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Various Forms of Chemically Induced Liver Injury and Their Detection by Diagnostic Procedures*

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A large number of chemical agents, administered for therapeutic or diagnostic purposes, can produce various types of hepatic injury by several mechanisms. Some agents are intrinsically hepatotoxic, and others produce hepatic injury only in the rare, uniquely susceptible individual. Idiosyncrasy of the host is the mechanism for most types of drug-induced hepatic injury. It may reflect allergy to the drug or a metabolic aberation of the host permitting the accumulation of hepatotoxic metabolites. The syndromes of hepatic disease produced by drugs have been classified as hepatocellular, hepatocanalicular, mixed and canalicular. Measurement of serum enzyme activities has provided a powerful tool for studies of hepatotoxicity. Their measurement requires awareness of relative specificty, knowledge of the mechanisms involved, and knowledge of the relationship between known hepatotoxic states and elevated enzyme activities.

Drug-induced liver disease accounts for only a small proportion (less than 5%) of instances of jaundice in general hospitals (*1,2*). As a cause of severe, acute, hepatic disease with hepatic failure, however, adverse reactions to therapeutic agents (for example, halothane or isoniazid) figure more prominently. Hepatic necrosis induced by drugs accounts for 25 to 30% of instances of fulminant hepatic failure (*3*). Hepatic damage caused by therapeutic agents is best reviewed in the context of the general aspects of hepatotoxicity (*4*). These include the character of the injury and the presumed mechanisms and circumstances of exposure to the respective agent.

Types of Drug-Induced Hepatic Disease

Chemical agents can produce several types of hepatic injury (Table 1). The injury may be cytotoxic, that is, characterized by necrosis or degeneration of the hepatic parenchyma, or cholestatic, that is, manifested by arrested bile flow and jaundice, but relatively little parenchymal injury. Some drugs characteristically produce injury that includes elements of both types and is referred to as mixed. The cytotoxic form includes necrosis (zonal, diffuse, and massive), steatosis, or combinations of necrosis and steatosis. Cholestatic injury may be bland, that is, manifested only by bile stasis, without significant inflammatory changes in the liver, as in that produced by the C-17 alkylated anabolic or contraceptive steroids; or it may be accompanied by impressive portal area aggregates of inflammatory cells, as in the cholestatic injury induced by erythromycin estolate or chlorpromazine.

The correlation between the morphological

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type of hepatic injury and the clinical and biochemical abnormalities is quite consistent. Hepatic necrosis induced by drugs leads to a syndrome which resembles that of viral hepatitis with markedly elevated transaminase valves and relatively slight elevations of the alkaline phosphatase levels. Most important is the tendency for this syndrome to present itself as massive hepatic necrosis and liver failure.

The hepatic steatosis produced by tetracycline resembles the histological picture the fatty liver of pregnancy and leads to similar biochemical features and clinical manifestations. Jaundice is usually modest and the transaminase values are only moderately elevated, but the syndrome of hepatic failure with a fatal outcome can develop.

Cholestatic injury resembles extrahepatic obstructive jaundice in its manifestation. The clinical picture is dominated by jaundice and itching. the biochemical parameters include modest transaminase elevations and alkaline phosphatase activities that resemble those of obstructive jaundice. This is the picture in the cholestatic jaundice associated with portal inflammation (hepatocanalicular jaundice). (*4*). Alkaline phosphatase activities are more modestly elevated in the bland cholestasis induced by C-17 alkylated steroids (canalicular jaundice) (*4*). Some drugs produce a mixed pattern of hepatic injury that includes both cytotoxic and cholestatic features. Hepatocanalicular jaundice with prominent parenchymal injury accompanying the predominantly cholestatic picture has been characterized as mixed-hepatocanalicular jaundice. Hepatocellular injury in which a predominantly cytotoxic form of damage is accompanied by very high alkaline phosphatase values has been designated mixed-hepatocellular jaundice (*4*).

