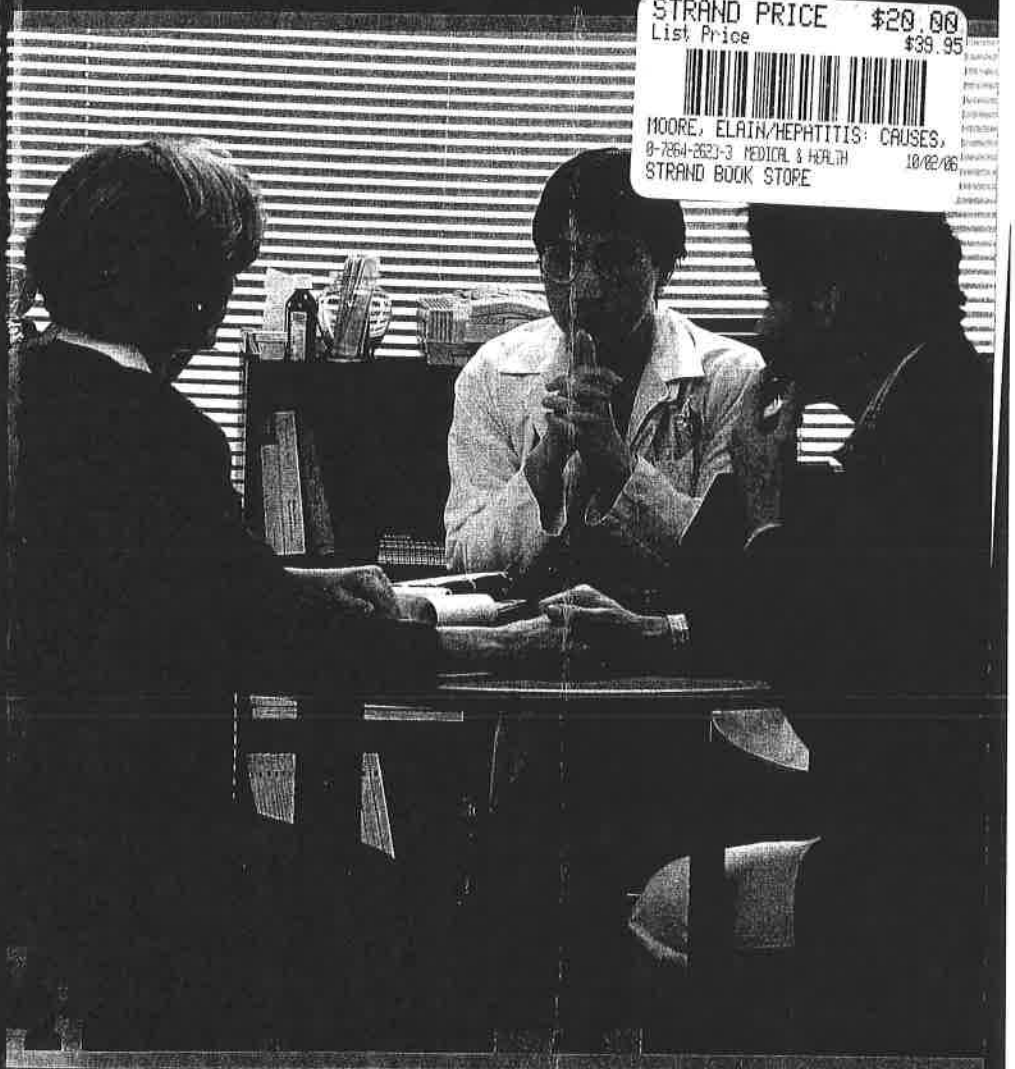
HEPATITIS

Causes, Treatments and Resources



ELAINE A. MOORE

Drug metabolism in liver disease

When liver cell function is impaired because of liver disease, drug metabolism is affected. In liver disease drug metabolism slows down and toxic compounds and drug metabolites can accumulate within the liver.

Development of Liver Toxicity

Hepatotoxins are capable of causing injury, but many hepatotoxins only affect a small number of people. In these people, toxicity is caused by rare idiosyncratic or unpredictable effects. This explains why drugs deemed safe in clinical trials involving thousands of patients are later found to have toxic effects after being introduced into the general population. In some cases, hepatotoxins only cause injury when high doses are used. Certain factors are known to promote the development of toxic hepatitis.

Table 11.1. Factors influencing the development of toxic hepatitis

- Individuals with genetic alterations of metabolic CYP 450 enzymes
- Enzyme induction by other drugs or chemicals, such as alcohol and cigarettes
- The dose or amount of toxin ingested
- Simultaneous ingestion of other hepatotoxins or drugs that alter drug metabolism
- General health; kidney and liver diseases can impair drug metabolism
- Glutathione depletion by fasting and alcohol ingestion
- Age, with drug toxicity more likely to occur in persons older than 50 years; children rarely develop drug toxicity except in the case of accidental overdoses and valproic acid toxicity. Elderly persons experience decreased disposition of drugs undergoing phase 1 but not phase 2 biotransformation caused by diminished hepatic volume and reduced liver blood flow.

Drug-Induced Hepatitis

Drug-induced hepatitis is a condition of liver inflammation and injury caused by many different drugs and chemical toxins. Drug-induced hepatitis occurs in approximately eight of every 10,000 people. Women are affected twice as often as men, and older people are more likely to be affected because their bodies lack the restorative properties of younger people.

All drugs have the potential to cause toxicity, and nearly every drug manufactured has been implicated in causing hepatic toxicity. Some drugs such as acetaminophen are well known for their hepatotoxic potential. Most toxic liver injury results from the reaction of drugs or their metabolites with cell proteins or DNA. If reactive compounds accumulate in the liver, they interfere with cellular oxidation and ultimately destroy cells.

Alternately, certain drugs can induce the production of intermediate compounds and free radicals that contribute to cellular injury. Hepatotoxins may cause liver cell damage, arrested bile flow, or both of these symptoms. Liver cell injury is caused by three different primary physiological responses: direct and indirect toxicity by intrinsic hepatotoxins; idiosyncratic reactions; and by immune system effects.

Intrinsic hepatotoxins— direct and indirect toxicity

Direct toxicity is considered a predictable side effect of certain drugs and chemicals. These chemicals can act as intrinsic hepatotoxins after sufficient bodily exposure. Intrinsic hepatotoxins are recognized by the high incidence of hepatic injury they cause in persons exposed to them and by similar reactions observed in animals under experimental conditions. In the past, occupational chemical exposures caused most intrinsic liver damage, whereas today medications are the primary cause.

Examples of direct toxins include cleaning solvents, *Amanita* mushrooms, carbon tetrachloride, the anticonvulsant valproic acid (Depakene), the cardiac drug amiodarone, the chemotherapeutic agent methotrexate, the anesthetic agent halothane, oral contraceptives, and the analgesic acetaminophen. Intrinsic hepatotoxins can cause necrosis, fibrosis, cholestasis, circulatory problems, angiosarcoma (tumors of blood vessels and tissue), and fatty liver disease.

Indirect toxicity is caused by intrinsic hepatotoxins when they interfere with specific metabolic pathways rather than directly injuring liver cells.

Idiosyncratic reactions

Idiosyncratic reactions are unpredictable responses that occur in a very small number of exposed individuals. Idiosyncratic reactions, which are sometimes called hypersensitivity reactions, are primarily caused by genetic changes affecting the metabolism of specific chemical compounds and immune system reactions, and they do not seem to be related to drug dosage.

Idiosyncratic hepatotoxins can cause hepatitis, cholestasis, and granuloma (type of tumor) formation. Drugs causing idiosyncratic reactions include the anti-tuberculosis drug isoniazid, the tranquilizer chlorpro-

mazine (Thorazine), and the anti-inflammatory agent phenylbutazone. Idiosyncratic reactions typically develop after a fixed incubation period of 1–5 weeks and they recur quickly when the offending drug is re-administered (challenge). Idiosyncratic reactions may be accompanied by fever, rash, elevated counts of eosinophilic white blood cells, a type of cell also increased in allergic reactions.

