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A TEXTBOOK OF LIVER DISEASE

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Drug-Induced Liver Disease

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CLINICAL PERSPECTIVES

Recent advances in the understanding of infectious liver diseases (including viral, bacterial, rickettsial, fungal, and parasitic diseases) have led to important improvements in methods of diagnosis and treatment. Moreover, public health measures and, in the case of viral hepatitis, immunization procedures, offer the hope that the incidence and prevalence of these disorders may eventually decrease. In this context, it is perhaps paradoxical that the incidence of chemically induced liver disease may be increasing. That this should be the case undoubtedly reflects, at least in part, the same broad and fundamental changes that have proved so beneficial in the case of the infectious disorders. These changes include the expansion of science and technology and the widened accessibility of the fruits of that expansion to an increasing number of individuals. Thus, whereas viral hepatitis, schistosomiasis, yellow fever, and amebiasis may diminish in the wake of advancing technology, drug-induced liver disease, quite the opposite, is a direct and increasingly significant result of it.

To address this area in generalities is far easier than to deal in concrete facts. With a few notable exceptions, most statistical data concerning incidence and natural history are subject to several undoubtedly important errors. For example, drug-induced liver disease, like other forms of liver disease, may be clinically subtle or completely inapparent, so that estimates of incidence will be influenced critically by the method used to identify cases. Thus, although laboratory screening of all persons at risk will almost certainly detect liver injury more often than would reliance on clinical symptoms or signs, this approach may be overly sensitive, since in certain circumstances minor abnormalities of liver function may appear only transiently, may revert to normal despite continued administration of the agent, and may or may not be indicative of significant "hepatotoxicity." Conversely, even routine tests may not be sensitive enough to detect other forms of drug-induced liver disease (e.g., chronic methotrexate administration), which may appear only after many months or years. Since most available incidence figures are probably underestimates, and since case reports in the literature tend to be skewed toward more severe or fatal reactions, it is quite likely that estimates of case fatality rates tend to be high, and perceptions of natural history biased. Perhaps the most notable exception to these difficulties is the currently available body of data concerning the incidence and prognosis of clinical and subclinical liver injury associated with isoniazid administration, specifically as employed in the setting of single-drug "chemoprophylaxis" of tuberculosis.

Despite these general difficulties, the subject of drug-induced liver disease has been reviewed extensively,[1,2] and some information is available that helps to place the broad problem of drug-induced liver disease in perspective. For example, 2 per cent of jaundiced patients admitted to general hospitals had drug-induced liver disease;[2,3] this figure was substantially higher for elderly individuals.[2,3] Drugs may account for approximately 25 per cent of instances of fulminant hepatitis,[4-6] and anywhere between a fourth and two thirds of patients with chronic active hepatitis.[7-9] Thus, among the more serious forms of liver disease (that is, those that have a chronic or fatal outcome), drugs are disproportionately represented.

Suspected drug-induced liver disease makes up between 4 and 7 per cent of all reports of adverse drug effects voluntarily reported to central registries.[10,11] Although data available from these sources point to a relatively small group of frequently used drugs as producing the bulk of reported liver-related adverse effects, the variety of drugs that have been reported to induce liver disease is nevertheless substantial and ever increasing. Two recently published tabular compilations of drug-related liver pathology list over 150 therapeutic agents that have been implicated in the etiology of a broad spectrum of hepatic diseases.[12,13]

CLINICAL SETTING—PROBLEMS IN DIAGNOSIS

Since drug-induced liver injury usually does not depend on pre-existing liver disease, its full range of severity may be expressed in any setting in which drugs are taken, from the relatively healthy ambulatory subject using an antibiotic or antidepressant to the more seriously ill or postoperative, hospitalized patient. Because of this, and because the presentation of drug-induced liver disease may be quite nonspecific (e.g., fever or a viral-like syndrome), it often is initially unclear whether a patient's deterioration represents progression or a complication of the underlying disorder, an unrelated event, or a drug reaction. Moreover, even if it becomes apparent (clinically or by laboratory testing) that liver function is impaired, a number of other diagnostic possibilities need to be considered, and these are not always easily distinguished from a drug-related problem. Among these are viral hepatitis (including posttransfusion), systemic bacterial infections, postoperative intrahepatic cholestasis, choledocholithiasis and/or acute pancreatitis, bile duct injury, congestive heart failure, and deterioration of pre-existing chronic liver disease that previously might have been well compensated or clinically inapparent. This broad differential diagnosis, together with the fact that the hepatotoxic potentials of most newly introduced agents are not known, makes it necessary for the clinician to remain constantly alert to the possibility that a seemingly nonspecific, unfavorable turn of events or change in liver function may represent drug-induced liver injury. Diagnosis is discussed in greater detail below; unfortunately, even when the diagnosis of drug-induced liver disease is considered, it may not be possible to confirm it with certainty. The exacerbation of liver disease upon reintroduction of a drug suspected of causing it in the first instance (rechallenge observation), although widely regarded as representing the most reliable "diagnostic test" for establishing a drug-related etiology, is potentially hazardous and rarely justifiable.

The prognosis of drug-induced liver disease is highly variable, and depends not only on the etiologic agent but also on the specific clinical circumstances. For some drugs, estimated case fatality rates may approach 50 per cent; such poor prognoses are for the most part limited to those agents that produce acute hepatic necrosis histologically similar to acute viral hepatitis. Other forms of drug-induced liver disease are virtually never fatal (e.g., estrogen-induced cholestasis), whereas still others may progress chronically and insidiously to cirrhosis (e.g., methotrexate-induced disease). Some are essentially benign in most respects, but uncertainties in their diagnosis may lead to unnecessarily expensive, invasive, or dangerous diagnostic or therapeutic interventions.

INDIVIDUAL SUSCEPTIBILITY AND MECHANISMS OF INJURY

It has long been recognized that most types of drug-induced liver injury can be classified as either predictable (usually dose-related), or unpredictable or "idiosyncratic" (usually unrelated to dose). Predictable forms often can be produced in experimental animals, and, if associated with liver cell necrosis, these characteristically affect predominantly a particular region of the hepatic lobule. Examples of agents causing lesions in this category include carbon tetrachloride and acetaminophen (centrilobular, or acinar zone 3), yellow phosphorus (mid-zonal, or acinar zone 2), and allyl alcohol (periportal, or acinar zone 1). Because of the predictability and dose-response relationships of the hepatic lesions they cause, these agents have been regarded as "direct hepatotoxins."

Most of the unpredictable or idiosyncratic forms of injury are more diffuse, consisting of necrosis and/or cholestasis, usually associated with a significant inflammatory reaction, but these processes, too, may be more localized. These reactions usually cannot be produced in experimental animals. Some agents (e.g., isoniazid, phenytoin) produce lesions histologically similar to viral hepatitis, which in some instances may be accompanied by systemic features such as fever, rash, arthralgias, or eosinophilia. Because of the unpredictability of these reactions with regard to both marked differences in individual susceptibilities and the apparent lack of dose-dependence, as well as the appearance, in some instances, of specific patterns of autoantibodies in the serum,[14] they had been assumed to represent forms of drug allergy in which the immune response is directed against the liver cell.

The validity of these earlier concepts increasingly has come into question because of important advances in the understanding of drug metabolism and the mechanism of hepatotoxicity. Thus, in several instances, so-called "direct" hepatotoxins actually do not injure the liver cell until after they have undergone biotransformation to toxic intermediates, which then interact with components of the cell.[15] Carbon tetrachloride and acetaminophen, among others, appear to act in this way. With regard to idiosyncratic hepatic drug reactions, not only has an immunologic mechanism not been established conclusively, but, at least in some instances, recent findings suggest an alternative mechanism in which the parent compound is converted to a toxic metabolite. For example, biotransformation of chlorpromazine converts it to a very large number of products, some of which are potentially toxic to the liver cell, whereas others are not, or are less so. It seems quite probable that idiosyncrasy (i.e., the apparent differences in individual susceptibilities to drug-induced liver injury) may represent corresponding and possibly genetically determined differences in either (1) the relative rates of several alternate pathways by which a drug may be converted to products of differing hepatotoxic potentials,[16] or (2) the efficiencies or completenesses with which a particular toxic product is "detoxified" via subsequent reactions.[17] An agent particularly well studied in regard to the multiplicity of potential influences on individual susceptibilities to hepatotoxicity is acetaminophen (discussed later in this chapter). The rate at which a toxic metabolite is formed from acetaminophen and the rate at which this metabolite is in turn "detoxified" may vary independently of each other and of the dose of the parent drug. Individual susceptibility, to the extent that it is related to rates of formation and disposition of the toxic products of drug metabolism, thus may be influenced by a variety of factors. It is important to keep in mind that a "toxic" product of drug metabolism could be immunogenic and lead to hepatic injury via immunologic mechanisms. Such mechanisms are not established, however. The factors influencing metabolism of drugs include genetic factors, age, sex, and other drugs or environmental agents that induce or otherwise influence the activity of metabolic pathways, or compete with the drug or its product for entry into a given pathway (Chap. 9).

Despite the significant advances that have led to the development of these concepts, it is important to recognize that the mechanism(s) by which various drugs and their metabolic products injure or kill the liver cell, or alter its function, is (are) largely unknown. Nonetheless, several concepts of drug hepatotoxicity have evolved that are useful and plausible in the formulation of an understanding of the area (Table 31–1).

