependent on glutathione cease. This causes an imbalance between Phase I and Phase II activity, causing severe toxic reactions as a result of the build-up of toxic intermediate forms.

Phase II detoxification involves conjugation, meaning a protective compound becomes bound to a toxin. Besides glutathione conjugation, the other pathways are amino acid conjugation, methylation, sulfation, sulfoxidation, acetylation, and glucuronidation. These enzyme systems need nutrients and metabolic energy to function. As noted earlier, if liver cells do not function properly, Phase II detoxification slows down and increases the toxic load of toxic intermediates.

The third essential detoxifying role of the liver is *synthesis and secretion of bile*. The liver manufactures approximately a quart of bile every day. Bile serves as a carrier to effectively eliminate toxic substances from the body. In addition, bile emulsifies fats and fat-soluble vitamins in the intestine, improving their absorption. When the excretion of bile is inhibited (cholestasis), toxins stay in the liver longer and subject the liver to damage.

## FREE-RADICAL DAMAGE AND LIPID PEROXIDATION

Oxidative damage from the production of free radicals has far-reaching consequences in the body. Lipid peroxidation is a term that describes fats that have been chemically damaged by oxygen free radicals. Cell membranes consist mainly of layers of phospholipids. As free radicals attack the cell membrane, injury and eventual death to the cell occur due to DNA strand breakage. DNA is the cellular blueprint that is required for replication. Oxidative stress also affects circulating lipids in the body including cholesterol, 80% of which is produced in the liver. Peroxidized cholesterol has been shown to damage arteries, leading to atherosclerosis, and a growing body of evidence supports a role for lipid peroxidation in the continued development of liver damage.

While cell damage in the human liver is likely multifactorial, free radicals have been implicated in a variety of liver diseases, particularly in the presence of iron overload, ethanol consumption, and ischemia/reperfusion injury, either initiating or perpetuating liver damage. Additionally, free radical-initiated lipid peroxidation appears to play a role in hepatic fibrogenesis (Britton et al. 1994). The role of free radicals is significant in toxic liver injury that is often induced by drugs and chemicals. Damage is first caused by the toxin itself and then is continued when the toxin is metabolized by the liver (Feher et al. 1992).

## TREATMENT OF DEGENERATIVE LIVER CONDITIONS

- Conventional Medical Therapy
- Natural Therapies
- Supplements that Maintain Metabolic Health
- Antioxidants that Reduce Free-Radical Damage
- Protecting and Improving Liver Function

### Conventional Medical Therapy

Unfortunately, liver damage caused by degenerative conditions is *irreversible*. There are no commonly accepted, effective, conventional drug therapy regimes to *prevent* or *reverse* liver damage. Treatment primarily consists of identifying the underlying causes of disease, determining possible steps to slow or stop progression of degeneration, and managing symptoms. One causal factor is alcohol: stopping the intake of alcohol will help stop progression. Ending the use of hepatotoxic drugs and removing sources of environmental toxins will also stop progression. The possible presence of metabolic diseases (hemochromatosis, Wilson's disease) should be investigated. Identifying the presence of hepatitis viruses is essential. Because obesity plays an important role in fatty liver, attention to weight control is essential.

Conventional drug therapies can include:

- *Colchicine*, a generic drug used to treat gout, also inhibits collagen (a protein in the body that makes up scar tissue) and has produced some improvement in liver function and patient survival (Nidus 1999).
- *Corticosteroids* that reduce inflammation have been helpful in improving liver function and symptoms, but these drugs have

potentially serious side effects (Glanze 1996). (If taking a corticosteroid, measures must be taken to monitor adverse side effects such as edema, hypertension, diabetes mellitus, osteoporosis, and ulcers.)