Precise description of the phenomenology of the forms of drug-induced injury may have several advantages. The type of injury has a clear bearing on the prognosis. The more prominent the hepatocellular injury, the more grave the syndrome, with hepatic failure and a fatal outcome possible (*4*). The more cholestatic the injury and the less prominent the parenchymal damage, the better the immediate prognosis. The mortality rate in hepatocellular jaundice ranges from 10 to 50%, while in drug-induced cholestatic jaundice it is less than 1%. Furthermore, the type of injury is related to the therapeutic category of drug. For example, the antidepressants tend to produce hepatocellular injury, the anticonvulsants lead to mixed-hepatocellular injury, the tranquilizers, to hepatocanalicular or mixed-hepatocanalicular injury and the anabolic and contraceptive steroids produce the canalicular type of injury (*5*).

Chronic hepatic disease can also result from drug-induced injury. Acute hepatocellular injury induced by cinchophen, iproniazid and repeated exposure to halothane has been reported to lead to cirrhosis of the macronodular type (*5*). Prolonged administration of methotrexate appears to lead, in some patients, to cirrhosis of the macro or micronodular type (*6*). In some patients, the hepatic injury induced by oxyphenisatin shows features of chronic active hepatitis, including cirrhosis (*7*). Cholestatic injury induced by chlorpromazine, organic arsenicals, tolbutamide, methyltestosterone and contraceptive steroids has led to instances of a cirrhosis resembling the "primary biliary" type (*5*). The Budd-Chiari syndrome, with congestive cirrhosis, can result from thrombotic occlusion of the hepatic veins induced by contraceptive steroids or by the venoocclusive disease and centrolobular hepatic sclerosis secondary to urethane poisoning (*5*).

Mechanisms of Injury

The chemical agents that produce hepatic damage fall into two broad categories: those that have the intrinsic property of injuring the liver (intrinsic or predictable hepatotoxins) and those that damage the liver of uniquely susceptible hosts (idiosyncracy-dependent or unpredictable toxins) (Table 2). The first group is recognizable by the high incidence of toxicity in exposed individuals, dependence on dose and reproducibility of the injury in a variety of species. Agents which produce hepatic injury in a small proportion of exposed individuals, whose toxicity is not dose-dependent and which do not produce hepatic damage in experimental animals, are recognized to depend on host idiosyncrasy rather than on the intrinsic toxicity of the agent (*4,5,8,9*).

Intrinsic hepatotoxins appear to include at least two subcategories, direct and indirect (Table 2). Direct hepatotoxins are protoplasmic poisons capable of injuring many tissues, particularly the liver. The prototype, carbon tetrachloride (CCl_4) disrupts all elements of the hepatocyte including the endoplasmic reticulum, mitochondria, lysosomes, and plasma membranes and, indeed, leads to almost immediate, destructive intracellular chaos. The membrane injury appears to result from peroxidative damage of the

Table 1. Types of drug-induced acute hepatic injury.

Histological	Biochemical[a]			Clinical		Prototype drugs
	GOT-GPT	Alkaline phosphatase	Cholesterol	Syndrome resembles	Mortality, %	
Cytotoxic						
Necrosis: zonal and diffuse	Markedly increased	Increased	Normal to decreased	Viral hepatitis (severe)	10-50	Halothane Isoniazid Iproniazid
Steatosis	Increased	Increased	Normal to decreased	Fatty liver of pregnancy	High	Tetracycline
Cholestatic						
Pericholangitis (present)	Increased	Markedly increased	Markedly increased	Obstructive jaundice	<1	Erythromycin estolate Chlorpromazine Organic arsenicals
(absent)	Increased	Increased	Normal to increased	Obstructive jaundice	<1	Anabolic and contraceptive steroids
Mixed[b]						
Features cytotoxic plus cholestatic	Increased to markedly increased	Increased to markedly increased	Decreased to increased	Atypical viral hepatitis Obstuctive jaundice		Paraminosalicylic acid Sulfonamides

[a] GOT=glutamate oxaloacetate transaminase; GPT=glutamate pyruvate transaminase.
[b] In mixed types, mortality seems to depend on the degree of cytotoxic injury.

Table 2. Classifications and characteristics of hepatotoxic agents.