Much recent research has focused on the final common pathway whereby drug-induced biochemical events such as covalent binding and lipid peroxidation ultimately lead to cell death. Disruption of cellular calcium homeostasis secondary to impairment of membrane calcium pump function has been intensively investigated in this regard. It is as yet unclear whether covalent binding or lipid peroxidation produced by direct hepatotoxins effect cell death specifically through disruption of calcium homeostasis, or if the observed alterations in cellular calcium flux are a terminal, nonspecific event in dying cells (see Chap. 30).[18,19]

It should be noted that the examples shown are in many instances not unique expressions of hepatotoxicity for the indicated agent. Thus, although rifampin appears to block hepatic uptake of organic anions through an effect at the liver cell surface, it also may be associated with a viral hepatitis–like reaction. Similarly, although certain metabolites of chlorpromazine may cause cholestasis, in part through their effects on the cytoskeleton and on membranes (see Chap. 12), it is not clear whether or how this is related to the inflammation and liver cell necrosis that regularly accompany clinical chlorpromazine-induced cholestasis. Estrogen-induced cholestasis seems readily attributable to a direct effect on the physical properties of membranes, but the long-term and less frequent association between administration of estrogen and hepatocellular ad-

TABLE 31–1. POSTULATED MECHANISMS OF DRUG-INDUCED HEPATIC DISEASE

Effect	Example
Alteration of the physical properties of membranes	Estrogens
Inhibition of membrane enzymes (e.g., Na^+, K^+-ATPase)	Chlorpromazine metabolites
Interference with hepatic uptake processes	Rifampin
Impairment of cytoskeletal function	Chlorpromazine metabolites
Formation of insoluble complexes in bile	Chlorpromazine
Conversion to reactive intermediates:	
Electrophiles producing covalent modification of tissue macromolecules	Acetaminophen
Free radicals producing lipid peroxidation	Carbon tetrachloride
Redox-cycling with production of oxygen radicals	Nitrofurantoin

enoma and carcinoma seems to require invocation of a more complex pathogenesis. To the extent that information regarding the mechanism of hepatotoxicity is available, it is considered in the sections of this chapter that deal with specific agents. This topic is also discussed in Chapter 30.

HISTOLOGIC PATTERNS OF DRUG-INDUCED LIVER INJURY

GENERAL CONSIDERATIONS

The spectrum of drug-induced liver injury encompasses an extremely wide diversity of histologic changes. These range from an acute, reversible, clinically benign, and nearly inconsequential interference with bile flow, at the one extreme, to fatal massive necrosis, chronic hepatitis, or malignant tumor at the other. Because many agents are associated with relatively characteristic lesions, histology has provided one basis for the classification of drug-induced liver injury. Selected examples of each form are shown in Table 31–2. For some agents, the reactions are relatively stereotyped. For example, tetracycline-induced liver damage is manifested histologically by a characteristic (but nonspecific) form of fatty liver, and isoniazid-induced hepatitis comprises a spectrum of acute focal, submassive, or massive hepatocellular necrosis, all resembling the range of lesions seen with viral hepatitis. For other agents, a much broader range of responses may be elicited. For example, oral contraceptives may cause a bland, reversible cholestasis with little or no associated cellular necrosis or inflammation, an alteration in the composition of bile, and an increased propensity to cholesterol gallstone formation, or the development of a benign or malignant liver tumor. Similarly, isoniazid and methyldopa have been associated with both acute and chronic hepatitis, and phenylbutazone with an acute viral hepatitis–like lesion or granulomatous hepatitis.

As a corollary, the histologic features of drug-induced liver injury, while often relatively characteristic for a particular agent, are rarely, if ever, specific. Equally important, virtually all forms of drug-induced liver injury closely resemble other forms of liver disease not presently perceived as having chemical causes. In the context of these limitations, then, any classification of drug-induced liver disease on the basis of histologic patterns must be based on the understanding that, whereas it is conceptually useful and may be diagnostically helpful, it often fails to provide specific or conclusive information regarding pathogenesis.

ZONAL NECROSIS

The hepatic injuries caused by many drugs and toxins appear to affect predominantly the cells in select regions of the hepatic lobule. Necrosis is either limited to the individual zones or at least is more prominent there, with apparent relative or absolute sparing of other zones. Agents that cause this type of injury are usually predictable direct or indirect hepatotoxins, the injurious effects of which are dose-dependent. Examples include acetaminophen and carbon tetrachloride, both of which cause predominantly centrilobular necrosis, and yellow phosphorus, which causes a mid-zonal lesion. Occasionally, halothane hepatitis may cause centrilobular necrosis, but often the lesion is indistinguishable from viral hepatitis. Often there is little or no inflammatory response or cellular infiltration, and damaged but not frankly necrotic cells may accumulate lipid (triglyceride). In addition to the morphologic changes, cellular injury is reflected by nonspecific clinical and laboratory evidence of liver dysfunction, which may range from asymptomatic abnormalities in the activity of liver enzymes in serum to fulminant liver failure. In most instances of acute injury of this kind, the process resolves completely or terminates fatally; there is no evidence that a chronic, self-sustaining form of liver injury is set in motion after a single acute exposure to the toxin. If exposure is chronic or recurring, however, the lesion may persist or progress, depending on the dose, the agent, and the patient's condition.

The basis for the relative selectivity of the lobular zone in which injury is most pronounced is not fully understood,

TABLE 31–2. HISTOLOGIC CLASSIFICATION OF DRUG-INDUCED LIVER DISEASE

Pattern	Examples
Zonal necrosis	Acetaminophen, carbon tetrachloride
Nonspecific hepatitis	Aspirin, oxacillin
Viral hepatitis-like lesion	Isoniazid, methyldopa
Granulomatous hepatitis	Quinidine, allopurinol
Chronic hepatitis	Methyldopa, nitrofurantoin
Fibrosis	Methotrexate
Cholestasis	
Inflammatory	Chlorpromazine, erythromycin estolate
Bland	Estrogens, anabolic steroids
Fatty liver	
Large globules	Ethanol, corticosteroids
Small droplets	Tetracycline, valproic acid
Vascular lesions	
Hepatic vein thrombosis	Oral contraceptives
Veno-occlusive disease	Certain antitumor agents
Non-cirrhotic portal hypertension	Vinyl chloride monomer
Peliosis hepatis	Anabolic steroids
Tumors	
Adenoma	Oral contraceptives, androgens
Focal nodular hyperplasia	Oral contraceptives
Carcinoma	Oral contraceptives, androgens
Angiosarcoma	Vinyl chloride monomer

but undoubtedly reflects to some extent intralobular differences in the determinants of the injurious process itself. For example, the abundance of the smooth endoplasmic reticulum and the activity of the cytochrome P450-dependent drug-metabolizing system are greatest in centrilobular hepatocytes. Those agents for which hepatotoxicity depends on the formation of a toxic metabolite via this system may be more likely to injure those cells in which the system is most active. This distribution, however, is undoubtedly influenced by the interaction of many other factors, including known or postulated lobular gradients in oxygen tension, drug concentration, rates of uptake, activity of alternative metabolic pathways (whose products may differ in toxicity), and cellular concentrations of potentially "protective" constituents, such as glutathione.

NONSPECIFIC HEPATITIS

This "pattern" of injury is characterized by a few scattered foci of hepatocellular necrosis, usually associated with a mononuclear cell infiltrate, and a variable portal inflammatory response. It lacks the characteristic features of viral hepatitis such as bile stasis, lobular disarray, and acidophil bodies, and, as its name implies, can be seen in a wide variety of clinical settings, including those in which the liver may not be primarily involved, such as sepsis or other systemic disorders. It is typical of many and diverse forms of drug-induced liver injury, including the clearly dose-dependent hepatotoxicity of aspirin and the lesions associated with certain semisynthetic analogs of penicillin. It virtually never is associated with serious or progressive hepatic decompensation or failure, and is fully reversible upon discontinuation of the responsible agent.

VIRAL HEPATITIS–LIKE REACTIONS

This form of injury is perhaps the most controversial and serious of all, and often poses especially difficult challenges to clinician, pharmacologist, and toxicologist alike. Because this lesion cannot be distinguished reliably from viral hepatitis, the resulting uncertainty of diagnosis may complicate management of the individual case. More broadly, over the years it has caused major confusion and controversy concerning the validity, incidence, significance, and natural history of such entities as halothane hepatitis and isoniazid-induced hepatitis, among others. Although in some instances, such as phenytoin-induced hepatitis, a prominent peripheral or tissue eosinophilia may suggest a nonviral etiology, this finding cannot be relied upon. Moreover, this group of reactions is characterized by a case fatality rate far in excess of that for acute viral hepatitis, and in the more severe cases, patterns of bridging, submassive, or massive necrosis may be seen. Indeed, of cases of acute bridging necrosis, a significant proportion may be accounted for by drug-induced hepatitis, but bridging necrosis per se does not necessarily indicate a chronic or fatal outcome.[20, 21] In addition to the above agents, this lesion has been associated with sulfonamides and inhibitors of monoamine oxidase.

As is true of most other forms of acute drug-induced liver disease, these lesions do not become self-perpetuating in the absence of continuing exposure to the injurious agent, although occasionally the course of disease may be prolonged, as in some patients with halothane hepatitis.[22] If chronic hepatitis develops, it is almost always the result of continuing or repeated exposure.

GRANULOMATOUS HEPATITIS

Granulomatous lesions, typically consisting of circumscribed aggregates of epithelial histiocytes accompanied by variable numbers and types of inflammatory cells, represent part of the spectrum of hepatic inflammatory responses to medicinal agents. Several drugs may lead to granulomas with or without other manifestations of hepatic injury; typical examples include quinidine, allopurinol, phenylbutazone, sulfonamides, and sulfonylurea derivatives. However, many others also may produce this histopathologic lesion and, according to recent estimates, up to a third of cases of granulomatous hepatitis may result from therapeutic agents.[23] Granulomas resulting from drug-induced hepatic injury are invariably non-caseating and may contain abundant eosinophils. Their presence is generally taken as evidence of a hypersensitivity-based mechanism of injury.

CHRONIC HEPATITIS

That certain drugs may cause chronic hepatitis has been recognized only relatively recently.[7-9] However, the number of implicated agents continues to increase, and it seems likely that the apparent clinical incidence and importance of this type of reaction also will increase. Drug-induced chronic hepatitis is, in fact, a heterogeneous group of disorders that differ among themselves in pathogenesis and in histologic features (Table 31–3).

A drug-induced lesion indistinguishable from that of classic chronic active hepatitis was recognized initially as a complication of methyldopa or oxyphenisatin treatment, and since has been associated with isoniazid, sulfonamides, and nitrofurantoin therapy. A similar lesion has been found in a small number of chronic abusers of alcohol. Other forms of chronic hepatitis take the form of a focal nonspecific hepatic necrosis (e.g., that caused by aspirin) or centrilobular necrosis (e.g., that caused by acetaminophen).