Immune system effects

In some people the immune system responds to noxious substances by launching an idiosyncratic immune response. As a result, white blood cells produce and secrete cytotoxic chemicals that contribute to liver cell injury and inflammation. This response is seen in less than .01 percent of the population and occurs twice as frequently in women.

Multiple medications— polydrug syndrome

Multiple drugs taken at about the same time compete for enzyme binding sites in the body. This causes the drug with lower affinity for absorption to be metabolized more slowly. This prolongs its action and causes the active drug to stay in the blood circulation longer. With multiple doses, drug concentrations can rise to toxic levels.

Incidence of Toxic Hepatitis

Hepatotoxins can cause liver injury resembling every type of naturally occurring liver disease, including hepatitis, steatosis (fatty liver), cholestasis (impaired bile flow), vascular liver injury, and liver tumors. About 10 percent of all cases of hepatitis are due to toxins, and most toxic hepatitis today results from adverse drug reactions [71]. In persons older than 50 years, adverse drug effects are responsible for about 40 percent of all hepatitis cases. Up to 25 percent of cases of fulminant hepatic failure may be attributed to adverse medicinal reactions.

Effects of Hepatotoxins

Specific hepatotoxins are associated with a specific type of liver injury. For instance the industrial chemical carbon tetrachloride causes severe zone 3 necrosis and fatty infiltration. Yellow phosphorus compounds produce zone 1 liver damage, and *Amanita* mushrooms causes a fatal hemorrhagic form of necrosis. Biopsy results help pinpoint the responsible hepatotoxin based on its known cellular effects.

Acute hepatitis

Toxic hepatitis occurs in only a very small proportion of persons taking a particular drug. With the exception of overdoses, the drug reaction in acute hepatitis is more likely to occur after multiple exposures. In acute toxicity, symptoms typically occur about one week after exposure. Most toxic hepatitis occurs as an acute inflammatory process that resolves when the drug is withdrawn.

Acute hepatitis is usually caused by toxic metabolites that either injure the liver or evoke a destructive immune response. An individual drug can cause more than one type of reaction and symptoms of acute hepatitis, cholestatic disease, and hypersensitivity reactions may overlap.

Fulminant hepatitis

Some cases of acute hepatitis, particularly those occurring in older women, emerge as fulminant reactions with a high mortality rate. About a quarter of all cases of fulminant hepatitis are caused by adverse drug reactions. Patients with acute, fulminant drug-related liver failure often require liver transplants for survival.

Liver failure

Liver failure can occur as a result of fulminant hepatitis caused by drugs and bacterial endotoxins. An example of a bacterial toxin is that produced by *Staphylococcus aureus* in cases of septic shock syndrome, which can cause liver failure.

Chronic hepatitis

Although most drug-related hepatitis causes acute hepatitis, certain drugs can cause a chronic form of hepatitis even after the drug is withdrawn. One example is chlorpromazine, a tranquilizer that rarely causes chronic liver disease. Similar reactions have been reported with tricyclic antidepressants such as amitriptyline, the antibiotic erythromycin estolate, and several other drugs.

Isoniazid, methyldopa, clometacin, and nitrofurantoin can all cause ongoing liver damage and chronic hepatitis. A chronic form of hepatitis with scarring and fibrosis can also occur in patients using long-term low doses of acetaminophen. This is more likely to occur in patients who abuse alcohol. The heart medication amiodarone can cause chronic hepatitis that causes liver tissue changes similar to those seen in alcoholism, such as the presence of Mallory bodies in biopsy specimens.

A sclerosing form of hepatitis can occur in patients receiving intra-arterial infusions of certain chemotherapeutic agents, especially floxuridine, and it has been reported in patients following liver transplants. Long-term methotrexate therapy for arthritis or psoriasis is known to cause chronic liver fibrosis. The clinical picture in chronic disease is similar to that of autoimmune hepatitis. However, in drug induced chronic hepatitis, improvement usually occurs when the drug is withdrawn.

Alcohol and Acetaminophen

Alcohol and acetaminophen are both intrinsic hepatotoxins capable of causing hepatitis ranging from mild disease to fatal injury depending on the circumstances. These two compounds are responsible for the majority of drug-induced liver disease. Their contributions to liver disease are described in the following sections.

Alcohol and the liver

Ethyl alcohol or ethanol is an intrinsic hepatotoxin. Alcoholic liver disease (ALD) is one of the major medical complications of alcohol abuse. ALD can result in alcoholic hepatitis, fatty infiltration of the liver, cirrhosis, accelerated progression of other liver diseases, a higher incidence of liver cancer, and liver failure. Approximately 90–100 percent of heavy drinkers show evidence of fatty liver, and transient episodes of fatty liver can occur after binge drinking. About 10–35 percent of heavy drinkers develop alcoholic hepatitis, and 8–20 percent develop cirrhosis.

The safe limits for alcohol intake are controversial and likely depend somewhat on the individual's genetic makeup, size, diet, and other factors. In general, 210 grams of alcohol in men and 140 grams of alcohol in women each week are considered safe amounts. The average intake in patients who develop cirrhosis is 160 grams/day for approximately 8 years. Symptoms of ALD range from asymptomatic to behavioral changes and the incidental findings of elevated liver enzymes. In overt disease, patients may have jaundice, ascites, spider veins, palmar erythema, testicular atrophy, and gynecomastia (enlarged breasts in males due to increased estrogen levels).

Studies show that alcohol only injures the liver in the presence of polyunsaturated fatty acids, and carbohydrates have a protective effect on alcohol-induced liver injury. If polyunsaturated fats are absent from the diet, the liver is not injured [31]. However, diseases related to fatty acid deficiency can occur, and alcohol ingestion increases the dietary requirements for specific nutrients, particularly B vitamins.

Table 11.2. Risk factors that increase susceptibility to ALD

Female gender
Lifetime intake of alcohol
Genetic factors
Drinking without eating
Binge drinking
High concentration alcoholic drinks
Consuming multiple types of alcohol

ALCOHOLIC STEATOSIS

Steatosis, a condition of fatty liver, is the most prevalent type of alcoholic liver disease. Steatosis invariably occurs when alcohol intake exceeds 80 grams/day. In steatosis, the liver cell cytoplasm is displaced by triglycerides. Liver function can remain normal until steatosis impairs liver function. With abstinence, steatosis is reversible.

ALCOHOLIC HEPATITIS

Alcoholic hepatitis typically occurs after 15–20 years of excessive drinking although it can occur much sooner. Factors influencing disease development include the quantity of alcohol consumed, the individual's nutritional status, and genetic and metabolic traits. It tends to be more severe in females and in Northern European descendants. Alcoholic hepatitis is characterized by hepatocellular necrosis, fibrosis, and inflammation, frequently accompanied by cholestasis. Fatty change is usual but it is not invariably present. The mortality rate is 30–60 percent, and patients often deteriorate after diagnosis, even if they abstain from alcohol. Alcoholic hepatitis is considered the first step in the development of alcoholic cirrhosis.

The major physiological cause of liver damage in ALD is cellular toxicity and necrosis caused by acetaldehyde, the primary metabolite of alcohol. Ethanol is oxidized to acetaldehyde inside liver cell mitochondria by the enzyme alcohol dehydrogenase. Acetaldehyde is then oxidized and transformed into acetate by the enzyme acetaldehyde dehydrogenase. These metabolites alter liver cell metabolism and promote fatty accumulations. Malnutrition and nutrient deficiencies also contribute to the disease process. Free radicals directly injure liver cells and invoke a cellular immune response, which also contributes to liver injury.