- *Malotilate* (a drug developed in Japan) prevents damage to liver cells (and cirrhosis) induced in laboratory animals. It has been shown by several researchers to prevent induced liver damage, the accumulation of collagen, and morphologic changes (such as accumulation of inflammatory cells and fibrosis and to reduce ethanol induced lesions) (Takase et al. 1989; Mirossay et al. 1996; Ryhanen et al. 1996).
- *Alpha interferon* (Intron A) and *ribavirin* (Rebetol and Virazole) are antiviral drugs used in treating the hepatitis viruses. These drugs are a mainstay for some persons (NIDA 2002). However, some patients are not responsive; experience relapse after the antiviral drugs are discontinued; or have great difficulty handling the side effects (Strickland 2002). Newer alpha interferon drugs are pegylated, meaning they contain polyethylene glycol combined with interferon. At this writing, only one pegylated drug has been approved by the FDA. *PEG-Intron* was approved by the FDA in January 2001 for once-weekly therapy for the hepatitis C virus. Another drug, PEGASYS, is undergoing Phase III clinical trials, awaiting approval by the FDA.
- *Gene therapy* as a treatment option is the subject of research, but even if research indicates that gene therapy appears feasible, human trials are years away.

Itching is a very troublesome symptom for patients with liver disease. It is also a very difficult symptom to manage for physicians. The reason why patients with liver disease itch is not understood. One thought is that certain substances accumulate in the blood as a result of liver disease and cause itching. The nature of these substances is under investigation, but some evidence suggests that normal substances found in blood plasma (e.g., endogenous opioids known as enkaphalins) for some unknown reason cause itching in liver disease patients. Itching/scratching studies have also shown that some patients manifest scratching in a 24-hour rhythm (circadian), suggesting that neurotransmitters in the brain may cause itching (Bergasa 2002). At this time, little treatment is available for itching secondary to liver disease:

- *Cholestyramine* (taken with food) and Naltrexone can help relieve itching (Nidus 1999). (High doses of Naltrexone are toxic for the liver, but low doses appear to be safe.)
- *Phototherapy* (light therapy) has been helpful in reducing itching (Nidus 1999).

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# Liver Degenerative Disease

## Natural Therapies

Scientific literature reports the results of research using natural or alternative treatments for liver conditions. Note that the vast majority of natural or alternative treatments act by having an antioxidant effect. As with almost all disease processes, research has demonstrated that good *antioxidant* levels are necessary for optimum health and to protect us from the physical assaults of trauma and disease. Some of the therapies listed in the following section also act by having an effect on the immune system (an *immune-modulating* effect). Other therapies have *anti-inflammatory* benefits. Additionally, some agents act by having both antioxidant mechanisms and immune modulating mechanisms.

For the liver to continue to perform essential functions, even when damaged, a healthy intake of vitamins, minerals, and essential trace elements from dietary sources such as fruits and vegetables is important. However, few people can consistently include enough fruits and vegetables in their daily diets to protect them from degenerative conditions, especially those related to age-related diseases; toxic agents; carcinogens; inflammatory agents; free-radical damage; and immune suppression. As an adjunct to maintaining a healthy diet, supplements can:

1. Maintain healthy metabolic functioning
2. Neutralize free-radical damage
3. Increase levels of glutathione, the liver's natural antioxidant
4. Detoxify the liver

## Supplements that Maintain Metabolic Health

**Vitamin B complex.** The vitamin B complex is a group of vitamins (B1, thiamine; B2, riboflavin; B3, niacin; B5, pantothenic acid; B6, pyridoxine; and B12, cyanocobalamin) that differ from each other in structure and the effect they have on the human body. The B vitamins play a vital role in numerous essential activities including enzyme activities (thiamine, riboflavin, niacin, pantothenic acid, pyridoxine). These enzyme activities also have many roles and are involved in the metabolism of carbohydrates and fats; functioning of the nervous and digestive systems; and production of red blood cells. The B vitamins have a synergistic effect with each other (AMA 1989). They are found in large quantities in the human liver as well as in many foods and yeast.

**Folic acid.** Folic acid is an important member of the B-complex family, important for reducing harmful levels of homocysteine, a sulfur-containing amino acid, known to be a major culprit in heart disease. The liver uses folic acid to facilitate healthy methylation patterns that are essential components of enzymatic detoxification. Decreased folate (folic acid) is also associated with increased levels of lipoperoxidases, that is, an indicator of increased oxidative stress. Therefore, folic acid is potentially beneficial if there is ongoing oxidative damage (Chern et al. 2001).