Usually, the chronic forms of drug-induced liver injury depend on continued exposure to the agent and do not result from a self-perpetuating process set in motion by an acute insult. On the other hand, in very advanced cases of drug-induced chronic active hepatitis, resolution may be very slow despite discontinuation of the drug, or the lesion may progress to a fatal outcome over a period of weeks to months. In chronic aspirin- or acetaminophen-induced hep-

TABLE 31–3. DRUGS IMPLICATED IN THE ETIOLOGY OF CHRONIC HEPATITIS

Acetaminophen
Amiodarone
Aspirin
Dantrolene
Ethanol
Isoniazid
Methyldopa
Nitrofurantoin
Oxyphenisatin
Perhexilene maleate
Propylthiouracil
Sulfonamides

atotoxicity, prompt and complete resolution of the hepatic lesion after cessation of therapy is the rule. Rarely, chlorpromazine-induced cholestasis may be quite prolonged; although it may cause a clinical picture suggestive of primary biliary cirrhosis, this unusual complication would not ordinarily be regarded as a form of "chronic hepatitis."

Because these chronic forms of drug hepatotoxicity can be seen in patients taking readily available agents in doses regarded as therapeutic rather than toxic, the importance of the association may easily be overlooked in a given patient. For this reason, careful inquiry into use of both prescription and nonprescription drugs is essential in the evaluation of all patients with chronic liver disease.

CHOLESTASIS

Drugs can impair the formation of bile by interfering with any or all of the various hepatocellular mechanisms and structures involved in this process (Chap. 12). Two general histologic patterns are associated with drug-induced cholestasis. In one, cholestasis is accompanied by an inflammatory process that is especially prominent in the portal triads and, to a lesser extent, in the lobule itself, and is associated with variable hepatocellular necrosis. The inflammatory infiltrate is predominantly mononuclear, but may contain polymorphonuclear neutrophils or eosinophils. This type of reaction is often associated with systemic manifestations that include fever, rash, and arthralgias. It can be caused by a wide variety of drugs, including tranquilizers, antithyroid and hypoglycemic agents, and macrolide antibiotics such as erythromycin estolate. Chlorpromazine is the prototype of this class of agents.

In the second type of cholestatic drug reaction, the histologic features of inflammation and necrosis are minor or absent, and the lesion is characterized by a bland accumulation of bile in cells and canaliculi, principally centrilobular. This pattern characterizes the injury that can be caused by natural and synthetic estrogens, and by all 17α-substituted anabolic and androgenic steroids. Unlike the aforementioned inflammatory type of cholestatic reaction, the latter type of drug reaction usually results in only relatively mild systemic symptoms, except for pruritus, which can be quite severe.

In neither form does the process evolve to massive necrosis or a fatal outcome. Recovery after cessation of drug therapy is the rule. Recovery usually occurs within several weeks, although chlorpromazine reactions rarely may be quite prolonged.

FATTY LIVER

The lipid that accumulates in the liver in almost all forms of hepatotoxicity is predominantly triglyceride. The pathophysiologic abnormalities vary, depending on the agent, but in general they may be viewed as reflecting a rate of triglyceride formation that exceeds the rate of triglyceride disposition; *disposition* includes secretion into plasma in the form of triglyceride-rich lipoproteins, or hydrolysis to fatty acids and oxidation. There is no conclusive evidence that triglyceride in greater than normal amounts is injurious per se to the cell. Rather, accumulation of triglyceride in liver may be viewed as indicative of an abnormality in cellular metabolism that also may influence aspects of cellular function other than lipid metabolism, and thereby mediate toxicity.

There are two general histologic patterns of fatty liver. In the more common form, triglyceride is deposited in relatively large globules, which effectively fill the hepatocyte, displace the nucleus and other intracellular constituents to the periphery, and give the hepatocyte an adipocyte-like appearance. This large globular form of fat deposition characterizes the fatty liver associated with ethanol and corticosteroid administration, as well as with metabolic and nutritional disorders such as diabetes mellitus, obesity, hypertriglyceridemia, malnutrition, and the fatty liver seen after jejunoileal bypass surgery. Liver function may be relatively well preserved in the presence of fat deposition of this type, but can be altered to the extent that other processes such as alcoholic hepatitis are associated with it.

In a second histologic form of fatty liver, the fat is deposited in small droplets dispersed throughout the cytoplasm; the nucleus remains centrally located, and the cell itself retains its recognizability as a hepatocyte. This pattern is seen in only a few unusual circumstances, including tetracycline and valproic acid hepatotoxicity, Jamaican vomiting sickness, Reye's syndrome, fatty liver of pregnancy and certain rare inborn errors of metabolism. The pathogenesis is unknown except in the case of Jamaican vomiting sickness.[24] In this disorder, hypoglycin, a toxic principle from the unripened fruit of the ackee tree, causes impaired fatty acid oxidation and a more generalized disturbance in cellular metabolism that at least in part reflects its conversion to nonmetabolized derivatives of coenzyme A and carnitine, and thereby limits the availability of these critically important cofactors (Chap. 32). All the disorders leading to deposition of fat in small droplets are characterized by clinical and laboratory evidence of significantly disturbed hepatic function that, in its more severe forms, may include marked increases in serum transaminase activity, hypoglycemia, hyperammonemia, hepatic encephalopathy, and death in liver failure. Thus, the small droplet form of fat deposition reflects a potentially more serious disturbance of hepatocellular metabolism than does the large globular form of lipid accumulation.

Drug-induced lysosomal phospholipid storage (phospholipidosis) represents another type of hepatic lipid accumulation that may arise from the use of certain drugs, notably perhexilene maleate and amiodarone. The mechanism and significance of this distinctive morphologic entity are discussed further under the relevant drug headings.

VASCULAR LESIONS AND PORTAL HYPERTENSION

Apart from the fact that a number of drugs may cause chronic liver disease and thereby lead to the development of cirrhosis and portal hypertension, there are three drug- or toxin-associated disorders that cause portal hypertension, independent of primary liver disease. These are (1) hepatic vein thrombosis, which has been associated with, but not conclusively linked pathogenetically to, oral contraceptive use; (2) hepatic veno-occlusive disease, which has been observed in patients treated with 6-thioguanine as well as after the ingestion of pyrrolidizine alkaloids from plants of the genera *Senecio* and *Crotalaria* ("bush tea poisoning") (Chap. 32); (3) non-cirrhotic portal hypertension after chronic exposure to vinyl chloride monomer (Chap. 32). Peliosis hepatis, a dilation of sinusoids accompanied by replacement of zones of hepatocytes by blood-filled spaces, has been associated with chronic administration of androgenic and anabolic steroids, as well as with a variety of chronic wasting neoplastic and infectious diseases. Peliosis is not generally accompanied by portal hypertension.

TUMORS

Hepatic adenoma, focal nodular hyperplasia, and hepatocellular carcinoma have been associated with oral contraceptive use; less commonly, adenoma and carcinoma have been linked to anabolic steroid therapy. Angiosarcoma has been attributed to chronic exposure to vinyl chloride monomer (Chap. 45).

ANALGESIC, ANTI-INFLAMMATORY, AND MUSCLE RELAXANT DRUGS

ACETAMINOPHEN

Acetaminophen has enjoyed a long history as a relatively safe and well-tolerated analgesic agent. Beginning in about 1970, however, it became evident that, when taken in very large doses, the drug causes severe liver injury and death due to liver failure. It became popular, initially in Britain and increasingly in the United States, as an easily available method for committing suicide.[25-27] As the incidence of acetaminophen hepatotoxicity has increased, so has the appreciation of the broader clinical spectrum of the disorder, the experimental basis for an understanding of its pathogenesis, and approaches to treatment based on this understanding.

It is now recognized that acetaminophen hepatotoxicity occurs not only in persons who ingest massive amounts of the drug with suicidal intent but also in some individuals who ingest quantities within the therapeutic range.[28-30] Use of ethanol, or other inducers of hepatic drug metabolism, and nutritional state are among what may be many important determinants of significant individual differences in susceptibility.[28, 30-32] In addition to its clinical importance, therefore, acetaminophen hepatotoxicity stands virtually alone as a model of drug-induced liver disease in which fundamental concepts of drug metabolism and toxicity have proved directly translatable to pathogenesis and management.

Clinical and Laboratory Findings

After a massive acute ingestion, there is often a period of several hours in which the patient may experience diaphoresis, nausea, and vomiting. Typically, these subside and the patient enters a phase, lasting perhaps 24 hours, in which there may be no clinical or laboratory evidence of liver disease.[26, 27] During this period the patient may be judged erroneously to be out of danger, on the false premise that the ingested dose either was too small to be of concern or was not absorbed because of emesis or gastric aspiration. Presumably, this "latent" phase is the period during which there is progressive formation of toxic intermediates derived from acetaminophen metabolism, with progressive hepatic injury.

The latent phase ends with the onset of overt acute hepatocellular necrosis, including anorexia, nausea, vomiting, tender hepatomegaly, and, in the more severe cases, increasing jaundice and signs of liver failure and encephalopathy. Laboratory findings include variable increases in serum transaminase activity and bilirubin, and in prothrombin time. Transaminase levels of 20,000 IU/L are not unusual.[26] Although the degree of abnormality in those tests approximately reflects the extent of liver cell necrosis, the correspondence is imperfect. Thus, whereas in virtually all fatal cases serum transaminase activity exceeds 1000 IU/L at some point, most patients with transaminases in this range will survive,[33, 34] and even significant increases in prothrombin time and bilirubin do not necessarily indicate a fatal outcome. Conversely, patients whose liver tests are only mildly deranged generally have a favorable prognosis.[34] In non-fatal cases, recovery appears to be complete with restoration of normal liver function and structure on subsequent follow-up.[35]

Chronic acetaminophen hepatotoxicity has been associated with daily doses in the range of 3 to 8 g.[28-30] It may produce few or no symptoms, and may be clinically manifest only as a moderate increase in transaminase activity detected by routine screening. This mild disorder is completely reversible.