ALCOHOL AND VIRAL HEPATITIS

Epidemiologic data show that the hepatitis B virus (HBV) and the hepatitis C virus (HCV) are important factors in the development of ALD. Evi-

dence of HBV, including the presence of HBsAg, is more prevalent in patients with ALD than in the general population. This suggests a higher than expected incidence of HBV infection in heavy drinkers. Infection with HBV or HCV in patients with ALD is associated with accelerated liver damage and lower survival rates compared with uninfected patients [7].

Studies suggest that the risk of alcoholic hepatitis proceeding to alcoholic cirrhosis varies from 10–20 percent. Patients who progress to cirrhosis are more likely to have HBV or HCV markers, and patients with ALD who have these markers are also more likely to develop hepatocellular carcinoma (HCC) at a younger age than people without evidence of viral hepatitis [7].

Synergism refers to effects that are greater when two factors are combined than if the individual effects of each factor were combined. The apparent synergistic effects of alcohol and viral hepatitis are also demonstrated by the fact that infected ALD patients are more likely to develop complications of liver disease, such as hepatic encephalopathy.

Acetaminophen and the liver

Acetaminophen is a safe analgesic, even in patients with liver disease, when used in recommended amounts, typically 2 grams daily or less. Taken as an overdose or as a therapeutic misadventure in which excessive doses are used, acetaminophen is the most common drug-induced cause of liver failure.

Normally, acetaminophen is efficiently metabolized. In the phase I reaction, about 90–95 percent of the drug is converted by glucuronide and sulfate pathways into inactive metabolites, and about 10 percent is converted into an intermediate, highly reactive, electrophilic metabolite known as N-acetyl-p-benzoquinone amine (NABQI). In the phase II reaction, NABQI is detoxified by glutathione substrate, converted into a nontoxic compound (mercapturic acid) and excreted.

Acetaminophen toxicity

In overdoses, high levels of acetaminophen deplete the glucuronide and sulfate pathways. This causes more of the drug to be converted into the toxic NABQI. Levels of NABQI quickly deplete glutathione. In the absence of glutathione, NABQI react with the thiol groups of liver proteins, injuring the cells and causing necrosis. When alcohol or other enzyme inducers are ingested and during periods of starvation, there is even less available glutathione and cellular necrosis is accelerated.

The reaction of toxic acetaminophen metabolites with liver proteins causes a diffuse type of necrosis. When large amounts of acetaminophen

are ingested, massive necrosis occurs and leads to complete liver failure. Other effects of acetaminophen toxicity include acute tubular necrosis (kidney tissue destruction), pancreatitis, and myocardial necrosis (heart muscle destruction).

Studies show that at therapeutic doses as low as 150 mg daily, gene changes can occur that increase susceptibility to liver injury when higher doses or other hepatotoxins are consumed. The usual adult dose of acetaminophen is 1,000 mg (one gram) taken every 4 hours. Doses as high as 4 grams daily are generally considered safe although people with liver disease or who abuse alcohol are advised to limit daily use to 2 grams.

Viral hepatitis, and other drugs besides alcohol that induce cytochrome P450 enzymes can predispose individuals to acetaminophen toxicity. These drugs include barbiturates, phenytoin, carbamazepine, rifampin, isoniazid, Phenobarbital and omeprazole.

Suicidal overdose and therapeutic misadventures

In fatal intentional overdoses and accidental therapeutic misadventures, the dose of acetaminophen usually ranges from 7 to 70 grams. The extent of injury is usually dose-related. In some cases, biochemical changes indicating toxicity do not occur until 24–36 hours after ingestion. Toxicity usually occurs in 4 phases.

Table 11.3. Phases of acetaminophen toxicity in overdoses

Phase 1) within 2–24 hours after ingestion, symptoms of nausea, vomiting, and loss of appetite occur; patients with acetaminophen concentrations higher than 300 mg/dl at 4 hours post ingestion, and higher than 15 mg/dl at 15 hours post ingestion, have a 90 percent risk of developing serious or fatal liver damage.

Phase 2) within 24–48 hours after ingestion, symptoms improve, but evidence of hepatic injury develops with transaminase enzyme, bilirubin, and prothrombin levels beginning to increase; right upper quadrant pain and liver enlargement may occur and urine output may increase;

Phase 3) within 72–96 hours after ingestion, nauseas and vomiting may recur or worsen and be accompanied by malaise, jaundice, and mental changes, including confusion, sedation, and coma; liver function declines and enzyme levels peak, with AST often exceeding 10,000 IU/L;

Phase 4) within 6–7 days after ingestion, resolution of hepatic damage occurs, and liver function tests return to normal. About 1–2 percent of patients, especially those who do not receive treatment, fail to show signs of recovery and usually progress to liver failure.

Acetaminophen levels. Risk of hepatotoxicity is typically assessed in suspected overdoses using a Rumack-Matthew nomogram that relates the blood acetaminophen level to hours passed since ingestion. For instance, an acetaminophen level of 150 mg/dl 2 hours after ingestion indicates toxicity. The nomogram is helpful for assessing toxicity, but it presumes a known time of dosage, no concomitant risk factors for liver disease, and it assumes that only a single dose of acetaminophen and no other drugs were ingested.

Treatment of acetaminophen toxicity. The primary treatment for acetaminophen toxicity is N-acetylcysteine (NAC), an amino acid that restores glutathione levels. Better results are observed the earlier that treatment is started. Optimal treatment should begin within 24–30 hours after drug ingestion, using 150 mg/kg NAC intravenously. The dose is reduced the second day, using 100 mg/kg over 16 hours until the patient has three consecutive normal prothrombin time levels.

Other treatments used in overdoses include charcoal lavage, which binds and absorbs acetaminophen that is still in the stomach, ventilators as supportive therapy, hemodialysis, plasmapheresis to rapidly dilute and reduce blood levels, and nutritional supplements.

Mortality in acetaminophen overdoses. Studies show that patients with acetaminophen-induced liver injury who have higher levels of the liver protein alpha fetoprotein (AFP) are more likely to survive the injury without undergoing liver transplants. AFP levels less than 3.9 ug/L 24 hours after overdose are highly predictive of death. Prothrombin levels with an INR ratio greater than 2.4 at 24 hours post exposure are also highly predictive of mortality.

Hepatotoxins and Types of Liver Injury

Hepatotoxins are often classified according to their status as intrinsic or idiosyncratic toxins. However, because most toxins cause a specific type of liver injury, some systems of classification group toxins together according to the primary type of liver injury they induce.

Direct and idiosyncratic effects

Usually, although there are notable exceptions, intrinsic hepatotoxins cause zonal necrosis (liver cell destruction occurring in specific regions of the liver). Unlike the necrosis seen in viral hepatitis, drug-induced necrosis is usually accompanied by only slight inflammation.

Idiosyncratic toxins are similar to hepatitis viruses in their ability to cause diffuse and, in severe cases, massive necrosis. In cases of massive

necrosis, the liver tissue suffers complete diffuse cellular destruction with complete tissue collapse.

Steatosis

Some drugs cause abnormal accumulations of liver fat, causing a condition of steatosis. Steatosis may be characterized by small microvesicular or large macrovesicular fat droplets. In some cases, abnormal accumulations of phospholipid fats are found in the liver, causing conditions of phospholipidiosis.

Vascular liver injury

The liver's vascular system (veins, arteries, sinusoids, capillaries) may be damaged in drug toxicity. Blood vessels may be dilated and stretched, or occluded and blocked by scar tissue. For example, anabolic and contraceptive steroids can cause focal dilation of zone 1 sinusoids, a condition causing enlarged liver, abdominal pain, and liver enzyme elevations. The condition improves when the hormones are stopped. In contrast, azathioprine administered after renal transplants may result in fibrosis and cirrhosis 1–3 years later.

Peliosis hepatitis

Peliosis hepatitis is characterized by large blood-filled cavities that may be lined with random distributions of sinusoidal cells. Red blood cells can pass through these cavities and, over time, fibrosis can develop. Peliosis has been reported in patients taking oral contraceptives, androgenic and anabolic steroids, and tamoxifen.