Category	Incidence	Experimentally reproducible	Dose dependence	Latent period	Mechanism	Histological lesion	Prototype drugs
Intrinsic toxicity							
Direct	High	Yes	Yes	Very short (minutes to hours)	Membrane injury indiscriminate of all elements of cell	Necrosis (zonal) and/or steatosis	CCl_4 Chloroform Tannic acid
Indirect							
Cytotoxic	High	Yes	Yes	Short (hours to days)	Interference with specific metabolic pathways	Steatosis or necrosis	Ethionine Urethane Mycotoxins Tetracycline Cancer chemotherapy agents
Cholestatic	High	Yes[a]	Yes	Short (days)	Interference with hepatic excretory pathways	Bile casts	Icterogenin C-17 alkylated anabolic and contraceptive steroids
Host idiosyncrasy							
Hypersensitivity	Low	No	No	Consistent, long (one to four weeks)	Drug allergy	Necrosis or cholestasis	Sulfonamides Paraminosalicylic acid Halothane
Metabolic abnormality	Low	No	No	Variable, long (weeks to months)	? Accumulation of hepatotoxic metabolites	Necrosis or cholestasis	Ipronaizid Cinchophen Isoniazid

[a] Experimental reproducibility difficult but possible.

lipid components, wrought mainly by a metabolite of the CCl_4.

Indirect hepatotoxins are antimetabolites or related compounds, which produce hepatic injury by the diversion or competitive inhibition of essential metabolites or by other forms of interference with specific metabolic or secretory processes of the hepatocyte. Indirect hepatotoxins cripple the hepatocyte selectively by interference with a specific pathway, while direct toxins appear to produce generalized, indiscriminate intrahepatocyte damage. Indirect hepatotoxins can be cytotoxic, producing steatosis or necrosis, or cholestatic producing jaundice (*4,5*).

Hepatic injury which depends on host idiosyncracy can also be divided into two types. The liver injury produced by some drugs after a fixed latent period (usually one to four weeks) is usually accompanied by systemic (fever, rash, eosinophilia) and histological (tissue eosinophilia or granulomas) features which suggest hypersensitivity to the drug as the cause. Often, the circumstances under which the injury occurs, and the response to a challenge dose, confirm drug allergy in these instances, and the inference is drawn that the drug or a metabolite has acted as a hapten (*4,5,8,9*).

The liver damage induced by other drugs, however, also in uniquely susceptible individuals, after a widely variable latent period and unaccompanied by ancillary features suggestive of hypersensitivity, may be deduced to be the result of some other mechanism, perhaps a metabolic aberration of the idiosyncratic patient, permitting the accumulation of hepatotoxic metabolites (*4,5*).

Knowledge of presumed mechanism and type of hepatic injury permits the classification of hepatotoxic agents shown in Table 2. While this classification may be subject to change as knowledge of mechanisms of injury increases, it has proved useful.

Hepatic Injury Due to Intrinsic Toxicity of Drugs

Direct Hepatotoxins

There are no known direct hepatotoxins that are used as therapeutic or diagnostic agents. CCl_4, formerly used as a vermifuge, has been largely abandoned, and tannic acid, which was at one time employed to treat burns and more recently in barium sulfate preparations to improve the quality of colonic radiographic studies, has been dropped from clinical use or employed in subtoxic concentrations for x-ray studies.

Indirect Hepatotoxins

Indirect hepatotoxins include a number of therapeutic agents (Table 2). Among the cytotoxic, indirect toxins are some antibiotics (e.g., tetracycline) and a large number of agents employed in the chemotherapy of neoplastic disease. Many of these agents produce hepatic steatosis by interfering with synthesis of appropriate apoprotein or with assembly of the lipoprotein complex required for the transport of lipid from the liver (*5*). Some drugs (e.g., urethane) that are categorized as cytotoxic indirect hepatotoxins produce necrosis by a mechanism that remains to be understood. Perhaps it is analogous to the necrogenic effect of bromobenzene which may be related to covalent binding to cytoplasmic proteins (*10*), although the means by which this leads to necrosis is obscure.