Histopathology

Very early changes in hepatocyte ultrastructure have been described in mice.[36] Clinically, the lesion of acute acetaminophen hepatotoxicity consists primarily of centrilobular or massive hepatic necrosis.[26, 27] Fat may be present, but the inflammatory response is relatively minor. As mentioned, available evidence suggests that histologically the liver returns to normal upon recovery.[35]

The chronic lesion is somewhat more variable and may consist of either centrilobular necrosis or a more nonspecific picture of focal or periportal hepatitis. Occasionally, it may resemble chronic active or chronic persistent hepatitis.[29, 37]

Diagnosis

Some patients will come to medical attention because of documented recent acetaminophen overdose. These patients may not have evident liver damage. Others may seek treatment for acute liver disease for which acute acetaminophen toxicity is one of several possible causes. Since active therapeutic intervention, if it is to be effective, must be initiated within 10 to 12 hours of ingestion (see below), it is important not only to document acetaminophen ingestion, but also to determine whether the dose was sufficient to cause life-threatening liver damage.

The latter question (i.e., the size and danger to life of the dose) has been particularly difficult to answer, for several reasons. First, although ingestion of 15 g or more is usually necessary to cause a severe or fatal case,[27] the history of the dose actually ingested, whether obtained from the patient or from others, is often unreliable.[38] Furthermore, the latent period between ingestion and the appearance of signs of liver damage may be quite misleading and may temporarily invalidate the clinical and laboratory findings customarily used for the assessment of liver disease. Finally, although acetaminophen hepatotoxicity is not immunologically mediated, there are important differences in individual susceptibilities such that serious toxicity may occur in one patient with a dose that in another would be relatively safe. For example, chronic ethanol use,[28, 31, 32] fasting,[39, 40] and prior induction of hepatic microsomal drug metabolism by other agents[41-45] all predispose to acetamin-

ophen hepatotoxicity, and in such circumstances serious liver injury or death may occur with otherwise tolerable doses.

To help deal with these difficulties, determination of acetaminophen levels in blood has been employed with some success, on the basis of the empirical observation that serious liver injury usually occurs only in those patients in whom the plasma acetaminophen concentration at a given time after ingestion exceeds the line joining 200 mg/L at 4 hours with 30 mg/L at 15 hours on a semilogarithmic plot of plasma concentration as a function of time.[25, 26, 34] Although there is overlap, measurement of the blood acetaminophen level is quite helpful, both in confirming the ingestion and in providing an indication of the probability of serious toxicity.

Severe hepatocellular disease has developed in patients with chronic alcoholism who had taken acetaminophen in doses in or near the therapeutic range.[31, 32] In these patients, elevation of serum transaminases far in excess of values consistent with alcoholic hepatitis have been observed, although in keeping with underlying alcoholic liver disease, levels of aspartate aminotransferase have invariably exceeded those of alanine aminotransferase. When soliciting a history of acetaminophen use in patients with chronic alcoholism and evidence of acute severe liver injury, it is also important to inquire about acetaminophen-containing nonprescription drug combinations that may have been ingested for their alcohol content.[46]

The differential diagnosis of acute acetaminophen hepatotoxicity includes all other causes of acute hepatic necrosis, such as viral hepatitis and ethanol-induced and other forms of drug-induced liver injury, as well as acute deterioration of pre-existing chronic liver disease. Although it is important that these conditions be considered and, where possible, excluded, the importance of early institution of specific treatment of acetaminophen hepatotoxicity and its apparent safety necessitates that in the absence of definitive evidence to the contrary (e.g., very low blood acetaminophen levels), any patient with documented substantial acetaminophen ingestion should be considered at risk and managed accordingly.

Mechanism

An impressive body of evidence accumulated over the past decade indicates that acetaminophen hepatotoxicity is mediated by the formation of one or more toxic intermediates during the biotransformation of the parent compound.[41–44, 47] Thus, in animal studies, toxicity correlates not only with dose but with the activity of microsomal drug metabolizing enzymes. The current view of this interaction may be summarized as follows.

At low doses acetaminophen is principally conjugated with glucuronic acid or sulfate (Fig. 31–1), and these harmless conjugates are largely excreted in the urine. A minor fraction of the parent compound undergoes biotransformation via a specific isoenzyme of the microsomal cytochrome P450-dependent drug-metabolizing system.[48] This results in the formation of toxic intermediates, the best characterized of which is *N*-acetyl-*p*-benzoquinone imine (NAPQI), a highly reactive electrophile.[41, 49] NAPQI forms a conjugate with glutathione, which after further conversion to cysteine and *N*-acetylcysteine derivatives in the intestinal mucosa and renal tubules is excreted in the urine as a mercapturic acid.[50, 51] Detoxification via the glutathione mechanism thus ordinarily provides the modest degree of protection needed at low doses of acetaminophen.[41–44]

Unfortunately, the glucuronide and sulfate conjugation pathways that predominate at low doses of acetaminophen are readily saturable.[52] As the dose of the drug increases, therefore, a correspondingly greater fraction becomes available for entry into the microsomal pathway, and subsequent conversion to toxic intermediates, the detoxification of which depends on conjugation with glutathione. As would be expected, as the ingested dose of acetaminophen is increased, cellular glutathione stores become progressively depleted.[44] If the formation of toxic intermediates is of sufficient magnitude, glutathione stores will fall below a critical level: that is, it no longer will be adequate to sustain this crucial detoxification reaction. At this point, the toxic intermediates react covalently with cellular constituents, especially proteins and other macromolecules essential for cellular homeostasis, and, presumably by this mechanism, effect their hepatotoxicity.[41–44, 53, 54]

The "threshold" phenomenon thus can be understood simply as the point at which the rate of formation of toxic intermediates exceeds the rate at which they can be detoxified by the glutathione mechanism. It is at once apparent that this threshold (which is, in effect, the determinant of individual susceptibility to acetaminophen toxicity) can vary up or down, depending on the rates of either or both of the two critical processes involved (microsomal production of toxic intermediates and their detoxification by glutathione), each of which is influenced in turn by several factors. For example, the rate of formation of toxic intermediates is not simply a function of drug dose or bioavailability, but also depends on the activity of the glucuronide and sulfate conjugating pathways, the availability of glucuronic acid and sulfate, and the activity of the cytochrome P450 pathway. Prior administration of drugs (e.g., phenobarbital and ethanol) that induce the microsomal cytochrome P450 pathway predisposes to acetaminophen hepatotoxicity,[27, 48] whereas inhibitors of the pathway,[41–44] including cimetidine,[55, 56] are protective. This undoubtedly accounts, at least in part, for the increased susceptibility to acetaminophen hepatotoxicity caused by prior use of ethanol, barbiturates, and other inducers. Indeed, there is evidence that ethanol induces the specific isoenzyme of cytochrome P450 responsible for the oxidation of both ethanol and acetaminophen.[48] This also provides an explanation, based on competitive inhibition, for the seemingly paradoxical protective effect of acute ethanol administration on acetaminophen-induced hepatotoxicity.[26, 48]

The threshold dose for hepatotoxicity will vary inversely with hepatocellular glutathione stores. For example, both fasting[39, 40] and ethanol[27] decrease hepatic glutathione concentrations and predispose to hepatotoxicity, whereas cysteine precursors, such as *N*-acetylcysteine and L-2-oxathiozolidine-4-carboxylate, increase hepatic glutathione stores by promoting glutathione synthesis and hence protect against acetaminophen toxicity.[58, 59] Although, to some extent, *N*-acetylcysteine also may increase the availability of sulfate,[60] the protective value of this is unclear.[61] Both propylthiouracil[62] and *N*-acetylcysteine[63] may also afford protection by acting as substitutes for glutathione, forming direct adducts with NAPQI, although in the case of *N*-acetylcysteine this probably represents a minor protective route.[59] Lipid peroxidation, possibly mediated via a free radical intermediate of acetaminophen metabolism,[64] also has been suggested as a mechanism for acetaminophen-induced liver injury.[40] Although the apparent protective

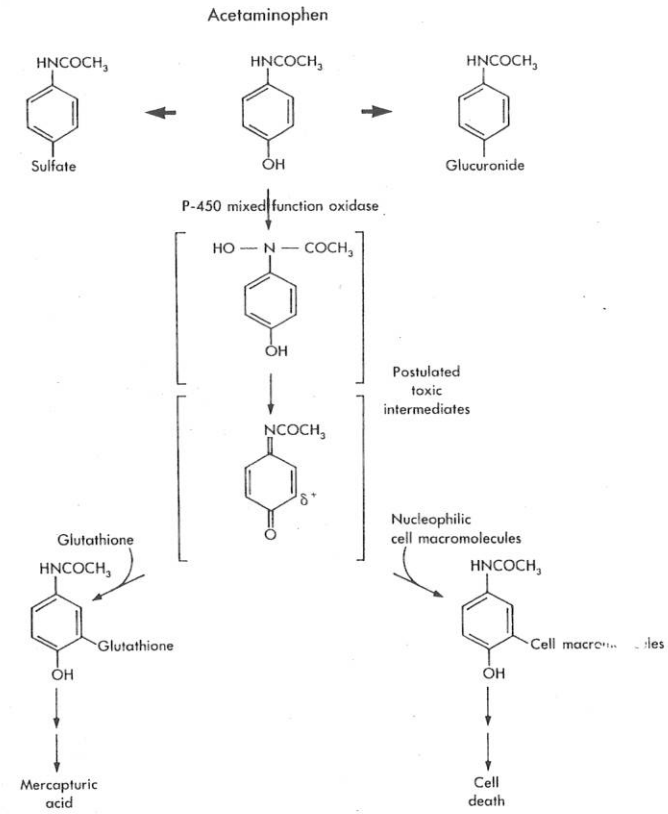

Figure 31–1. Pathways of acetaminophen metabolism. (From Mitchell JR, Jollow DJ. Gastroenterology 68:392, © by Williams & Wilkins, 1975.)

effect of vitamin E[65] as well as agents that increase glutathione[66] are explicable in relation to such a mechanism, available evidence does not support a causal role for lipid peroxidation in the injury but suggests, rather, that it may simply be a result of the injury.[67]

Although the evidence that cellular glutathione is protective against acetaminophen hepatotoxicity is compelling, there is less certainty that cellular injury is mediated primarily by the formation of covalent bonds between toxic intermediates of acetaminophen biotransformation (e.g., NAPQI) and cellular constituents. The covalent binding hypothesis has been challenged by reports that the protective effects of cimetidine,[68] *N*-acetylcysteine,[69] and α-mercapto-propionylglycine[70] are not associated with diminished overall formation of covalent adducts of acetaminophen to macromolecules. Subsequent work has criticized the methodology of these earlier studies and substantiated the inverse relationship between the protective effects of cimetidine[56] and *N*-acetylcysteine[71] and covalent modification of cellular macromolecules.