Veno-occlusive disease (VOC)

The earliest reports of VOC came from Jamaica and were caused by toxic injury to small hepatic veins by pyrrolidizine alkaloids taken as senecio in medicinal bush teas. Later instances, some of which were related to contaminated wheat, have been reported in India, Israel, Egypt and Arizona.

Rhabdomyolysis

Rhabdomyolysis is a condition of muscle fiber breakdown caused by injury from toxins, shock, and burns, and it may occur as a complication of hyperthermia (heat stroke). In up to 10 percent of patients with hyperthermia, liver damage contributes to death. Liver damage is characterized by microvesicular fat deposits, congestion, necrosis, cholestasis, and blocked or occluded blood vessels.

COCAINE

Cocaine toxicity is caused by production of a hepatotoxic metabolite, norcocaine nitroxide. This highly reactive metabolite causes liver injury by peroxidation, free radical formation, and by binding to hepatic proteins. Up to 59 percent of patients with cocaine intoxication that develop rhabdomyolysis show evidence of liver damage. Changes include necrosis in zones 1,2, or 3 and accumulations of microvesicular fat in zone 1 [56].

Granulomas

Up to 60 different drugs, including penicillin, ampicillin, sulfasalazine, cotrimoxazole (Septrin), and pyrimethamine-sulfadoxine (Fansidar), may also cause granulomas, which are tumors composed of inflammatory tissue and white blood cells [71]. In the following lists, drugs and environmental chemicals that cause similar types of liver injury are grouped together.

Table 11.4. Hepatotoxins that cause toxic hepatitis

Acebutalol
Acetaminophen
Allopurinol
Amitriptyline
Anabolic steroids
Atenolol
Carbamazepine (Tegretol)
Chloramphenicol
Chlorpropamide
Chlorzoxazone
Cincophen
Cocaine
Colchicine
Dantrolene
Diclofenac
Ecstacy (MDMA)
Erythromycin
Etretinate
Fenoprofen
Gold compounds
Halothane
Ibuprofen
Indomethacin
Isoniazid
Ketoconazole
Mephenytoin
Methyldopa
Metoprolol
Naproxen
Nifedipine
Oral contraceptives
Oxyphenisatin laxatives
Penicillamine
Phenytoin (Dilantin)
Phenacemide
Phenobarbital
Piroxicam
Pirprofen
Retinoids
Rifampin
Salicylates (aspirin)
Statins (cholesterol-lowering)
Sulfa compounds
Sulindac
Trichloroethylene (found in glue)
Urethane
Valproic acid
Vitamin A
Zidovudine

Table 11.5. Hepatotoxins that produce hepatic necrosis without steatosis

Acetaminophen
Aniline dyes
Beryllium compounds
Dioxin
Ferrous sulphate (iron supplements)
Manganese compounds
Selenium
Urethane
Yellow phosphorus

Table 11.6. Hepatotoxins that produce hepatic necrosis and steatosis

Aflatoxins
Amanita mushrooms
Carbon tetrachloride
Chlorinated diphenyls
Chloroform
DDT insecticide
Dinitrotoluene
Ethylene dichloride
Galactosamine
Halothane
Iodoform
Naphthalene
Tannic acid

Table 11.7. Hepatotoxins that cause steatosis

Alcohol
Antimony
Barium salts
Chromates
Hydrazine
Methotrexate
Phosphorus
Tetracycline
Thallium compounds
Uranium compounds
Warfarin (coumadin)

Table 11.8. Hepatotoxins that cause microvesicular steatosis

Cocaine
Tetracycline

Table 11.9. Hepatotoxins that cause macrovascular steatosis

Alcohol
Corticosteroids
Methotrexate

Table 11.10. Hepatotoxins that produce Mallory bodies and phospholipid accumulations

Alcohol
Amiodarone
Corticosteroids
Nifedipine
Perhexilene maleate
Thioridazine (Mellaril)
Stilboestrol

Table 11.11. Hepatotoxins that can cause hepatic granulomas

Allopurinol
Aspirin
Carbamazepine
Cephalexin
Chlorpromazine
Contraceptive steroids
Dapsone
Diazepam
Gold compounds
Halothane
Isoniazid
Mineral oil
Nitrofurantoin
Oxacillin
Penicllin
Phenylbutazone
Phenytoin
Procainamide
Quinidine
Quinine
Ranitidine
Sulphadiazine
Sulphamethoxazole-trimethoprim
Sulphathiazole
Tocainide
Tolbutamide

Table 11.12. Hepatotoxins that can lead to chronic hepatitis

Acetaminophen
Dantrolene
Diclofenac
Isoniazid
Methyldopa
Nitrofurantoin
Oxyphenisatin laxatives
Papaverine
Pemoline

Clinical Trials and Drug-Induced Liver Injury

During a drug's development, before it is released to the public, manufacturers conduct animal tests that assess the drug's effects on liver function. Additionally, liver function testing is conducted on humans, and in many cases, the results keep the drug from entering the market. Liver failure, due to a new drug, is a rare event, and, unfortunately, it may not show up until after a drug has been approved.

Why do adverse drug effects occur after a drug has been approved? Most clinical trials involve 3,000 subjects. Rare adverse drug effects including liver failure may only show up in one per 50,000 exposures. In addition, genetic variations cause individuals to metabolize drugs differently, and individuals may be taking more than one drug.

New drug scrutiny

The FDA also monitors newly reduced drugs for adverse effects. In March 2000, the FDA asked Parke-Davis/Warner Lambert to voluntarily withdraw the diabetes drug Rezulin (troglitazone) because it appeared to cause greater liver toxicity than similar drugs on the market. The FDA also asked Wyeth-Ayerst Laboratories to voluntarily remove the analgesic Duract (bromfenac) from the market after receiving reports of liver failure when the drug was used for longer than the 10 days specified in the labeling.

Sometimes drugs that are reported to cause liver toxicity may be kept on the market if there are no other effective drugs in their category. In this case, changes in labeling are often recommended or their use is restricted to hospitalized patients. The FDA has also developed a web page on drug-induced liver toxicity at www.fda.gov/cder/livertox.

The FDA also advises consumers to follow dosing requirements and study labels for adverse effects. In addition, consumer should learn to recognize the signs of liver disease, which can include nausea, dark urine, jaundice, and mental confusion.

Drugs with Limitations

The FDA lists the following drugs as having limitations on their use due to potential liver problems (warnings, dose restrictions, monitoring):

Table 11.13. Drugs with potential to cause liver problems

Niaspan Extended Release Tablets (niacin)
Dantrium (dantrolene)
Tylenol (acetaminophen)

Table 11.13. (cont.)

Normodyne (labetalol)
Cylert (pemoline)
Felbtol (Felbamate)
Zylo (zileuton)
Tasmar (tolcapone)
Trovan (trovafloxacin, alatrofloxacin)

Source: U.S. Food and Drug Administration, FDA Consumer Magazine, May-June, 2001.

Environmental and Plant Toxins

Numerous plants and chemicals have the potential to injure the liver and cause acute and chronic hepatitis. Some of these toxins are described in the following sections.

Plants and household chemicals

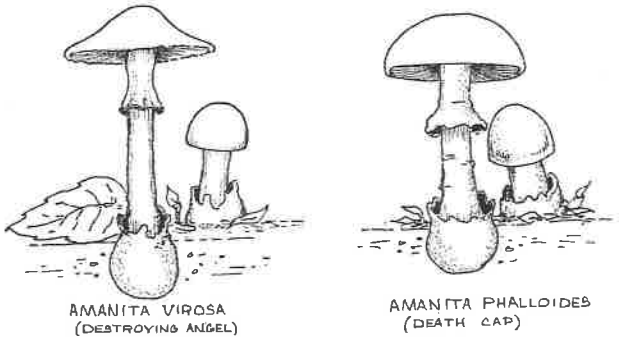
Amanita mushrooms cause hepatitis and liver injury in some parts of the world, outside of the United States. Aflatoxin molds cause severe liver disease and liver cancer in many undeveloped countries. In the United States, liver injury is rarely linked to aflatoxin consumption although there are reports of aflatoxin being present in contaminated peanuts and peanut products.