**Choline.** Another of the B complex vitamins is choline, essential for the use of fats in the body. It comprises a large part of acetylcholine (a nerve signal carrier). Choline also stops fats from being deposited in the liver and helps move fats into the cells. Deficiency of choline can lead to degenerative diseases such as cirrhosis with associated conditions such as bleeding, kidney damage, hypertension (high blood pressure), cholesterolemia (high blood levels of cholesterol), atherosclerosis (cholesterol deposits in blood vessels), and arteriosclerosis (hardening of the arteries) (Glanze 1996).

**Acetyl-L-carnitine.** Acetyl-L-carnitine has been shown to convert some hepatic parameters to more youthful levels. Acetyl-L-carnitine is the biologically active form of the amino acid L-carnitine that has been shown to protect cells throughout the body from age-related degeneration. By facilitating the youthful transport of fatty acids into the cell mitochondria, acetyl-L-carnitine facilitates conversion of dietary fats to energy and muscle. Acetyl-L-carnitine has also been shown to regenerate nerves (Fernandez et al. 1997), to provide protection against glutamate and ammonia induced toxicity to the brain (Rao et al. 1999), and to reverse the effects of heart aging in animals (Paradies et al. 1999).

## Antioxidants that Reduce Free-Radical Damage

**Vitamin C.** Vitamin C is a potent antioxidant that is found naturally in many fruits and vegetables. According to Garg et al. (2000), vitamin C has protective effects against liver oxidative damage, particularly when used in combination with vitamin E. Researchers have found inadequate levels of vitamin C in patients with degenerative diseases. Garg et al. (2000) found that supplementation in rats lowered plasma and liver lipid peroxidation, normalized plasma vitamin C levels, and raised vitamin E above normal levels.

**Vitamin E.** Vitamin E protects the lipid membrane from oxidative damage. Adequate levels of vitamin E also protect cholesterol from oxidative damage. Oxidized cholesterol damages arteries and contributes to atherosclerosis (Mydlik et al. 2002). Hepatocytes incorporate vitamin E into lipoproteins, which then transport it to various tissues in the body.

**Coenzyme Q10 (CoQ10).** CoQ10 is an antioxidant that is protective for a liver that has been damaged by ischemia (reduced blood flow) (Genova et al. 1999). CoQ10 is also an important component of healthy metabolism. It protects the mitochondria and cell membrane from oxidative damage and helps generate ATP, the energy source for cells. CoQ10 is absorbed by the lymphatic system and distributed throughout the body. Japanese researchers studied the effects of the toxic drug hydrazine on liver cells. Hydrazine caused remarkable increases in intracellular levels of reactive oxygen species in hepatocytes, which were suppressed by CoQ10 (Teranishi et al. 1999).

**N-acetyl-cysteine (NAC).** N-acetyl-cysteine is an amino acid that acts as an antioxidant or free-radical scavenger. Most scientific articles related to liver protection with NAC emphasize this effect. NAC is frequently used in medical settings to treat liver toxicity associated with ingesting Tylenol (also poisonous mushrooms) (Hazai et al. 2001; Attri et al. 2001).

**Alpha-lipoic acid (ALA).** Alpha-lipoic acid is an antioxidant that has been shown to decrease the amount of hepatic fibrosis associated with liver injury. Both of these mechanisms suggest it has promise for cirrhosis. Because alpha-lipoic acid is fat soluble, it can penetrate the cell membrane to exert therapeutic action. It has been shown to effectively scavenge harmful free radicals, chelate toxic heavy metals, and help to prevent mutated gene expression (Biewenga et al. 1997). Another of its most beneficial functions is to enhance the effects of other essential antioxidants including glutathione, which is vital to the health of the liver (Lykkesfeld 1998; Khanna et al. 1999).