It is still disputed whether the primary pathway of acetaminophen-induced toxicity involves glutathione depletion via adduct formation with toxic intermediates and subsequent covalent binding of intermediates to cellular proteins, or whether toxic intermediates of the drug result in glutathione depletion via oxidation to glutathione disulfide with subsequent oxidation of cellular protein thiols.[62, 72-74] However, these two mechanisms are not necessarily mutually exclusive, although the predominance of one over the other may depend upon the experimental model investigated (e.g., isolated or cultured hepatocytes versus intact animals). Notwithstanding these uncertainties, available evidence suggests that either mechanism may result in impairment of proteins and/or cofactors involved in cellular calcium homeostasis,[75, 76] with accumulation of calcium in the cell cytosol leading to cell death. (See Chap. 30).

Treatment

On the basis of the available data, acetaminophen hepatotoxicity should be regarded as a potentially treatable disorder, not merely by discontinuation of the toxin and supportive care but by active pharmacologic intervention. As currently understood, the objective is to increase the stores of hepatocellular glutathione, thereby averting the toxicity of acetaminophen metabolites, which presumably have not yet reacted with critical cell constituents.

N-acetylcysteine is the drug of choice for patients with acetaminophen overdose. Thus, in the study by Prescott et al.,[24] only one of 62 patients treated with *N*-acetylcysteine within ten hours of taking acetaminophen developed severe liver damage (defined as a serum transaminase activity greater than 1000 IU/L), whereas 20 of 38 patients treated after ten hours and 33 of 57 given supportive care alone developed severe liver damage. Similarly, in the Rocky Mountain Poison Center multicenter study,[26] only four of 57 patients treated with *N*-acetylcysteine within ten hours of taking acetaminophen developed severe liver damage, whereas 15 of 52 patients treated between ten and 16 hours and 24 of 39 patients treated between 16 and 24 hours developed severe liver damage. Since the prognostic value of the serum transaminase activity could be questioned, it is significant that in the British trial[24] there were no deaths in the group treated early with *N*-acetylcysteine, but two and three deaths in the late treatment and untreated groups, respectively. *N*-acetylcysteine is both effective and relatively innocuous. It may be administered orally or (in Britain) intravenously, but only if initiated within the first 10 to 12 hours after acetaminophen ingestion will it influence morbidity and mortality. As mentioned above, the decision to use the drug must often be made under circumstances in which information concerning the actual risk of severe acetaminophen hepatotoxicity (e.g., blood acetaminophen levels) is incomplete or inconclusive. Despite this, because of the importance of early institution of the drug, as well as the safety of *N*-acetylcysteine treatment, it should be employed in two clinical settings: (1) when acetaminophen blood levels and/or plasma disappearance $T_{1/2}$ indicate that the patient is at risk; (2) when blood acetaminophen levels are not rapidly available, but there is good reason to believe that a significant overdose has occurred. In these patients with documented or probable serious acetaminophen overdose, the threshold for institution of *N*-acetylcysteine treatment should be even lower when additional risk factors can be identified, such as chronic use of ethanol or drugs that induce microsomal drug metabolism, fasting, starvation, or protein malnutrition.

The treatment schedules currently employed involve administration of an initial dose of 140 mg/kg, p.o., followed by maintenance doses of 70 mg/kg q. 4 hr p.o. for a total of 72 hours.[26] The schedule employed by Prescott et al.[24] with a preparation appropriate for intravenous use was an initial dose of 150 mg/kg in 200 ml 5 per cent glucose over 15 minutes, followed by 50 mg/kg in 500 ml over 4 hours, and 100 mg/kg in 1 liter over the next 16 hours, for a total of 300 mg/kg over 20 hours. Unfortunately, the intravenous preparation is not generally available in the United States. In addition, other more standard approaches to drug overdose and acute hepatic injury are essential components of the care of these patients. They include initial gastric intubation and aspiration to recover any residual drug; the monitoring of vital signs; maintenance of fluid and electrolyte balance, oxygenation, and blood pressure; and customary management of severe liver injury and encephalopathy, if needed, as described in Chapter 17. Well over 90 per cent of patients may be expected to recover completely.

ASPIRIN

Like acetaminophen, aspirin is a well-documented cause of a dose-related, reversible form of hepatotoxicity. Unlike acetaminophen, neither its mechanism nor the basis for apparent differences in individual susceptibilities are understood.

The disorder is most commonly encountered in patients with chronic rheumatic diseases treated for several days or weeks with high-dose aspirin therapy and is manifest in most instances as an asymptomatic, subtle disturbance in liver function, as reflected by mild to moderate increases in serum transaminase activity and, much less commonly, subclinical hyperbilirubinemia.[77-81] Jaundice is quite uncommon, and severe clinical hepatitis rare, although nonfatal cases with hypoprothrombinemia and encephalopathy have been reported.[80, 82]

The histologic process associated with these functional abnormalities is a nonspecific focal hepatitis.[80] Massive or submassive necrosis has not been established as a consequence of high-dose aspirin therapy, and there is no apparent increase in hepatocellular fat. Thus, although the rare occurrence of acute encephalopathy and anicteric liver dysfunction in a child has suggested the possibility of a

Reye's-like syndrome,[83] hepatotoxicity in the setting of long-term high-dose aspirin therapy is associated with neither the characteristic histopathology nor the ominous prognosis of Reye's syndrome.[82, 83] Despite this, there is persisting concern regarding a possible association of aspirin use and Reye's syndrome.[84] Microvesicular hepatocellular fat, similar to that seen in Reye's syndrome, has been described in children with fatal salicylate intoxication,[85] but this is not a typical histologic feature of hepatotoxicity of high-dose aspirin therapy. In a patient with systemic lupus erythematosis, the biopsy picture resembled that of chronic active hepatitis,[78] but this is exceptional. Aspirin hepatotoxicity is rapidly and completely reversed when the drug is discontinued.

The dose dependency of the lesion is well established, but there are substantial differences in individual susceptibilities. Thus, whereas the injury usually is associated with serum salicylate levels in excess of 25 mg/dL (a daily dose of about 3 to 5 g in adults), there are numerous exceptions, and about 2 per cent of instances of toxicity occurred at levels of less than 10 mg/dL.[80] Certain groups of patients seem to be at greater risk, including those with juvenile rheumatoid arthritis, systemic lupus erythematosus, and rheumatoid arthritis. Indeed, it has been suggested that as many as 50 per cent of patients with juvenile rheumatoid arthritis taking therapeutic doses of aspirin will have increased serum transaminase activity.[81] It is not clear whether this apparent predisposition reflects only that these patients are more often exposed to potentially toxic doses of aspirin. It has been suggested that reduced serum albumin concentrations, by increasing the unbound fraction of aspirin, might predispose to injury.[86] Evidence in support of this concept has been obtained in studies of aspirin toxicity in monolayer cultures of hepatocytes,[87] but its significance with regard to clinical hepatotoxicity remains to be determined. It also has been suggested that alleviation of juvenile rheumatoid arthritis might in some way be promoted by hepatic dysfunction, regardless of cause.[81, 88] Hepatotoxicity also appears to occur with other salicylates, including sodium and choline salicylate,[77] but experience with these agents is limited.

An unusual reaction to aspirin was observed in a patient with adult onset of Still's disease.[89] This patient developed significant hepatotoxicity, microangiopathic hemolytic anemia, and disseminated intravascular coagulation while taking 3 to 6 g aspirin daily. This episode and a similar reaction occurring in response to aspirin rechallenge were treated with corticosteroids, and the patient's condition improved. It is not known whether this represented a distinctive form of aspirin hepatotoxicity or the superimposition of an aspirin-associated complication of the underlying disease process on otherwise ordinary aspirin hepatotoxicity.

OTHER AGENTS

Phenylbutazone. Phenylbutazone has been associated with overt hepatic injury in about 0.25 per cent of patients. The onset of the reaction usually occurs in the first six weeks of treatment but may be delayed by as much as one year. It is more common in adults than in children.[2, 90]

The reaction may take several forms. Most often the illness resembles viral hepatitis in its presentation, and in about 50 per cent of patients there may be antecedent fever, rash, or arthralgia. Clinical and laboratory findings are consistent with an acute hepatitis, and liver biopsy may show a typical viral hepatitis–like picture, submassive or massive necrosis. Fatal hepatitis may occur but is unusual. Less commonly, the appearance of the disorder may be cholestatic, with or without pruritus, and with little clinical or histologic evidence of significant hepatocellular necrosis. Non-caseating granulomas may accompany the hepatic reaction, usually in association with minor hepatocellular injury.[90] Histologic changes indistinguishable from those seen in primary biliary cirrhosis have been observed in one patient.[90]

The prognosis for all forms of phenylbutazone-associated hepatic injuries is good, although both the viral hepatitis–like and the granulomatous reaction have been associated with fatal outcomes. In the remainder, improvement accompanies discontinuation of the drug. There are anecdotal reports of the use of corticosteroids but their actual effect on the course of the disease is not defined.