Food products can contain toxic preservatives or they may be accidentally contaminated with toxic chemicals. Flour contaminated with the chemical methylene dianaline caused cholestatic jaundice and a condition of Epping jaundice in hundreds of customers at a bakery in Epping, England.

Insecticides often contain toxic chemicals such as DDT that can persist in the body for decades, possibly causing liver damage years later. Carbon tetrachloride, a chemical once widely used for dry cleaning, can cause neurological symptoms, hepatitis, liver failure and kidney failure. Phosphorus, once widely used in the manufacture of matches and firecrackers, can cause fulminant hepatitis and liver disease.

Herbs

Numerous herbs can damage the liver and cause hepatitis as a result of direct toxicity or idiosyncratic reactions. However, because herbal use is not always suspected in cases of hepatitis, cases of hepatitis may go unrecognized. The compounds listed in table 11.14 have been reported to cause



***Amanita* species (Marvin G. Miller).**

toxic hepatitis although in some reports high doses, much higher than the recommended amounts, were used before toxicity developed, and, in some cases, other medications and supplements were used simultaneously.

In addition to those listed, some herbal products, such as St. John's Wort, that are not hepatotoxins, can affect the metabolism of other drugs. Others have been found to be contaminated with bacteria. When using herbal medicine, it is important to buy products from reputable manufacturers that have labels documenting the authenticity of the ingredients. Side effects and drug interactions with herbal products can be found by consulting the *PDR for Herbal Medicine* and Mark Blumenthal's *The Complete German Commission E Monographs* listed in the resource section.

Table 11.14 Herbs and supplements reported to cause hepatitis/liver injury

Amanita species
Asafetida
Atractylis gummifera
Black cohosh
Buckthorn (*Rhamnus cathartica*)
Bush tea
Cascara sagrada
Celandine
Chaparral
Coltsfoot
Comfrey (*Symphytum*)
Crotalaria
Echinacea
Jin bu huan
Kalms tablets
Kava-kava (*Piper methysticum*)
Kombucha
Lobelia
Ma huang
Mate
Mistletoe
Nicotinic acid (niacin, Nicolar)
Noni (*Morinda citrifolia*)
Nutmeg
Pau d'arco
Pennyroyal oil (*Mentha pulegium*)

Gentian
Germander (*Teucrium chamaedrys*)
Groundsel (*Senecio vulgaris*)
Impila (*Callilepsis laureola*)
Irish tea
Iron supplements
Pyrrolizidine alkaloids, especially comfrey
Senna
Skullcap (*Scutellaria gaericulata*)
Valerian
Vitamin A

Dietary supplements

Dietary supplements can cause hepatitis in overdoses, in idiosyncratic reactions, and in individuals with impaired liver function. Some of the most well known hepatotoxic supplements include vitamin A and extended-release formulations of niacin.

Vitamin A

Excessive doses of vitamin A used for extended periods can cause chronic hepatitis. Symptoms include headache, appetite loss, weight loss, fatigue, itching, dry skin and loss of body hair. Clinical signs include enlarged liver and spleen, ascites, and, occasionally, jaundice. Liver biopsies show zone 3 fibrosis, chronic hepatitis, cirrhosis, peliosis hepatitis, and occlusive disease. Toxicity has occurred in people taking 20 times the recommended dose and in people using recommended doses daily for many years.

Vitamin A derivatives, a class of drugs known as retinoids, may also damage the liver. Similar to vitamin A, these compounds can cause cirrhosis and chronic hepatitis.

Niacin

Niacin or vitamin B3 is known to lower cholesterol levels. Low doses of niacin can cause an unpleasant flush. To reduce severe flush in people requiring doses sufficient to lower cholesterol levels, manufacturers have developed high-dose, time-release (extended release) niacin preparations. Extended release preparations containing more than 500 mg of niacin are hepatotoxic and can cause both acute and chronic hepatitis.

Bacterial toxins

During bacterial infections, many bacteria release potent enterotoxins and endotoxins and other extracellular proteins such as urease that contribute to the symptoms seen in infection. In severe infections, such as toxic shock syndrome, which is caused by *Staphylococcus aureus*, the toxins that they release, exotoxin C and enterotoxin F, can contribute to hepatic failure. Another cause of toxic shock syndrome, *Streptococcus pyogenes*, also produces exotoxins that can cause hepatitis.

Reye's syndrome

Reye's syndrome, a potentially fatal condition of hepatitis and coma, occurs in children with viral infections. A higher incidence of Reye's occurs in children with viral infection who are treated with low doses of aspirin. Although the link with aspirin has not been confirmed, numerous studies have strongly implicated aspirin as a causative agent.

Environmental hepatotoxins

Environmental toxins include chemicals used in the munitions industry, rocket assembly, plastics, pharmaceutical, cosmetic and chemical industries, and agriculture. Today environmental agents rarely cause hepatitis. However, because injury develops over a long period of time, the offending agent may not be implicated.

Arsenic

Organic arsenic compounds, such as arsenic trioxide (Fowler's solution) used for extended periods to treat psoriasis, can cause portal hypertension. Acute arsenic poisoning can cause fibrosis and vascular occlusive liver disease. In some regions arsenic is found in drinking water and in folk remedies or locally prepared (native) drugs.

Vinyl chloride

Workers exposed to vinyl chloride for many years develop hepatotoxicity. Early changes include sclerosis or scarring in zone 1, enlarged spleen, and portal hypertension. Later changes include peliosis hepatitis and angiosarcoma.

Radiation

Radiation treatments using 35 Gy over time or 3000–6000 rads to the upper abdomen leads to a hepatic lesion and a syndrome termed radiation hepatitis. Symptoms, which typically develop within 2–12 weeks after treatment, include ascites, enlarged liver, enlarged spleen, jaundice and abdominal pain. Liver biopsy shows sinusoidal congestion, zone 3 necrosis and hemorrhage, and fibrotic occlusions of hepatic veins [71]. Venous occlusion may be a transient condition or a fatal disease caused by liver failure.

Disease Course In Toxic Hepatitis

Drug reactions may be immediate in acute overdoses. In reactions that occur over a prolonged course of treatment, disease development may be subtle. Some drugs, such as sulphonamides, phenytoin, and dapsone, may also cause an idiosyncratic hypersensitivity syndrome resembling mononucleosis with fever and rash.

In idiosyncratic reactions, symptoms may occur within a few weeks of drug use. In some cases, they develop on the second course of drug treatment after a period of sustained drug withdrawal. In most intrinsic and idiosyncratic drug-induced liver injuries, symptoms of liver toxicity improve after the drug is withdrawn. Some drugs, such as halothane, cause a mixed intrinsic/idiosyncratic reaction.

Halothane hepatitis

With the anesthetic halothane, liver injury typically occurs after multiple exposures although it may occur after the first exposure. Obese, elderly females are at particular risk for halothane toxicity although children can also be affected.

Symptoms that occur after the first exposure usually develop more than 7 days (range 8–13 days) later and include fever, usually with rigors, malaise, and upper right quadrant pain. Jaundice usually develops after 10–28 days. After several exposures to halothane, the temperature rise occurs 1–11 days after surgical use, and jaundice develops within 3–17 days [56].

Bilirubin levels are typically very high especially in fatal cases. Transaminase levels are similar to those seen in viral hepatitis although alkaline phosphatase levels can occasionally be markedly elevated. In patients who develop jaundice mortality is high, especially if the prothrombin time rises markedly even when vitamin K is administered. Halothane administration should not be repeated in patients who even show a very mild reaction after the first drug exposure, and halothane should not be administered within six months of a previous dose.