Tetracycline (and its congeners) is an antibiotic in clinical use which is illustrative of the indirect, cytotoxic hepatotoxins. High doses lead, in patients and experimental animals, to a diffuse vacuolization of hepatocytes that consists of tiny droplets of lipid and nonlipid material. It appears as a clinically important lesion only when high blood levels of tetracycline are produced by IV doses in excess of 1.5 g/day. The lesion seems particularly prone to occur if the recipient is in the last trimester of pregnancy or has renal disease. Smaller IV doses or oral administration usually produce no clinical evidence of hepatic disease, although minor degrees of steatosis can be observed in biopsy sections of the liver even after oral doses (*5*).

The mechanism for the steatosis has been demonstrated to be rapid inhibition by tetracycline of movement of lipid from the liver (*5,11*). Whether this is related to the known ability of these antibiotics to interfere with protein synthesis, perhaps by binding of tRNA or by interference with some other element of the complex system of synthesis or assembly of the lipoprotein necessary to transport the lipid from the liver, is unknown (*5,11*).

Ethanol also warrants classification as a drug which is an indirect hepatotoxin. It leads to fatty metamorphosis by a number of adverse effects on hepatocyte metabolism (*12*), but this is not within the scope of this paper.

Cholestatic Indirect Hepatotoxins

These toxins produce jaundice or impaired liver function by selective interference with hepatic mechanisms for excretion of substances

into a canaliculus or uptake from the blood (*5*).A number of C-17 alkylated anabolic steroids are in this category. The effect of these agents is dose-related, but modified by the individual susceptibility of the recipient. Hepatic dysfunction is produced in most individuals, but jaundice in only a few. Impairment of bromosulfhalein excretion occurs within a few days. Continued administration of the agent usually leads to a plateau or even to some decrease in the degree of abnormality of hepatic function. This would suggest that adjustment to and compensations for the adverse effects of the drug occur in most individuals, and that patients who develop jaundice after prolonged administration of one of these steroids are unable to make this adjustment, perhaps on a genetic basis (*4*).

Similar to this phenomenon is the high incidence of a relatively slight degree of hepatic dysfunction in women who take oral contraceptive steroids, which consist of C-17 alkylated estrogen and progesterone derivatives. Curiously, the oral contraceptive agents are particularly likely to produce jaundice in women who have had the benign, cholestatic jaundice of pregnancy, a syndrome with a probable genetic basis (*5*). Also probably related to this phenomenon is the impairment of liver function produced by estradiol and a number of other estrogenic agents (*13*).

The mechanism for the impaired function induced by these anabolic, progestational and estrogenic steroids is unknown. The available evidence suggests precise structural requirements, namely, an alkyl group at C-17. Testosterone, which lacks this type of substituent, does not lead to impaired function, while methyltestosterone, identical in structure except for the C-17 methyl substituent, does. A number of other agents with C-17 alkyl substituents also produce jaundice. This suggests the still unconfirmed hypothesis that these steroids might lead to impaired excretion of bile and its constituents by competitive interference with the transcanalicular transport (*4*) or excretory (*14*) role of a bile acid or other metabolite.

A variant of the cholestatic type of indirect hepatotoxicity includes that caused by agents that produce unconjugated hyperbilirubinemia and interfere with the uptake of foreign dyes from sinusoidal blood. In this category are flavaspidic acid, gallbladder dyes, and rifampicin (*5,9*). Rifampicin also appears to interfere with clearance of bilirubin and foreign dyes by competitive inhibition of their biliary excretion (*15*). Novobiocin can also lead to unconjugated hyperbilirubinemia, especially in neonates, apparently by interfering with bilirubin conjugation (*9*).

Hepatic Injury Due To Host Idiosyncrasy

Many drugs produce hepatic injury, unpredictably, in a small proportion of recipients. The hepatic injury appears to be an expression of unique, individual susceptibility rather than of intrinsic toxicity of the offending agent (*4,5,8,9*). Some analyses have referred to these as hypersensitivity reactions, a designation that tacitly assumes or explicitly regards the mechanism to be that of drug allergy, and the two terms have been employed interchangeably in this context. Indeed some instances, described below, of drug induced injury probably are a manifestation of allergy. Others appear to represent a different mechanism, presumably an aberrant metabolic pathway for the drug in the susceptible patient. Accordingly, to avoid confusion, hepatic injury induced by a drug sporadically, unpredictably and in low incidence should be designated as an idiosyncratic response to the drug. The term hypersensitivity should be reserved for hepatic injury which appears to result from allergy to the drug (*5*).

