One of the primary harmful effects on the human body of the consumption of beverage alcohol is its damaging and destructive impact on the liver. Along with those of the central nervous system, this is the human organ most negatively affected.

In urban areas such as New York City, cirrhosis of the liver is the third most frequent cause of deaths between the ages of 25 and 64. When the consumption of alcohol in a population goes up, so does the incidence of cirrhosis. Most North American and European people who have cirrhosis admit to their own excessive drinking.

The amount of alcohol consumed is clearly related to the incidence of cirrhosis. Chronic alcohol use can lead to the development of liver injury, even when the diet contains all required nutrients in recommended amounts.

In one study volunteers consumed the equivalent of at least a six-pack of beer a day, along with high protein diets enriched in minerals and vitamins. After one “weekend” of drinking, fat accumulation in the liver was already detectable by chemical analysis. In another study, baboons were given an adequate diet, but had alcohol as 50 percent of their total calories. All developed fatty liver. In addition, after two to four years 30 percent developed cirrhosis.

Alcoholics commonly suffer from malnutrition. They may not eat enough as a result of socioeconomic factors. In addition, alcohol, unlike other drugs, has a high caloric value. It is not unusual for an alcoholic to drink 200 grams of alcohol per day, which represents about 1500 calories. This decreases the appetite, so alcohol displaces other nutrients in the diet.

The calories that come from alcohol are "empty calories" without proteins, vitamins, or minerals. Furthermore, continued alcohol use can create changes in the digestive system which make nutrient absorption difficult. Alcohol may interfere with the body's ability to use vitamins.

In experimental animals, malnutrition may also produce a variety of liver diseases. Under some circumstances, however, protein deficiency may actually prevent the development of cirrhosis. In infants, severe protein deficiency results in fatty liver (Kwashiorkor) which does not proceed to cirrhosis. The extent to which malnutrition contributes to the development of liver disease in the alcoholic remains unclear.

Alcohol is readily absorbed from the digestive tract. Only 2 to 10 percent is eliminated through the kidneys and lungs; the rest must be oxidized in the body, principally in the liver. This is aggravated by the fact that no feedback mechanism adjusts the rate of alcohol oxidation. And alcohol, unlike other major sources of calories, cannot be stored or metabolized in surrounding tissues, which have a much lower affinity for alcohol.

Because of the exceptionally high concentration of alcohol in the stomach after it is ingested, metabolism of the alcohol begins there. This decreases the bioavailability of the alcohol and presents a “protective barrier” against its effects, at least when it has been consumed in what is considered to be small "social-drinking" amounts.
The main way that the body disposes of alcohol is with the help of an enzyme called alcohol dehydrogenase (ADH). The ADH catalyzes the transfer of hydrogen so that the alcohol can be converted to acetaldehyde and acetate, which are released into the bloodstream. This process, in turn, results in an excess of byproducts in the liver.

These byproducts of the oxidation of alcohol contribute to a number of disorders. They cause the liver to produce more lactate, but use less. This condition is known as hyperlactacidemia, and it in turn reduces the excretion of uric acid from the kidneys, leading to hyperuricemia. This may be why excessive consumption of alcoholic beverages frequently aggravates gout.

The byproducts also create a condition that favors triglyceride accumulation by trapping fatty acids. Normally oxidation of fatty acids serves as the main energy source of the liver, but when these byproducts are present they are used instead, so dietary fat is deposited in the liver.

A dramatic but uncommon complication of acute alcohol use is severe hypoglycemia, which may cause some of the unexplained sudden deaths in acute alcoholic intoxication. Byproducts of alcohol oxidation can block the use of glucose; this can lead to hypoglycemia in people whose glycogen stores are already depleted because they haven’t been eating right. On the other hand, alcohol sometimes can accelerate rather than inhibit glucose use, leading to hyperglycemia.

Intoxicated individuals are more sensitive to several medications, probably because of the additive effects of alcohol and various drugs on the central nervous system. Evidence suggests that the body utilizes a common system for the metabolism of alcohol and drugs. Therefore this increased sensitivity could be explained by the effect of alcohol on the drug-detoxifying system. Alcohol slows metabolism of a variety of drugs and conversely, drugs may alter alcohol metabolism.

Prolonged intake of large amounts of alcohol results in the growth of the membranes of the liver’s smooth endoplasmic recticulum. The changes that accompany this growth involve the metabolism of fats, drugs, and alcohol. They also are associated with increased activity of a variety of drug detoxifying enzymes and result in the acceleration of the metabolism of various drugs, including anticoagulants and tranquilizers. Thus, the tolerance of the alcoholic for various drugs (which has been attributed to central nervous system adaptation) is also a result in part to metabolic tolerance.

The alcoholic, when sober, has an increased capacity to metabolize a variety of drugs. In the intoxicated state, however, the opposite will occur because alcohol competes with other drugs for the detoxification process.

Severe liver injury may result in normal or decreased rates of drug metabolism and lowered drug tolerance. Alcoholics also develop a tolerance to alcohol itself, primarily because of central nervous system adaptation. However, in the early stages of the disease, acceleration of alcohol metabolism may also be present.

During the early stages of alcoholic liver injury, a condition called hyperlipemia may develop, leading to abnormal metabolism of fats or carbohydrates. The degree of hyperlipemia is influenced by the duration of alcohol intake. Hyperlipemia develops progressively and is accompanied by an increased activity of enzymes involved in lipoprotein production.

This increased lipoprotein production enables the liver to dispose of the excess fats. Fatty liver will develop when this disposal system is overwhelmed. And it cannot respond with hyperlipemia when more severe liver injury develops as a result.