Phases of drug-induced liver injury

Symptoms of drug-induced hepatitis usually occur in three distinct phases: 1) an immediate, severe pre-icteric (before jaundice develops) condition causing moderate to severe neurological or gastrointestinal symptoms, 2) a period of improvement, and 3) a phase of severe liver injury with marked jaundice, elevated liver enzyme levels, increased gamma globulin levels, and liver tenderness that can be accompanied by kidney failure.

In those who recover, maximum serum bilirubin levels are seen after 2–3 weeks. People with severe toxicity experience liver atrophy and death from hepatic failure. If hepatic pre-coma or coma develops, mortality is as high as 70 percent. Liver damage is particularly extensive in persons who continue to use the offending drug after liver damage has started. For this reason, all medications that a person takes should be listed and considered suspect in persons with emerging liver disease.

Diagnosis

Liver enzyme tests and bilirubin levels are used to diagnose liver disease. Viral marker tests are used to determine if jaundice is due to viral infection. A careful medical and drug history can help diagnose liver injury due to toxins. The International Consensus Criteria for Drug-Induced Hepatoxicity have been developed to help determine if liver damage is drug-induced. These criteria include:

1. Time of drug intake compared to onset of symptoms is suggestive of drug injury if it occurs from 5–90 days and compatible with drug injury if less than 5 days or more than 90 days from initial drug intake.
2. Course of reaction after cessation of drug is very suggestive of drug injury when liver enzyme levels fall by 50 percent within 8 days after drug withdrawal; liver enzyme decreases of 50 percent within 30 days in hepatocellular disease and within 180 days in cholestatic illness.
3. Alternative causes of hepatitis have been excluded by other tests including liver biopsy
4. Positive response to re-challenge, with at least a doubling of liver enzymes, when the drug is re-administered, when available.

The reaction is considered "drug related" if all of the first 3 criteria are met, or if 2 of these criteria are met and the re-challenge test is positive.

Liver function tests

Hepatotoxins causing necrosis cause marked elevations of transaminase liver enzymes that reflect the extent of liver damage. Levels are typically higher than those seen in acute viral hepatitis. Alkaline phosphatase levels are slightly elevated, and bilirubin levels are moderately elevated.

In severe necrosis, plasma coagulation factors are depressed and the prothrombin time is elevated. In the early stages of necrosis, albumin lev-

els are normal although they fall late in the clinical course and in chronic disease.

Blood levels of acetaminophen and alcohol are used to diagnose acetaminophen overdoses and alcohol abuse. In alcoholism, levels of the enzyme gamma glutamyl transferase (Gamma GT) are also elevated.

In microvesicular steatosis serum transaminase enzyme levels are modestly elevated to 5–20 times the normal range, and bilirubin levels are only moderately increased. The prothrombin time is usually prolonged, and low blood glucose levels may occur causing a condition of hypoglycemia.

Biopsy specimens cause characteristic symptoms of drug toxicity that are specific for the offending agent. Biopsy results are discussed further in chapter fifteen.

12

Metabolic Causes of Hepatitis

Hepatitis results from several metabolic disorders and inborn errors of metabolism that cause minerals, fat deposits, or amino acids to accumulate in the liver. These accumulations can directly destroy liver cells, interfere with liver function, and cause inflammation. Causes of metabolic hepatitis include: Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, galactosemia, fructose intolerance, tyrosinemia, non-alcoholic fatty liver disease (NAFLD), infantile giant cell hepatitis, obesity, and sarcoidosis. Fulminant hepatitis may also occur in conditions of shock. The metabolic causes of hepatitis and the effects on the liver caused by these abnormalities are described in chapter twelve.

Wilson's Disease

Wilson's disease is a rare inherited disease predominantly seen in young people characterized by increased deposits of copper in the body's tissues. Wilson's disease results in hepatic and neurological changes, deposits in the cornea known as Kayser-Fleischer rings, and lesions in the kidney and other organs. The Kayser-Fleischer ring is a greenish-brown ring near the margin of the cornea next to the sclerus (white of the eye) that results from deposits of copper.

Inheritance and prevalence

For disease to develop, both parents must contain the autosomal recessive gene on chromosome 13 responsible for Wilson's disease. The prevalence is about 1 in 30,000 and about 1 in 90 people are carriers [56] of this gene. Wilson's disease is seen worldwide but occurs most frequently in Jews

children, although peak incidence occurs in people in their fifties. NAFLD is much more likely to occur in obese people and people with diabetes.

Patients with NAFLD usually are asymptomatic and are diagnosed incidentally during physical exams when an enlarged, smooth, firm liver is discovered. Liver function tests are often normal although transaminase enzyme and alkaline phosphatase levels may be slightly elevated. Patients with acute fatty liver are at risk of sudden death due to shock caused by pulmonary fat clots that block blood circulation.

DISEASE COURSE OF FATTY LIVER

Fatty liver by itself does not cause liver disease. However, it can lead to liver cell inflammation and steatohepatitis, and it can signify other metabolic problems. Steatosis in NAFLD is often accompanied by insulin resistance, liver cell inflammation, and fibrosis that can progress to cirrhosis, liver cancer, and liver failure.

Abnormalities of lipid metabolism, such as elevated cholesterol and triglycerides, in conjunction with NAFLD are seen in the condition called Metabolic syndrome or Syndrome X. About 56 percent of patients with NAFLD are reported to have Metabolic syndrome, and the prevalence is higher in patients with steatohepatitis.

Studies show that the fat accumulations in NAFLD are composed of fatty acids produced within the liver and also fats derived from diet. Excessive dietary fats and sugars contribute to NAFLD as the amount of dietary fat and sugar exceeds the liver's ability to process these substances. Insulin resistance also contributes to increased liver fat production.

Patients with NAFLD and hepatitis C usually have a more severe disease course than patients with hepatitis C alone. For this reason patients with hepatitis C who have fatty liver are treated with interferon even in the absence of other symptoms.

Non-alcoholic steatohepatitis (NASH)

Non-alcoholic steatohepatitis (NASH) is an advanced form of NAFLD in which steatosis is accompanied by inflammation and liver cell necrosis. Insulin resistance and lipid abnormalities are typically severe and about 88 percent of patients are reported to have Metabolic syndrome.

Patients with NASH may be asymptomatic or have mild symptoms of fatigue, malaise and abdominal discomfort. In about 20 percent of affected people, NASH progresses to cirrhosis. Because symptoms in NASH are often vague, liver disease may not be diagnosed until cirrhosis develops. This accounts for the high mortality rate in NASH. Patients with NASH

also have a higher risk of progression to hepatocellular cancer than other patients with cirrhosis.

Diagnosis

NAFLD is suspected in patients with mild to moderate liver enzyme elevations, obesity, insulin resistance, or lipid abnormalities. Ultrasonography can be used to show large accumulations of fat in the liver. Computed tomography (CT) is a more sensitive technique that detects smaller fat accumulations. A definitive diagnosis requires a biopsy. Biopsy specimens show steatosis, inflammation, and, in advanced disease, fibrosis.

Treatment

If fatty liver is related to obesity, diabetes, or high lipid levels, treatment or better control of these conditions is the first step in treating fatty liver. Studies show that regular exercise and weight loss can slow disease progression. In NAFLD caused by intestinal bypass surgery, surgical reversal may be required. Drugs such as Actigall are being evaluated in clinical trials as treatments for NAFLD. Liver transplantation is rarely used as a treatment.

Miscellaneous Causes of Hepatitis

Sarcoidosis

Sarcoidosis is a chronic disease that causes the production of nodules containing nests of tissue cells. These nodules affect the function of the liver, lungs and lymph nodes. Sarcoidosis can cause an inflammatory process in the liver that progresses to hepatitis. Sarcoidosis is more common in African-Americans than other ethnic groups.

Shock (ischemic) liver

Shock caused by infection, trauma, or heart disease impairs blood circulation and interferes with cellular processes and organ functions. Shock can cause massive liver cell necrosis, causing a condition of hepatitis that can rapidly progress to fulminant liver failure.

.ange, are seen in massive hepatic necrosis (for instance, acetaminophen overdoses), viral hepatitis, severe alcoholic hepatitis and severe ischemia.