Hypersensitivity

Allergy is presumed to be the mechanism when the hepatic injury is characterized by (a) a relatively fixed "sensitization" period of one to four weeks; (b) prompt recurrence of hepatic dysfunction or jaundice on readministration of small doses of the agent; (c) a high incidence of fever, rash and eosinophilia; (d) eosinophil-rich inflammatory infltration, or granulomas in the liver; and (e) the coincidence of blood dyscrasia that also appears to depend on hypersensitivity for its pathogenesis (*8*). These features, however, provide only circumstantial evidence for drug hypersensitivity as the cause of hepatic disease (*5*). Efforts to demonstrate a role for humoral or cell-mediated immunity by the study of clinical cases have yielded variable results, and there are no experimental counterparts.

Indeed, no firm evidence for the role of hypersensitivity in drug induced hepatic injury has been available. The significance of the demonstration of antiliver antibodies in apparently drug-induced hepatic disease and of antimito-

chondrial antibodies in the serum of patients with several forms of apparently drug-induced injury, is uncertain (*5*). The studies of Paronetto and Popper (*16*) and those of Opolon et al. (*17*), suggest that in vitro tansormation of lymphocytes can be employed to demonstrate a relationship between an administered drug and hepatic injury in the recipient. While this technique has been useful for the study of generalized hypersensitivity reactions to drugs (*17*), a firm relationship to hepatic injury has not yet been shown.

The search for evidence of drug allergy as the cause of hepatic injury is hampered by the realization that the anitgen responsible for the presumed allergic state might be an unknown metabolite of the drug rather than the administered molicule (*18*). Despite the lack of concrete evidence, drug allergy is probably responsible for many instances of hepatic disease. For example, sulfonamides, *p*-aminosalicylic acid, chlorpromazine, organic arsenicals, oxyphenisatin, methyldopa and halothane produce hepatic injury under circumstances which suggest that drug allergy plays an important role (*5*). Other drugs, however, produce hepatic injury in an equally small proportion of exposed individuals, but unaccompanied by clinical features that suggest drug allergy (*4,5*).

Even agents which appear to satisfy the criteria for hypersensitivity warrant closer scrutiny. While chlorpromazine, erythromycin estolate and triacetyloleandomycin produce clinically apparent hepatic injury in approximately 1% of recipients, the incidunce of hepatic dysfunction has been observed to be much higher (40–50%) (*4,5*). These figures are too high to permit the assumption of hypersensitivity alone as the mechanism for the hepatic abnormality. Furthermore, some agents (e.g., penicillin) which produce overt generalized hypersensitivity, rarely produce hepatic injury (*5*). These observations have led to the hypothesis that some agents have a mildly adverse effect on the liver, which, when accompanied by hypersensitivity, may be expressed a overt liver disease (*5,19*). Support for this hypothesis has derived from studies utilizing suspensions of Chang liver cells maintained in tissue culture, suspensions of rat hepatocytes and the perfused rat liver (*20–24*). These studies have demonstrated a correlation between the adverse effects on these *in vitro* models of several phenothiazines (*20–22*) and several erythromycin derivatives (*23,24*), and the potential of these agents to cause hepatic injury in patients.

Metabolic Abnormality

A number of drugs produce hepatic injury in a small proportion of exposed individuals, under conditions that do not conform to the criteria for hypersensitivity as the mechanism (*4,5,19*). These reactions are characterized by a variable latent period rather than a fixed period of sensitization, no accompying rash, fever, or eosinophilia, no eosinophilic or granulomatous inflammatory response in the liver, and failure to reproduce the hepatic injury with a single challenge dose of the drug. To produce the hepatic injury caused by these agents seems to require readministration of the drug for a period of days or weeks. The possibility has already been cited that this form of hepatic injury results from a metabolic abnormality that permits very high levels of the drug or the accumulation of hepatotoxic metabolites. Evidence to support this view, however, remains to be developed.