Stimulation of these enzymes can also affect the conversion of drugs to toxic compounds. Furthermore, this enhanced activity is associated with increased energy requirements leading to energy wastage.

Accelerated metabolism of drugs such as steroids can enhance breakdown of the male hormone testosterone, which contributes to a lowering of blood testosterone. Testosterone production is also depressed by alcohol’s toxicity. Breakdown of vitamin A also accelerates and may lead to vitamin A depletion in
the liver.

Even early stages of alcohol use show functional and structural evidence of injurious effects. In addition to fat accumulation, the alcoholic fatty liver also suffers from protein accumulation, which is almost as damaging. The combination of protein and fat accumulation leads to "ballooning" of the hepatocytes.

Already at the fatty liver stage, the liver undergoes profound structural changes beyond the proliferation of the smooth endoplasmic reticulum. The mitochondria, which convert food to energy, and altered and distorted. Their functions are decreased, promoting fat accumulation. They are less able to handle the byproducts of alcohol oxidation. This may exacerbate a number of complications of alcoholism in the brain, heart, and liver.

Sometimes acetaldehyde, a byproduct of alcohol oxidation, will bind with some proteins which can alter some key functions and may lead to an antibody response. It may also bind with an amino acid, leading to reduced glutathione, an important substance in the liver. Glutathione offers one of the mechanisms for the scavenging of toxic-free radicals. The damage may be compounded by an increased amount of active radicals following chronic alcohol consumption.

A severe reduction in glutathione can lead to peroxidation. Studies have been made on the role of peroxidation in alcohol induced fatty liver in the rat, but its involvement has been controversial. Alcohol induced peroxidation is even more striking in the baboon. The propensity of the baboon to develop more severe lesions than the rat after chronic alcohol consumption may be related in part to the greater susceptibility of primates to glutathione depletion and the initiation of peroxidation. It is apparent, however, that glutathione depletion per se does not suffice to produce liver damage. The accompaniment of enhanced production of active radicals may be required.

Fatty liver invariably develops after heavy alcohol intake. It can progress to alcoholic hepatitis and cirrhosis, but this occurs only in a minority of heavy drinkers. In experiments only one third of baboons fed high doses of alcohol developed lesions more severe than those of fatty liver. The reason for individual susceptibility to more severe complications is not known. Hereditary predisposition may play a role in its development.

It is unclear how alcoholic hepatitis eventually develops into cirrhosis. It may be that alcohol affects collagen metabolism directly, either through increased production, decreased disposal, or both. At the earlier stages of fatty liver, collagen is detectable by chemical means only. When collagen is sufficient to become visible by light microscopy, usually it appears first around the central venules, resulting in perivenular fibrosis.

In cases of alcoholic hepatitis, an increased number of mesenchymal cells are present. Even in the absence of alcoholic hepatitis, and prior to any fibrosis, the number of mesenchymal cells can be increased. Already at the early fatty liver stage an increased number of myofibroblasts appear in the perivenular areas. This is eventually accompanied by the deposit of abundant collagen bundles, first in the perivenular areas, leading to myofibrosis and ultimately to cirrhosis. Thus, perivenular fibrosis indicates development of cirrhosis if heavy drinking is continued.

Alcoholic fatty liver is completely reversible in most cases. In some extremely severe cases, it may have a fatal outcome, but as a rule even patients needing hospitalization improve within a few days or weeks after they quit drinking. The clinical spectrum of alcoholic fatty liver may extend from no symptoms at all to severe liver failure. Most patients with pure fatty liver, however, are virtually asymptomatic.

In contrast to those of alcoholic hepatitis, abnormal laboratory values for fatty liver return to normal levels. Fat mobilization may be delayed in extreme cases of if complicated by obesity or pre-diabetes. Other than alcohol withdrawal (with continued abstinence) and the provision of a diet with sufficient calories, vitamins, and protein, no other treatment is generally needed for fatty liver.

A mortality of 1.5 to 8 percent has been reported in individuals who have alcoholic hepatitis II seriously enough to require hospitalization but who are well enough to permit liver biopsy. Survival of patients with alcoholic hepatitis is dramatically improved when they quit drinking or reduce alcohol consumption. Clinical and pathologic signs of alcoholic hepatitis regress within weeks or months in most of these cases.

The general treatment of the patient with alcoholic hepatitis is the same as for that of alcoholic.
fatty liver. Anorexia may be so severe as to require intravenous feeding, including the infusion of amino acids. Risk of encephalopathy as a result of amino acid infusion, however, renders this form of therapy inadvisable on a routine basis.

Several drugs have been used to effect a positive response in patients with alcoholic hepatitis. The most extensively tested drugs in this regard have been steroids. Some controlled studies using steroids as treatment reported significantly improved survival of patients with alcoholic hepatitis and signs of encephalopathy; but this did not occur in patients with a milder illness. Several other controlled studies, however, have not confirmed these findings. Furthermore, one of the controlled studies reported an increased risk of fungal infection associated with this therapy.

Other drugs are being tested, but often long-term beneficial effects occur only in moderate drinkers in whom a favorable effect can be anticipated even in the absence of treatment with drugs. Further studies are needed.

Treatment of the medical disorders associated with alcoholism can and should be detected at an early stage prior to the medical or social disintegration of the patient. A special effort should be made to arrest the disease process through the discontinuation of alcohol consumption.

Charles S. Lieber, MD is director, Alcohol Research and Treatment Center and GI-Liver Training Program, chief, Section of Liver Disease and Nutrition, Bronx VA Medical Center, and professor of medicine and pathology, Mt. Sinai School of Medicine of the City University of New York.

References