Table 14.1 Enzyme reference values

Note: these are the most commonly used ranges; values may vary depending on the testing method used.

ALT: The reference range for ALT is 2–45 IU/l
AST: The reference range for AST is 2–40 IU/l
ALP: The reference range for Alkaline phosphatase is 35–130 IU/l
Gamma GT: The reference range for Gamma glutamyl transferase (GGT) is 3–60 IU/l
Aldolase: The reference range for aldolase is <6 U/L
Cholinesterase: The reference range for cholinesterase is 8–18 UU/L
Lactic dehydrogenase (LDH): The reference range for LDH is 100–190 U/L

Cholestatic enzymes

The cholestatic enzymes alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT or Gamma GT) are increased in conditions in which bile flow is impaired, including bile duct defects and liver cell injuries that impair bile release. GGT is primarily produced in the bile ducts, whereas ALP is also found in bone, and smaller amounts are found in the placenta, bile ducts, intestines, and kidneys. When both GGT and ALP are increased, the liver is presumed to be responsible. If only ALP is elevated, and the cause is uncertain, an alkaline phosphatase fractionation test can be used to help determine if the elevation is from bone or liver.

Levels of alkaline phosphatase rise in cholestasis and to a lesser extent in liver cell damage. Levels of GGT rise in cholestasis and in hepatocellular disease. Levels are also increased by certain drugs and in alcoholism, even in the absence of liver disease, and occasionally in metastatic liver cancer. A high elevation of ALP in the presence of normal or only modestly elevated AST and ALT levels suggests disease of the bile ducts. An isolated elevated GGT with no other liver test abnormalities does not need to be further evaluated unless there are other risk factors and clinical signs of liver disease.

Other liver enzyme levels

Certain liver enzyme tests, such as lactic dehydrogenase (LDH), were once widely used to help diagnose liver disease. Because these enzymes are primarily elevated in other conditions, they are no longer routinely used to diagnose hepatitis except in the case of diagnostic challenges and special circumstances.

Aldolase

Aldolase is an enzyme found in various tissues and muscles that facilitates the breakdown and conversion of energy of the sugars glucose, fructose and galactose. Aldolase levels are increased in conditions of muscle damage, including the rhabdomyolysis caused by certain drugs, and in acute hepatitis.

Cholinesterase

Cholinesterase is an enzyme produced by the liver necessary for metabolism of the neurotransmitter acetylcholine. Decreased levels are seen in hepatocellular disease, especially cirrhosis, and reflect diminished synthesis and malnutrition. Decreased levels of cholinesterase cause increased susceptibility to chemicals.

Lactic dehydrogenase (LDH)

Lactic dehydrogenase is an enzyme found in cardiac muscle and, in lower concentrations, in the liver. Marked increases in LDH are seen in patients with cancers that affect the liver.

Enzyme elevations in hepatitis

The transaminase enzymes and the alkaline phosphatase level are the primary tests used to diagnose and monitor hepatitis. The predominant enzyme to rise and the pattern of enzyme elevation can help differentiate the various types of hepatitis. The degree of enzyme elevation and the ratio of ALT relative to AST also vary in different types of hepatitis. Before the discovery of hepatitis C and blood tests to identify HCV infection, blood donors in the United States were tested for ALT, and donors with high levels were excluded.

Acute hepatitis

In the early stages of acute hepatitis AST levels are typically higher than ALT levels. Liver cells contain one and a half to two times as much AST as ALT. However, AST has a shorter half-life of 18 hours (time in the circulation before breaking down) than ALT, which has a half-life of 48 hours. Therefore, after one or two days of illness, ALT is typically higher than AST. Later in the disease course, if fibrosis or cirrhosis develop, the AST: ALT ratio can rise as liver damage exceeds liver cell regeneration.

In acute hepatitis caused directly by toxins or shock, AST and ALT levels increase rapidly, often to extremely high values, accompanied by a marked increase in prothrombin time. Peak abnormalities usually occur 24–48 hours after onset of injury and then rapidly fall to normal (accord-

may be the first change seen. Urine urobilinogen is measured as a semi-quantitative test with positive results graded from 1–4, with 4 indicating highest concentrations.

Protein levels

One of the liver's major functions is protein synthesis. Synthesis may be impaired in liver disease, and proteins may be released from injured cells. Some proteins, such as fibrinogen, haptoglobin, C3 complement, and alpha-1-antitrypsin are also released during inflammation. The proteins commonly measured to assess liver function include albumin, clotting proteins, and immunoglobulins.

ALBUMIN

The two major constituents of protein include albumin and globulin. Albumin is the major protein that circulates in the blood. Here, it carries or transports other substances including drugs and hormones. Albumin is produced in the liver and secreted into the blood, where it helps maintain fluid levels within tissues. Low levels of albumin lead to a release of fluid from tissues, causing a condition of edema. Individuals with chronic liver disease, especially those with cirrhosis, frequently have low albumin levels. Low albumin levels are seen in liver disease, malnutrition, and in some kidney disorders.

Reference range for albumin: 4.0–5.0 mg/dl

PROTHROMBIN TIME (PT)

The liver produces several different clotting proteins. When levels are deficient the blood's ability to clot is impaired. The time it takes blood to clot can be measured in a blood test called the prothrombin time (PT). During the testing process the amount of time that it takes for a specimen to clot is compared to a normal control, and a ratio known as the INR is calculated. Vitamin K can usually return the PT level to normal unless liver disease is particularly severe.

Reference range for prothrombin time= 9–11 seconds

Reference range for INR= 0.8–1.2

IMMUNOGLOBULINS

Immunoglobulins (Ig) are a class of proteins with several subtypes, including gamma globulin (IgG). Immunoglobulin proteins are produced in the liver and by white blood cells. Increases in specific immunoglobulins are seen in various liver diseases. For instance, levels of immunoglobulin G are increased in hepatitis C and autoimmune hepatitis, and levels of immunoglobulin A are increased in alcoholic liver disease.

Blood ammonia tests

Ammonia is a nitrogen-rich compound primarily produced in the colon during the metabolism of protein. As it passes through the liver ammonia is further metabolized to urea by hepatocytes. Certain factors, such as genetic mutations, can interfere with the metabolic process causing elevated blood ammonia levels (hyperammonia).

Severe or chronic liver failure, particularly in fulminant liver disease and advanced cirrhosis, can impair normal ammonia metabolism and cause hyperammonia. Ammonia levels are also elevated in most conditions of hepatic encephalopathy and in Reye's syndrome which is primarily a central nervous system disorder with only minor changes in liver function. The fasting ammonia level is helpful in diagnosing Reye's syndrome and in helping to determine if conditions of encephalopathy are related to liver dysfunction. The reference range for ammonia is 15–45 ug/dl or 11–32 umol/L.

Blood lipids tests

The liver plays a major role in producing, transporting, and metabolizing fatty lipid substances, primarily cholesterol, phospholipids, and triglycerides. The liver produces most of the body's cholesterol and a smaller amount, about 15 percent of the total cholesterol stores, is derived from diet. The liver metabolizes lipids into bile acids that are used to form cell membranes, hormones, and lipoproteins. Impaired lipoprotein synthesis, in turn, contributes to fatty liver.

About one-third of the fatty acids consumed daily are processed by the liver where they are either transformed into triglycerides or oxidized. Oxidation usually occurs in the fasting state, and transformation into triglycerides occurs in the non-fasting state. Excess triglyceride production results in a condition of fatty liver. In fatty liver, triglycerides lodge into liver cells displacing other cellular components. Triglyceride levels are usually increased in hepatitis and fatty liver disease.

Elevations of cholesterol are commonly seen in cholestatic liver disease although the reasons for this increase are uncertain. Fasting and states of malnutrition reduce cholesterol production. Consequently, in patients with advanced cholestatic tumors cholesterol levels may be normal [56].