**Selenium.** Selenium is a trace element that acts by several mechanisms, including detoxifying liver enzymes, exerting anti-inflammatory effects, and providing antioxidant defense. The presence of selenium helps induce and maintain the glutathione antioxidant system (Sakaguchi 2000).

**Zinc.** Zinc is an essential dietary nutrient and is used in numerous drugs and preparations that are protective. Zinc helps remove copper from the body and is used as an adjuvant treatment in Wilson's disease (Brewer et al. 1999).

### **Protecting and Improving Liver Function**

**S-adenosylmethionine (SAME).** SAME is a methylation agent (a methyl group donor) and is necessary for the synthesis of glutathione. Medical studies have shown that SAME has beneficial antioxidant effects on the liver and other tissues, particularly in protecting and restoring liver cell function destroyed by the hepatitis C virus. SAME decreases the production of liver collagen, which leads to the formation of fibrous tissue (Deulofeu et al. 2000). SAME is found naturally in every cell of the body. It is synthesized from a combination of the amino acid L-methionine, folic acid, vitamin B12, and trimethylglycine, provided all these ingredients are present and performing (Anon. 2002).

**Phosphatidylcholine (PC).** Phosphatidylcholine is a type of fat that is part of cell membranes. PC is one of the most important substances for liver protection and health and is a primary constituent of cell membranes. PC acts by several mechanisms: exerting potent antioxidant effects; inhibiting the tendency of stellate cells to progress to cirrhosis; decreasing apoptotic death of liver cells and thereby prolonging the life of liver cells; stabilizing the cell membrane, thus improving the integrity and function of the liver cell; and exerting an antifibrotic effect related to the breakdown of collagen (not only slowing the progression of fibrosis, but also encouraging regression of existing fibrosis) (Ma 1996; Lieber 1999; Pniachik 1999; Wolf 2001). A special form of PC called polyenylphosphatidylcholine has been shown to prevent the early changes in the damaged liver from occurring before the actual development of cirrhosis (Navender 1997).

**Silymarin.** Silymarin, (also known as milk thistle or *Silybum marinum*) is a member of the aster family (Asteraceae). The active extract of milk thistle is silymarin (Bosisio et al. 1992), a mixture of flavolignans, including silydianin, silychristine, and silybin, with silybin being the most biologically active. Silymarin has proven to be one of the most potent liver-protecting substances known. Its main routes of protection appear to be the prevention of free-radical damage, stabilization of plasma membranes, and stimulation of new liver cell production. It has also been shown to inhibit lipid peroxidation and to prevent glutathione depletion induced by alcohol and other liver toxins, even increasing total glutathione levels in the liver by 35% over controls (Valenzuela et al. 1989). Early studies show that silymarin has the ability to stimulate protein synthesis, resulting in production of new liver cells to replace older, damaged ones (Sonnenbichler et al. 1986a; 1986b). Studies also demonstrate the benefits of silymarin for protection from numerous toxic chemicals.

**Branched-chain amino acids.** Branched-chain amino acids (leucine, isoleucine, and valine) are considered to be *essential* amino acids because humans cannot survive unless these amino acids are present in the diet. Branched chain amino acids (BCAAs) are needed for the maintenance of muscle tissue and appear to preserve muscle stores of glycogen (stored form of carbohydrates that can be converted into energy). Dietary sources of BCAAs are dairy products and red meat. Whey protein and egg protein supplements are other sources. Most diets provide the daily requirement of BCAAs for healthy people. However, in cases of physical stress, we have increased energy requirements, in particular persons with cirrhosis. Studies on alcoholic cirrhosis patients have shown benefits from supplementing valine, leucine, and isoleucine. These branched-chain amino acids can enhance protein synthesis in liver and muscle cells, help restore liver function, and prevent chronic encephalopathy (Shimazu 1990; Chalasani et al. 1996) In studies, BCAAs have also been shown to have therapeutic value in adults with cirrhosis of the liver. According to the

## SUMMARY

If you already have a degenerative liver condition, or have symptoms of liver disease, consult a qualified physician who is experienced in treating liver disease and who will coordinate your treatment. Supplementation with antioxidants, branched-chain amino acids, and all of the B complex of vitamins except B3 (niacin) has been shown to have protective qualities and to be beneficial for the liver. The following are important in preventing liver disease and for providing beneficial supportive effects.