The mechanism of the injury is unknown. Although certain clinical features suggest hypersensitivity to the drug, phenylbutazone is hepatotoxic in laboratory animals,[2] and overdoses with this drug have produced acute hepatic necrosis in humans.[90]

Allopurinol. Several case reports indicate that allopurinol may lead to liver cell injury, usually within a period of five weeks.[91-92] Fever, skin rash, and eosinophilia are not uncommon, with moderate transaminase elevation and jaundice. Occasionally, there is a severe systemic reaction with vasculitis and renal failure.[93] Diuretic use and renal impairment may predispose toward the development of allopurinol hepatotoxicity.[91] The pathologic findings include centrilobular necrosis as well as features indistinguishable from viral hepatitis, with eosinophils being prominent. Massive hepatic necrosis also has been described,[94] but the disorder is rarely fatal. Granulomas, which may show a fibrin-ring structure similar to those seen in Q-fever,[95] are reported in about 50 per cent of liver biopsies and have also been described in bone marrow.[92]

Gold. Several case reports suggest that gold salts used in the treatment of rheumatoid arthritis occasionally cause a relatively noninflammatory, cholestatic form of liver injury.[96-98] The onset usually has occurred within a few weeks after the start of the course of drug administration, and has responded well to cessation of treatment. The prognosis has been uniformly good. The incidence and mechanism of toxicity are unknown.

Indomethacin, Ibuprofen, Naproxen. These and a number of other anti-inflammatory agents have been associated with variable hepatotoxicity.[2, 99, 100]

Sulindac. Several cases of painless jaundice with evidence of a mild hepatitis and variable cholestatic features have been attributed to sulindac.[101] Recovery upon withdrawal of the drug may take several months.

Benoxaprofen. This drug has been withdrawn following 31 deaths, mainly in elderly patients, from hepatorenal toxicity. The liver disease was typically cholestatic, with characteristic laminated concretions filling proliferated bile ductules, seen on histology.[102]

Dantrolene. This is an antispasmodic agent related to phenytoin. In a prospective study, prolonged (more than two months) use of the drug was associated with a 1.8 per cent incidence of liver function abnormalities; of the 19 affected patients, 6 were jaundiced and 3 died.[103] Additional experience indicates that significant liver injury caused by dantrolene occurs only after a month or more of use and is more likely to occur among patients 30 years old or older or when doses exceed 300 mg/day.[103] Clinically, the disease resembles acute or chronic viral hepatitis, and histologically

tion for such phenomena in the postoperative patient, the true incidence of this mild form of the disease is unknown. Similarly, although most patients with clinically overt halothane hepatotoxicity in retrospect have had previous exposures to halothane, and many of these have had unexplained postoperative fevers, it is not known what proportion of the patients with mild or inapparent initial reactions would, if re-exposed, develop more overt liver injury. Despite this uncertainty, the generally accepted dictum that such patients, once identified, should not be exposed to halothane again is valid as a clinical guideline. It does seem clear that among patients with histories of recent halothane exposure, those who are re-exposed are more likely to have abnormal liver test results than is a control population.[161, 162] In neither of these reports were there serious reactions. In this respect, the situation may possibly be analogous to isoniazid hepatotoxicity, in which 10 to 20 per cent of patients develop mild and apparently self-limited reactions, whereas only 1 per cent have overt hepatitis; similar dichotomies are observed with other drugs. The relationship, if any, between these two patterns of hepatic dysfunction is unknown.

Laboratory findings are equally nonspecific and are chiefly characterized by prominent elevations in transaminase activity and, in more severe cases, prolonged prothrombin times.

On the basis of reported cases, the fatality rate among patients with halothane-associated fulminant hepatic failure approaches 80 per cent.[117] The overall mortality rate for all cases of halothane hepatotoxicity is undoubtedly lower. In some cases, especially those with more severe acute courses, resolution may be delayed considerably. Although it has been suggested that a chronic hepatitis may ensue,[163] more recent evidence suggests that even in the prolonged cases eventual resolution may be expected.[164]

Diagnosis and Differential Diagnosis

The nonspecificity of the clinical, laboratory, and histologic findings associated with halothane hepatotoxicity, and the multiplicity of causes of postoperative liver injury, make the diagnosis quite difficult. Indeed, it is likely that in most instances the diagnosis can only be inferred on the basis of a compatible history of exposure, post-exposure interval, and clinical and laboratory findings. Because of the potentially high case fatality rate, rechallenge with halothane is not recommended. If the findings are consistent and if other causes of postoperative jaundice, such as viral or drug-induced hepatitis, bile duct obstruction, postoperative cholestasis, sepsis, and hemolysis, can be excluded, it is best to assume that the patient has experienced a halothane reaction and to advise that this and related haloalkanes be avoided in the future. (See also Chap. 34.)

Prevention and Management

As noted, a careful history of prior anesthetic exposure is essential if halothane use is considered. For individuals in whom a series of anesthetic exposures is anticipated, another agent is preferred. Because halothane has been reported to contaminate vaporizer-equipped anesthesia machines and thereby cause a recurrence of hepatitis,[165] this potential should be dealt with in any patient with a history suggestive of halothane hepatitis.

The management of halothane hepatotoxicity is entirely supportive, including, if necessary in severe cases, measures directed against the complications of hepatic failure, such as encephalopathy, bleeding diathesis, hypoxia, and hypotension. Corticosteroids are of no proven value (see Chap. 17).

OTHER HALOALKANES

Methoxyflurane. This agent causes a hepatic injury very similar to that associated with halothane. Indeed, there is evidence for "cross-reactivity," in that some patients with a history of exposure to one agent may develop a reaction to the other.[117, 166] Methoxyflurane may also lead to hyperoxaluria and renal failure. Both methoxyflurane and halothane have caused hepatitis in individuals who have abused ("sniffed") these agents.[173–175]

Enflurane. Enflurane has been reported to cause liver injury.[167–169] The syndrome is similar to halothane hepatitis clinically and is associated with centrilobular necrosis. Prior exposure to either enflurane or halothane apparently is predisposing and shortens the latent period between exposure and clinical onset of illness.[168] It should be noted that the causal role of enflurane is disputed and that this issue remains unresolved.[170, 171] Both enflurane and methoxyflurane influence microsomal electron transport in vitro, but the possible relationship of this effect to hepatotoxicity is not known.[172]

Isoflurane. Isoflurane is the member of this class of agents that is least likely to cause hepatotoxicity, consistent with its extremely limited metabolism.[176] Its major disadvantage appears to be its greater cost.

ANTICONVULSANTS

PHENYTOIN

Chronic phenytoin use has been associated with a significant incidence of abnormal liver tests,[177] and structural abnormalities on liver biopsy.[178, 179] In addition, at least 45 cases of acute phenytoin-associated hepatic injury have been recorded. The acute cases have been remarkably similar to one another in clinical, laboratory, and histologic findings, and there is little doubt that the apparent causal relationship is valid.[180–183] The onset usually occurs after four to six weeks of drug administration, although it may be as early as one to two weeks, and is characterized by malaise, fever, lymphadenopathy, maculopapular rash, and vague abdominal complaints. Physical findings, in addition to rash and adenopathy, include variable hepatomegaly and jaundice, and, occasionally, splenomegaly. There is a moderate to marked leukocytosis; total leukocyte count occasionally may exceed 30,000/mm³, with atypical lymphocytes and a relative and absolute eosinophilia. Liver function is significantly deranged, with moderate to marked increases in transaminase and alkaline phosphatase activity, bilirubin concentration, and prothrombin time. In the most severe cases, encephalopathy and other signs of progressive liver failure may ensue, and are poor prognostic signs. Histologically, the lesion resembles acute viral hepatitis, although there may be more than the usual number of eosinophils. In the most severe and fatal cases, there is massive hepatic necrosis, occasionally with a predominantly centrilobular localization. A granulomatous reaction also has been documented.[184] Treatment of the disorder is largely supportive.

Corticosteroids have been employed in a number of instances. They may improve the systemic, serum sickness–like features of the illness, but there is no evidence that they influence the course of the hepatic lesion or survival.[183] High dose (pulse) corticosteroids also have been employed with similar results.[185]

The pathogenesis of liver injury may involve both immunologic and toxic mechanisms. The apparent rarity of the disorder and its serum sickness and pseudolymphoma-like clinical features,[186] together with laboratory evidence suggestive of an immunologic response,[181, 187] are suggestive of drug hypersensitivity. That there may well be a component of this in the overall reaction is consistent with the fact that in several instances, rechallenge with the drug has led to a rapid reappearance of the systemic features.[188–192] It is of interest, however, that in only two of these cases[182, 192] was the response to rechallenge associated with abnormalities in liver tests. This would be consistent with the possibility that the liver injury is at least in part toxic, mediated by the formation of a reactive intermediate. In this connection, it is of interest that in its biotransformation, phenytoin is in part converted to a dihydrodiol derivative, possibly by way of an epoxide.[193] (Also see Chap. 9.) Epoxides are capable of reacting with sulfhydryl and other important reducing groups and may, in a manner analogous to that proposed for acetaminophen hepatotoxicity, cause liver cell injury via the formation of covalent bonds with critical cell constituents. If this is indeed the case, differences in individual susceptibilities could be explained by genetic or induced differences in rates and pathways of drug biotransformation. In fact, evidence has been presented that suggests that at least some of these patients are genetically predisposed to toxic liver injury related to a relative deficiency in their ability to detoxify arene oxides (e.g., via epoxide hydrolase).[17] On the other hand, such a mechanism would not appear to account for the prominent systemic features of the illness, for which an immunologic mechanism seems more plausible. Whereas it is conceivable that a toxic product of drug biotransformation might also elicit (as a hapten) an immune response, the relationship between the hepatic and systemic components of this drug-induced disorder remains speculative.