Hematology tests

The complete blood count (CBC) is used to evaluate the red blood cell count, white blood cell count, platelet count, and red blood cell morphology. If anemia is present, the red blood cell count and its protein content, hemoglobin, are decreased. In hemochromatosis, the red blood cell count

and hemoglobin are usually increased. The parameter most likely to be affected in hepatitis, however, is the platelet count.

PLATELET COUNTS

Platelets are small blood components necessary for blood clotting. In hepatitis, the spleen often becomes enlarged and traps platelets intended for the blood circulation. Consequently, a low platelet count, which causes a condition called thrombocytopenia, may be seen in hepatitis. Thrombocytopenia causes an increased bleeding tendency, characterized by bruises. The reference range for platelets is 150–375K/ml. Patients with platelet counts less than 50K/ml are considered at risk for abnormal bleeding.

Renal (Kidney) Function Tests

Kidney function may be impaired by immune complex deposits as an extrahepatic manifestation or complication of alcoholic cirrhosis or viral hepatitis. More often, decreased renal function and renal failure occur as a complication of fulminant or end-stage liver disease. In end-stage liver disease, the kidneys show no abnormalities. Their inability to function is due to alterations in renal blood flow, causing a condition of hepatorenal syndrome. Kidneys removed from dying patients with hepatorenal syndrome assume normal function when transplanted into transplant recipients [54].

The tests most often used to evaluate kidney function are the blood urea nitrogen (BUN) and creatinine tests, which measure the kidney's ability to clear protein. Both of these tests are elevated in kidney disease.

Reference range for BUN= 8–23 mg/dl

Reference range for creatinine= 0.1–0.6 mg/dl

Fibrosis Indexes and Tests

Several protocols for evaluating fibrosis or liver function based on laboratory test results have been proposed, and several blood tests have been developed for evaluating fibrosis. The most commonly used protocols are the Child-Turcotte Class modified by Pugh, which is often called the Child class, and the APRI index. The FibroTest and FibroSpect tests are new experimental procedures used to evaluate the degree of fibrosis in patients with hepatitis C who prefer to not have liver biopsies.

Child-Turcotte Class

In the Child-Turcotte class, liver function is graded from A through D, with patients in class A having a higher predicted survival rate. This

index is particularly important in assessing a patient's suitability for liver transplantation. The index is based on measures of albumin, bilirubin, prothrombin time, and the demonstration of ascites or encephalopathy.

APRI Index

The APRI index is a calculated index derived from laboratory test results used to assess the severity of liver damage. The calculation is based on the laboratory's reference range for AST and the patient's AST result and platelet count.

FibroSpect

The FibroSpect test developed by Prometheus Laboratories is used to evaluate degrees of cirrhosis in patients with hepatitis C. Results are reported in a range from 0–4, indicating no liver scarring to severe liver scarring. Its use in evaluating fibrosis in other types of liver disease is under evaluation.

FibroTest

Manufactured in France, the FibroTest is a commercial test that is also able to determine staging in fibrosis in hepatitis C.

Other tests for fibrosis and cirrhosis

The liver biopsy remains the gold standard for detecting and evaluating fibrosis and cirrhosis. However, certain blood test abnormalities are typically seen in cirrhosis, and these results offer insight into the progression of liver disease. Abnormalities seen in liver disease that has progressed to fibrosis or cirrhosis include: elevated iron, ferritin, transferrin, and alpha-fetoprotein, and a low platelet count.

Tests for Metabolic Disorders

Metabolic causes of hepatitis are diagnosed by using specific tests, such as iron and transferrin levels in suspected hemochromatosis or fructose tolerance tests for hereditary fructose intolerance. Certain genetic tests for amino acid and other mutations can also be used. For instance, the HFE gene test for the C282Y homozygote is used to diagnose hereditary hemochromatosis. Other tests used to diagnose metabolic causes of hepatitis are described in chapter twelve.

Tests for iron overload disorders

Although iron and ferritin levels are typically increased in hemochromatosis, elevations of these levels are also seen in any condition of hepatocyte injury as the liver cell contents are spilled into the blood circulation. Conditions of acute inflammation occurring in other organs can also falsely elevate these results. In patients with viral hepatitis or other conditions of liver cell necrosis, the results of liver function tests may be identical to that seen in iron overload disorders.

Also, in sudden presentations of acute iron overload, iron levels may not show significant elevations. When diagnosis is in doubt, genetic tests, liver biopsy, and imaging tests capable of detecting iron stores may be necessary. There are five distinct types of hereditary hemochromatosis: Type 1, Type2A, Type 2B, Type 3, and Type 4.

The gene mutations characteristic of hereditary hemochromatosis can be identified with blood tests. For hereditary hemochromatosis Type 1, one of two different mutations of the HFE gene known as C282Y and H63D mutations, are seen. Genetic mutations at gene JHV (hemojuvelin) are seen in hemochromatosis Type 2A, and mutations in the transferrin receptor 2 (TFR2) are seen in hemochromatosis type 2. A mutation of the SLC 40A1 gene that regulates the protein ferroportin is seen in hemochromatosis type 4.

Biopsy has the advantage of being able to measure iron content corrected for age and to predict the degree of fibrosis or cirrhosis. Bone marrow aspirations are not recommended as the iron content in marrow is not adequate for a proper determination of iron stores.

Liver Autoantibody Tests

In autoimmune disease, the immune system produces antibodies that react with the body's cells and tissue. Autoantibodies to liver cells are seen in autoimmune liver diseases, such as autoimmune hepatitis, although occasionally low titers of liver antibodies are seen in viral hepatitis and other autoimmune conditions. For instance, anti-mitochondrial antibodies, which are always seen in primary biliary cirrhosis, are sometimes seen in low titers in patients with the autoimmune thyroid disorder Graves' disease. The liver autoantibody tests used to diagnose autoimmune liver disorders are described in chapter ten.

Viral Markers

Most patients with elevated transaminase enzymes, jaundice or other signs and symptoms of liver disease will be tested for hepatitis viruses.

The basic screening tests for viral hepatitis detect viral antigens and antibodies, and the more specific confirmatory tests measure viral DNA or RNA.

Viral antigens and antibodies

Viruses are made up of various specific protein components known as viral antigens. These viral antigens can be identified in blood tests to diagnose viral infection. Viral antigens, however, may not show up for several weeks to several months after the onset of infection, and in most cases viral antigens only persist for short periods.

As the disease resolves, the immune system attempts to clear the virus by producing specific antibodies that can sometimes neutralize or destroy the viral antigens. Tests for viral antibodies can be used to diagnose current and past infections. The earliest antibodies produced by the immune system are IgM antibodies. The presence of IgM HAV antibodies, for instance, indicates active HAV infection. Over time, the immune system produces longer acting IgG antibodies. Tests for IgG antibodies are used to detect past infection or immunity from vaccinations.

Hepatitis viral panels

Viral panels include several different tests that measure either antigens or antibodies to HAV, HBV and HDV using enzyme immunoassay, chemiluminescence or recombinant immunoblot assays. In patients who show evidence of hepatitis B infection, tests for hepatitis D may also be performed. Equivocal results for HAV IgM and HBcIgM suggest that the patient is forming antibodies that haven't yet reached the detection limit or that acute infection is resolving and the titer is dropped. Equivocal reports are reported as such with a recommendation that the test be repeated in 1–2 weeks.

Tests for hepatitis E are used in patients from or who have recently traveled to endemic regions. Nucleic acid tests for viral particles are used to confirm infection, determine the level of infectious particles, and monitor treatment response. Genotype profiles are used to determine the type and subgroup of HBV and HCV.

Hepatitis testing is important in four periods of patient care: 1) time of diagnosis, using genotype testing to identify types of hepatitis that are more aggressive or more difficult to treat; 2) during therapy to see if viral load is falling in response to therapy; 3) at the completion of therapy to determine if there is an end therapy response; and 4) 6 months after the completion of therapy using nucleic acid tests to see if there is a sustained response to therapy [1].