1. The B vitamins are essential for healthy metabolic functioning. Working individually and synergistically, they facilitate energy release and the manufacture of new cells.
  - B1 (thiamine), 500 mg
  - B2 (riboflavin), 75 mg
  - B5 (pantothenic acid), 1500 mg
  - B6 (pyridoxine), 200 mg
  - B12 (cobalamin), sublingual methylcobalamin is recommended for better absorption, one 5-mg lozenge 1-5 times daily
  - Folic acid, 800 mcg daily

Vitamin B3 (niacin) should be avoided by people with liver conditions as it disrupts healthy methylation patterns.
2. Choline helps reduce the amount of fat deposited in the liver, 1500 mg daily.
3. Acetyl-L-carnitine will help to maintain mitochondrial health, take 2 daily doses of 1000 mg.
4. Antioxidants afford protection to the liver from the damaging effects of free radicals produced from environmental toxins.
  - Take at least 2500 mg of vitamin C daily.
  - Vitamin E (400 IU of D-alpha tocopheryl succinate and 200 mg of gamma tocopherol daily provide broad-spectrum antioxidant protection).
  - CoQ10 protects the mitochondria from oxidative damage and provides cellular energy, 100-300 mg daily.
  - N-acetyl-cysteine (NAC) enhances the production of glutathione and has protective benefits for the liver from toxins. Take 600 mg daily.
  - Alpha-lipoic acid can dramatically increase glutathione levels inside of cells. Suggested dose is 250 mg 2-3 times a day.
  - The trace mineral selenium has shown antioxidant protection in the liver. Zinc is often deficient in the cirrhotic liver and acts as a chelator in removing copper from the system. Take selenium, 200 mcg daily, and zinc, 30-85 mg daily.
5. Several supplements can benefit a damaged or diseased liver:
  - S-adenosylmethionine (SAME) is needed to synthesize glutathione and has restored liver function from damage due to hepatitis C. The suggested dose of SAME is 400 mg 3 times daily. Do not take SAME on an empty stomach.
  - Polyenylphosphatidylcholine (PPC) has been shown to prevent the development of fibrosis and cirrhosis and to prevent lipid peroxidation and associated liver damage from alcohol consumption. PPC is sold as a drug in Europe. A product called HepatoPro (formerly GastroPro) is one of the few American dietary supplements to provide pharmaceutical-grade polyenylphosphatidylcholine. Take two to three 900-mg capsules daily.
  - Silymarin extract from milk thistle can raise glutathione levels and has shown multi-faceted protective benefits to the liver. The most active flavonoid in silymarin is silibinin. A product called Silibinin Plus is formulated to provide the same silibinin extract used in European prescription drugs. One 325-mg capsule taken twice daily is recommended for healthy people. Patients with liver disease may take up to 6 capsules daily.
  - Branched-chain amino acids can enhance protein synthesis in the liver and are particularly beneficial in alcoholic cirrhosis. The suggested dose is 2-4 capsules daily between meals with fruit juice or before eating. Each capsule should contain 300 mg of leucine, 150 mg of isoleucine, and 150 mg of valine.

## FOR MORE INFORMATION

More information on conventional therapies is available by contacting the American Liver Foundation, (800) 223-0179.

## PRODUCT AVAILABILITY

HepatoPro (formerly GastroPro) (polyenylphosphatidylcholine), Silibinin Plus, branched-chain amino acids, choline capsules, B vitamins, SAME, vitamin C, vitamin E (tocopheryl succinate and gamma tocopherol), selenium, zinc, coenzyme Q10, acetyl-L-carnitine, alpha-lipoic acid, and N-acetyl-cysteine (NAC) may be ordered by calling (800) 544-4440 or by ordering online.

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