The hepatic injury that results from host idiosyncrasy to drugs may be cytotoxic, cholestatic or mixed (*4,5*). The mechanism by which host idiosyncrasy induces cytotoxic or cholestatic jaundice is unknown. A look at the phenomenon of the curious form of hepatic injury that has been observed after halothane anesthesia (*25*), provides a basis for fruitful speculation (*19*). The incidence of halothane-induced jaundice is very low. Most observers consider it to be the result of allergy to the agent. This view is supported by the occurrence of fever and eosinophilia in more that 50% of patients with apparent halothane-induced jaundice, and by the observation that previous exposure to halothane appears to predispose to hepatic injury form the anesthetic (*19*). Not all patients with jaundice, however, have collateral evidence of allergy after halothane exposure. Furthermore, the nature of the hepatic lesion observed in many fatal cases, centrizonal necrosis (*26*), is much like that produced by CCl_4 (*19*). The lesion produced by CCl_4 appears to be caused mainly by a metabolite (the free radical, $\cdot CCl_3$) (*27*). The centrizonal localization of CCl_4 necrosis has been attributed to the relative concentration in the centrizonal area of drug-metabolizing enzyme systems (*28*). Accordingly, the centrilobular necrosis observed in fatal cases of halothane- and methoxyfluorane-induced jaundice, suggests that individuals whose metabolic aberration permits production or accumulation of hepatotoxic metabolites may develop, by a similar mechanism, the lesion which resembles that of CCl_4 (*19*). The metabolic aberration responsible

for the enhanced susceptibility might be genetic or acquired as the result of prior exposure to the agent or to other drugs and chemicals (*19*). Combined effects of generalized hypersensitivity and mild toxicity due to hepatotoxic metabolites might, in a manner similar to that proposed for other drugs, also be responsible for the hepatic injury of halothane (*19*).

This inference would suggest the hypothesis that the type of hepatic injury resulting from idiosyncratic metabolism of a drug depends on the nature of the hepatotoxic metabolite (*19*). If it injured, in a manner analogous to that of CCl_4, the membranes of intracytoplasmic organelles, it would produce lesions like those of the direct hepatotoxins. If the metabolite resembled the mediators of cytotoxic or cholestatic indirect hepatotoxins, the respective lesions might be expected. It may also be speculated that the form of hepatic injury produced as a manifestation of drug allergy might depend on tissue antibodies in the respectively injured cell type, or on localization to the respective cell type of tissue-damaging antigen antibody complexes or cytolytic factors from stimulated lymphocytes. Evidence for these speculations remains wanting.

Analysis of Hepatotoxic Reactions Induced by Drugs According to Clinical Circumstances of Exposure

Some of the many drugs which can produce hepatic injury are listed in Table 3, according to category of clinical use. Table 3 indicates the type of injury produced and the apparent mechanism of toxicity. For some drugs, there is sufficient information to describe the type of hepatic injury with some confidence. For the drugs designated as indirect toxins, there is reasonable experimental basis to support this mechanism of injury. For most drugs, the mechanism remains largely speculative and no distinction has been made in the Table between apparent hypersensitivity or metabolic abnormality as the basis for idiosyncrasy.

Despite the difficulties in assembling reliable data on drug-induced hepatic injury, a number of general relationships between the category of pharmacological effect and the apparent mechanism and form of hepatic injury can be derived. As mentioned earlier, the hepatic injury owing to all the tranquilizing drugs is usually hepatocanalicular, and it appears, at least in part, to be induced by hypersensitivity, while almost all the antidepressants produce hepatocellular injury as a result of host idiosyncrasy, not necessarily of the drug allergy type. The hydrazine derivatives used in the treatment of tuberculosis produce hepatic injury, similar to that of the chemically related antidepressants (*5*). Diphenylhydantoin and other anticonvulsant drugs generally produce hepatocellular or mixed-hepatocellular injury apparently induced by hypersensitivity. The C-17 alkylated steroids usually produce canalicular jaundice ("bland cholestasis") as indirect hepatotoxicity. The patterns of injury are less consistent for the oral antidiabetic drugs, the antithyroid drugs and sulfonamide derivatives.