VALPROIC ACID (2-PROPYL-PENTANOIC ACID)

This newer agent is used principally in the treatment of petit mal epilepsy. It is a branched, medium-chain-length fatty acid, and is administered orally as the sodium salt. Although it is generally well tolerated, a number of side effects have been reported, including incidences as high as 44 per cent (average about 11 to 12 per cent) of mainly transient, asymptomatic, usually slight (< two fold) increases in serum transaminase activity.[194, 195] These usually occur after 10 to 12 weeks of drug therapy, and at least in some instances appear to be dose-dependent.[195]

Clinically overt liver damage is much less common, but its true incidence is unknown.[194–201] Whereas severe and sometimes fatal reactions are common among the available case reports, the full clinical, pathologic and prognostic spectra of the disease await definition. The clinical manifestations of overt valproic acid hepatotoxicity are similar to those of other forms of acute liver disease. There may be nonspecific systemic and digestive symptoms, such as fever, anorexia, and nausea, followed by the appearance of jaundice and, in severe cases, encephalopathy. Laboratory studies show variable increases in serum transaminase activity, bilirubin, alkaline phosphatase, and prothrombin time. Rash and eosinophilia are absent.[200]

Histologically, the disease is associated with centrilobular necrosis and the accumulation of fat in small droplets in the liver cells, similar to that observed in Reye's syndrome. Unlike Reye's syndrome, however, valproic acid hepatotoxicity also may be associated with evidence of bile ductular injury and submassive necrosis.[196] Indeed, it has been suggested that the bile secretory apparatus, canaliculi and ductules are the principal sites of injury, rather than the mitochondria. Perhaps reflecting this cholestatic component, the disorders also differ in that clinical jaundice is common in valproic acid toxicity, but distinctly uncommon in Reye's syndrome (Chapter 54). Nonetheless, at least three fatal cases have been reported in which elevated blood ammonia and transaminases, normal bilirubin, and microvesicular fat were reminiscent of Reye's syndrome.[200]

There has been considerable progress toward an understanding of the effects of valproic acid and its metabolites on intermediary metabolism and of their possible relationship to hepatotoxicity. Several studies, including some involving healthy human subjects, indicate that this agent significantly impairs mitochondrial oxidation of long-chain fatty acids, associated with a decrease in hepatocellular acetyl CoA and in serum levels of β-hydroxybutyrate and ketones and with impaired urea synthesis and gluconeogenesis.[202–208] Dicarboxylic aciduria may occur,[206, 209] but peroxisomal oxidation of fatty acids is not impaired.[210] Mice that are genetically deficient in ornithine transcarbamylase are far more sensitive to valproic acid than their normal counterparts,[211] consistent with the clinical impression that children with inborn errors in the urea cycle or other aspects of mitochondrial-dependent intermediary metabolism are most susceptible to valproate hepatotoxicity. The precise mechanism for the apparent valproate-induced aberration in mitochondrial function is not known, but accumulation of the coenzyme A derivatives of valproate and its major metabolites has been suggested,[203, 212] and is supported by the observation that phenobarbital enhances the ability of valproate to cause steatosis.[205, 213] Presumably, the accumulation of lipid as microvesicular steatosis is secondary to the impaired oxidation of fatty acids, analogous to other disorders associated with this picture, but this is not established.

Available evidence suggests that, unlike the hepatotoxic effects, valproic acid teratogenicity does not require its conversion to the coenzyme A derivative.[214] Over 90 per cent of the valproate excreted in bile is present as the glucuronide conjugate, and it causes an immediate bile acid-independent choleresis.[215] Valproic acid glucuronides, retained in plasma for prolonged periods because of hepatic and/or renal dysfunction, may undergo rearrangement, the biological consequences of which are unknown.[216]

There is no effective treatment for valproic acid hepatotoxicity, but spontaneous recovery after discontinuation of administration of the drug is the rule; fatalities appear to be rare. Rechallenge may elicit a recurrence,[202] although not invariably.[217] Routine monitoring of liver tests have been suggested, especially during the first six months of treatment when liver injury appears to be more common.[194, 199] However, as in other instances in which the incidence of asymptomatic and transient hepatic dysfunction greatly exceeds that of overt liver injury, the real usefulness of such monitoring is uncertain.

Carbamazepine. Hepatic injuries caused by this agent

have been well documented and, although the incidence is unknown, such injuries may be more common than has been appreciated.[218-223] The usual form of injury is a granulomatous reaction.[218, 219, 221, 223] The lesion, which may be associated with clinical and histologic evidence suggesting cholangitis,[220, 223] may be very slow to resolve, with residual abnormalities in alkaline phosphatase persisting for several months.[218] Occasionally, carbamazepine is associated with a predominant hepatocellular necrosis.[220] In one patient, carbamazepine induced a nonhereditary acute porphyria syndrome via direct inhibition of uroporphyrinogen I synthetase.[224] In another patient, this agent was believed to have predisposed to isoniazid hepatitis, secondary to induction of the latter's metabolism.[225] Management of carbamazepine hepatitis is supportive.

ANTIMICROBIALS

ANTIBACTERIAL AGENTS

Penicillins. Penicillin G has an excellent record of safety with regard to hepatotoxicity, and very few cases of penicillin G–induced liver damage have been recorded.[226] In contrast, a number of the semisynthetic penicillins apparently have been responsible for liver injury, and among these oxacillin is the best documented and characterized with respect to its hepatotoxic effects.

Oxacillin. Oxacillin hepatotoxicity has been the subject of several reports and in almost all instances has occurred in patients receiving large doses of the agent intravenously.[227-233] Although the serious infections for which this patient population is undergoing treatment also may adversely affect liver function, the causal relationship of the antibiotic itself to the liver dysfunction is well established. Thus, in some patients liver dysfunction appeared only after the infection was under control. Also, the reported clinical and laboratory features have been quite uniform in different patients, and generally there is rapid improvement after discontinuation of the drug.

The disorder, which usually first becomes manifest after a week or more of high-dose, intravenous oxacillin therapy, may be either asymptomatic or associated with low-grade fever; upper gastrointestinal symptoms such as anorexia, nausea, and vomiting; variable upper abdominal and right upper quadrant discomfort; and hepatomegaly. Laboratory findings include elevated serum transaminase (occasionally in excess of 1,000 units) and normal or slightly elevated alkaline phosphatase; bilirubin concentration is almost invariably normal. Rash, arthralgia, and eosinophilia are unusual. In the few cases in which biopsies have been performed, a nonspecific focal hepatitis has been present. The prognosis is uniformly excellent; in virtually all cases, rapid clinical and laboratory improvement has followed cessation of oxacillin therapy, and in most cases, liver tests have returned to normal within several weeks.

The mechanism of the injury is not known. Although an association of oxacillin hepatotoxicity with previous or subsequent evidence of penicillin allergy was reported in one series,[230] a convincing case cannot be made for an immunologic basis for the lesion. Rather, a toxic mechanism is suggested by the fact that almost all reported cases have followed high-dose administration of the drug for at least a week, and in many instances improvement has followed substitution of another penicillin analog, such as nafcillin,[227-230, 232, 233] for the oxacillin.

Although serious or lasting liver damage has not been attributed to oxacillin, it may be appropriate to monitor liver tests before, and at intervals during, prolonged parenteral high-dose administration of this agent. If significant abnormalities occur, substitution of an alternative drug should be considered.

Carbenicillin. This agent has been associated in four patients with a clinical, laboratory, and histologic syndrome similar to oxacillin hepatotoxicity. In all four, the disorder was elicited by subsequent rechallenge with the drug.[234] Liver tests in all patients improved when another penicillin analog was substituted, despite the fact that in one patient the hepatotoxicity had been associated with a serum sickness–like illness.

Cloxacillin. In a single, well-documented case report, cloxacillin has been associated with a hepatic injury quite unlike the nonspecific, anicteric focal hepatitis caused by oxacillin and carbenicillin.[235] In this case, proved by rechallenge, the patient developed marked cholestasis, with a serum bilirubin concentration of nearly 15 mg/dL, primarily direct-reacting, a fivefold elevation in alkaline phosphatase activity, and a normal to slightly increased transaminase activity. Recurrence of the syndrome within four days of rechallenge with oral cloxacillin and a positive macrophage migration-inhibition factor test were interpreted as suggesting a hypersensitivity reaction. *Flucloxacillin* has also been implicated in hepatic injury similar to that caused by cloxacillin, which was confirmed by rechallenge, in a single case.[236]

Erythromycin. A cholestatic reaction associated with significant portal inflammation and focal hepatic necrosis is a well-documented complication of erythromycin estolate administration,[226, 237-239] and more recently has been associated with erythromycin ethylsuccinate and erythromycin lactobionate.[238, 240, 241] Although the true incidence is unknown, it appears to occur more commonly in adults than in children. Among children, in fact, the incidence of liver test abnormalities caused by erythromycin estolate, erythromycin ethylsuccinate, and penicillin V are similar and occur with an incidence of generally less than 6 per cent.[242] Typically, the onset is one to four weeks after the agent is first administered, although it may occur earlier upon reexposure. The symptoms are usually those of a nonspecific gastrointestinal upset, with or without fever, but upper abdominal or right upper quandrant pain is often prominent and may dominate the presentation. Hepatomegaly may or may not be present, and liver tests usually indicate both cholestasis and hepatocellular necrosis, with increased serum alkaline phosphatase and transaminase activities; serum bilirubin, if increased, is primarily direct-reacting. Liver biopsy demonstrates portal infiltrates, often with eosinophils, centrilobular cholestasis, and a few scattered foci of liver cell necrosis and acidophil bodies. The prognosis is excellent, with rapid and complete restoration of normal liver function and structure after withdrawal of the drug. Subsequent readministration of the drug usually elicits a similar clinical and laboratory response, often after only a day or two. This feature, together with the finding that eosinophils may be increased in the blood or the hepatic inflammatory infiltrate, suggests that the lesion has an allergic basis. However, erythromycin estolate causes a concentration-dependent impairment of bile flow in the isolated perfused rat liver and inhibition of canalicular membrane Mg- and NaK-ATPases,[243] and this and other in vitro studies suggest a direct hepatotoxic effect,[244-246] so that at the present time the pathogenesis remains undefined.

Two particularly important aspects of erythromycin hepatotoxicity deserve special emphasis. First, it was believed that only erythromycin estolate caused this lesion, but it is now evident that other preparations, including erythromycin ethylsuccinate and erythromycin lactobionate, may do the same, possibly with cross sensitization,[247] although their relative hepatotoxic potentials are unknown. Second, the clinical presentation of the lesion can resemble that of acute cholecystitis or ascending cholangitis so closely that it may not always be possible to distinguish erthyromycin hepatotoxicity from biliary tract disease on clinical grounds alone. Indeed, a false-positive ^{99m}Tc-DISIDA scan has been reported in this setting[248] and some patients with cholestasis secondary to erythromycin hepatotoxicity have been subjected to abdominal exploration.

Tetracyclines. This group of antibiotics rarely may cause an unusual and severe form of acute liver injury.[249-252] It has followed intravenous administration of the drug in high doses to patients with compromised renal function. The initial reports mostly involved women with acute pyelonephritis in the latter stages of pregnancy, but it later became apparent that nonpregnant patients were also at risk, and that oral tetracycline administration also could cause the syndrome.[250] Despite the latter variants, common features of the illness appear to be its occurrence in a setting in which blood levels of tetracycline are unusually high, and that for reasons as yet unknown, women, especially during pregnancy, appear to be at increased risk.

The clinical illness resembles viral hepatitis in its presentation, with nonspecific systemic and digestive complaints such as malaise, anorexia, nausea, vomiting, and upper abdominal discomfort. In pregnancy, premature labor may be precipitated. The course is often progressive, with deepening jaundice, encephalopathy, and hypoprothrombinemia, usually associated with azotemia and hyperamylasemia. Leukocytosis is often profound. Transaminase activities and bilirubin concentrations are moderately increased, and usually do not exceed 1,000 IU/L and 10 mg/dL, respectively. The advancing course of the illness may be complicated by hypoglycemia and its effects on mental status, as well as by hemorrhagic diathesis or gastrointestinal bleeding, and metabolic acidosis.

The histopathology of tetracycline hepatotoxicity consists of the accumulation of lipid, primarily triglyceride, in hepatocytes. The lipid is dispersed throughout the cell in small droplets, but the nucleus remains centrally located. Thus, this pattern differs strikingly from the fatty liver associated with ethanol ingestion, obesity, and diabetes mellitis, and superficially resembles that seen in only a few other disorders, including Reye's syndrome, fatty liver of pregnancy, Jamaica vomiting sickness, and valproic acid hepatotoxicity. Accordingly, this lesion, if found in a patient to whom tetracycline has recently been administered, strongly suggests the diagnosis of tetracycline hepatotoxicity, and in this respect it differs from the relatively nonspecific histologic abnormalities associated with most drug reactions.

The pathogenesis of the lesion has not been elucidated fully. The fact that high blood and tissue levels of the drug appear to be prerequisite suggests that hepatotoxicity represents a toxic effect of tetracycline or a metabolite rather than an immunologic phenomenon. Moreover, animal experiments clearly show that tetracycline interferes with the hepatic secretion of triglyceride-rich lipoproteins, both in vivo and in the isolated perfused rat liver.[253] Thus, although the precise mechanism for this secretory impairment is not known, the accumulation of fat seems understandable, at least in part, as the result of decreased lipid export from the cell. Not resolved by these animal experiments, however, is the basis for the more general and profound failure of hepatocyte function that characterizes the clinical syndrome. The presence of lipid in the hepatocyte per se does not satisfactorily explain these functional changes, and appears only to reflect the underlying metabolic disturbance, the nature and pathogenesis of which await elucidation. Since tetracycline is an inhibitor of protein synthesis, it conceivably could influence the availability of certain cell constituents that turn over rapidly, but this remains speculative.

Sulfonamides. Sulfonamides have been implicated in a form of hepatocellular necrosis, often associated with "allergic" features such as fever, arthralgia, rash, and eosinophilia.[226] The incidence is unknown. Agents for which the documentation is more or less adequate to support causality include sulfanilamide, sulfadimethoxine, azulfidine,[254-263] sulfamethoxazole,[264-268] sulfones,[267] sulfamethizole,[268] and sulfamethoxypyridizine.[268, 269] The latter two agents have been associated with a picture of chronic active hepatitis.[268, 269] Occasionally, a granulomatous reaction may be seen.[255, 260, 262]

The clinical onset of the reaction normally occurs within two weeks after the drug is started, but reactions may be delayed. As mentioned, the presentation is nonspecific, and is associated with laboratory evidence of liver cell necrosis, especially increased serum transaminase activity. Because of an expected bias toward more severe reactions among case reports, the case fatality rate is unknown, but it may exceed 10 per cent.[226] In the substantial majority of cases, however, complete recovery may be expected within several weeks to a few months after the medication is discontinued. If there is massive hepatic necrosis, death may occur early; late deaths may result from submassive necrosis. Although corticosteroids have been employed in the treatment of sulfonamide hepatitis, there is no clear evidence that they are beneficial.

Nitrofurantoins. These agents are now well established as an unusual cause of acute, usually cholestatic, and chronic forms[270-273] of liver injury. The incidence appears to be especially high in women, but this may reflect an increased exposure to the drug during treatment of urinary tract infections.

The acute syndrome is often associated with fever, rash, jaundice, and eosinophilia, and usually appears within a few weeks of the onset of drug administration. The clinical, laboratory, and histologic picture is predominantly cholestatic, although hepatocellular necrosis may be present. A granulomatous reaction has been documented.[274] The prognosis for complete recovery is good, and thus far none of the patients with overt acute disease has died of liver disease or has clearly progressed to chronic hepatitis.

Chronic active hepatitis with "lupoid" features has now been associated convincingly with chronic nitrofurantoin administration in several cases. The affected patients have been women who have taken the drug for at least four months, and often they are found to have hyperglobulinemia and positive tests for antinuclear and anti–smooth muscle antibodies. Cirrhosis developed in four patients. Two of 20 reported cases in one series died with massive necrosis, both having taken the drug for more than a year, and having continued to take it after the appearance of jaundice.[271] In the others, improvement followed discontinuation of the drug. Corticosteroids have been employed, but without clear benefit.

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Hemochromatosis: Iron Metabolism and the Iron Overload Syndromes

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HISTORY

The association of diabetes, cirrhosis of the liver, fibrosis of the pancreas, and pigmentation of the skin was first described by Trousseau in 1865.[1] Six years later Troisier reported a case of "pigment cirrhosis in sugar diabetes."[2] In 1889, Von Recklinghausen termed the association of these clinical features *hemochromatosis*, and although he established that the increased pigment in tissues was iron, he suspected that it originated from the blood.[3] Thereafter, the favored synonyms for this syndrome were bronze diabetes or pigment cirrhosis (French literature) and hemochromatosis (German literature), although it was not recognized at that time that they represented different stages of development of the same disease. Little new information was forthcoming on the natural history of hemochromatosis until Sheldon published his classic monograph in 1935.[4] With his detailed review of 311 published cases, he established for the first time a unifying concept of the multiple organ involvement of a single disease and offered evidence for its familial occurrence. On the basis of his family studies, he concluded that hemochromatosis was a hereditary disease resulting from an inborn error of metabolism. The genetic basis of the disease was initially questioned by Macdonald,[5] and it took another four decades after Sheldon's study for workers to establish firm phenotypic evidence for the genetic transmission of hemochromatosis based on the association between the histocompatibility antigen (HLA) alleles and predisposition to the disease.[6] Likewise, the association between excessive iron deposition and tissue damage has been supported conclusively in the clinical setting by careful evaluation of family members of affected individuals.[7, 8]

The term *hemochromatosis* is currently used to denote the pathologic deposition of excessive iron in the parenchymal cells of many organs, which leads to cell damage and functional insufficiency. *Hemosiderosis* is used virtually synonymously by pathologists to indicate excessive stainable iron in tissues, without regard to the specific target cell primarily involved or to the underlying pathogenesis of the iron deposition. When the condition is genetically determined by inappropriately high absorption of iron in the intestinal mucosa, it is termed *genetic* or *hereditary* (primary, idiopathic) *hemochromatosis*. Other conditions, many of disordered or ineffective erythropoiesis, lead to excessive iron absorption and tissue deposition. They have been termed *secondary iron overload*, because the increased absorption of intestinal iron is promoted by the underlying condition or by increased availability of intestinal iron. Both genetic hemochromatosis and secondary iron overload have to be distinguished from parenteral iron overload, which leads to iron deposition initially confined to the reticuloendothelial system. When transfusion requirements are met in disorders of erythropoiesis, a combination of reticuloendothelial and parenchymal iron overload may coexist, and the total iron burden may be very large. Likewise, in transfusional hemosiderosis, late parenchymal iron overload has been explained as a spillover from the reticuloendothelial system. The degree of structural and functional damage to the organ parallels the extent of parenchymal cell involvement, regardless of the underlying cause.

Since methods are now available for the detection of genetic hemochromatosis in presymptomatic relatives of patients with the disease, the diagnosis can be applied legitimately to individuals in whom the toxic consequences of iron overload have not yet developed. It is no longer justified to confine the diagnosis only to those individuals who manifest the classic triad of cirrhosis, diabetes, and skin pigmentation. Rather, all those relatives who can be shown to share both haplotypes with a proven proband should be regarded as homozygous for genetic hemochromatosis. This concept has promoted the early diagnosis and treatment of the disease and undoubtedly has already led to increased survival and reduced morbidity.

CAUSES OF IRON OVERLOAD IN HUMANS

Although Sheldon postulated the hereditary basis for so-called idiopathic or primary hemochromatosis in 1935, the use of the older nomenclature has persisted until recently because of the lack of firm genetic markers of the disease. With the advent of detailed pedigree analyses combined with determination of HLA to assign significance to indirect markers of iron overload, idiopathic or primary hemochromatosis can be renamed, with confidence, genetic hemochromatosis. This is in contradistinction to the many causes of secondary iron overload, in which an identifiable underlying disorder leads to excessive accumulation of parenchymal iron, with the potential for pathologic and clinical consequences that are ultimately similar to those in the genetic form of the disease. The most important of these causes are listed in Table 48–1. In secondary iron overload, a combination of enhanced iron absorption and dietary or transfusional iron overload, or both, may be responsible for the accumulation of body iron stores that are comparable to those seen in genetic hemochromatosis. Particularly in situations of ineffective erythropoiesis, iron may accumulate very rapidly because of these combined factors, and patients may present with the consequences of

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