These observations of the similarity of the hepatic injury produced by different members of a class of therapeutic agents pose an intriguing question. Is the mechanism for, and type of toxic effect on the liver related to the mechanism for the intended therapeutic effect on other organs?

Serum Enzyme Measurement in Experimental Hepatotoxicity

Serum enzymology and experimental hepatotoxicity have had an intimate relationship. Development of clinically or experimentally useful enzyme tests for the recognition of hepatic disease [e.g., glutamate-oxaloacetate transaminase (aspartate aminotransferase; GOT), ornithine carbamyl transferase (OCT), sorbitol dehydrogenase (SDH), arginase, guanase, isocitrate dehydrogenase (ICDH)]has depended on the study of the effects of experimental hepatotoxic states on serum levels of the enzyme. For this, known hepatotoxins, e.g. carbon tetrachloride, employed under standardized conditions, have been used.

Measurement of serum enzyme activities has provided a powerful tool for studies of hepatotoxicity. It has been employed in testing for toxicity of agents whose effects are unknown and in studying the circumstances and factors which influence the effects of known hepatotoxins. Study of factors that enhance (e.g., phenobarbital pretreatment) or depress (e.g., inhibition of metabolism) CCl_4 toxicity has been critically aided by monitoring the extent of injury with serum enzyme assay. Moreover, demonstration of the promptness of injury is facilitated by serum enzyme measurement [GOT, glutamate pyruvate transaminase (alanine aminotransferase, GPT), ICD, OCT, SDH], as is identification of organelle injury, by measuring serum levels of enzymes

Table 3. Mechanism of types of hepatic injury produced by drugs in various therapeutic categories.

Type of agent	Pattern of injury		
	Hepatocellular or mixed hepatocellular	Hepatocanalicular or mixed hepatocanalicular	Canalicular
General anesthetics	Chloroform[a] Trichlorethylene[a] Halothane Methoxyfluorane Fluoroxene		
Neuro-and psychotropic agents		Chlorpromazine and related phenothiazines	
Tranquilizers		Ectylurea Chloridiazepoxide Diazepam	
Antidepressants	Iproniazid and congeners Amytriptylene	Imipramine	
Anticonvulsants	Diphenylhydantoin Phenylacetylurea and congeners		
Drugs employed in rheumatic and musculoskeletal disease and as analgesics	Cinchophen Zoxazolamine Ibufenac Indomethacin Phenylbutazone Salicylates[b] Acetaminophen[c] Probenecid	Propoxyphene	
Drugs used in endocrine disease or as hormonal substitutes	Propylthiouracil Carbutamide Metahexamide Acetohexamide	Methimazole Thiouracil Chlorpropamide Tolbutamide	C-17 alkylated anabolic steroids[c] Contraceptive steroids[c] Estradiol[c]
Antimicrobial agent	Tetracycline and congeners[c] Chloramphenicol Triacetyloleandomycin[b] Penicillin Griseofulvin Paraminosalicylic acid Isoniazid Ethionamide Pyrazinamide Rifampicin Sulfonamides Sulfones	Erythromycin estolate Novobiocin[c] Rifampicin[c] Organic arsenicals Nitrofurantoin Idoxuridine Xenylamine	
Agents used in cardiovascular disease	Phenindione Procainamide Quinidine α-Methyldopa Nicotinic acid Papaverine	Ajmaline (?)*p*-Aminobenzylcaffeine hydrochloride	
Antineoplastic chemotherapeutic agents	Cause steatosis[c] Actinomycin D 4-Aminopyrazolo pyrimidine L-Asparaginase Azacytidine Azauridine Bleomycin Cycloheximide	4,4'-Diaminodiphenylamine Busulfan Azathioprine	

Table 3. Mechanism of types of hepatic injury produced by drugs in various therapeutic categories (Cont'd.).

Type of agent	Pattern of injury: Hepatocellular or mixed hepatocellular	Hepatocanalicular or mixed hepatocanalicular	Canalicular
Antineoplastic chemotherapeutic agents (Cont'd.)	Cause steatosis Chromomycin Mitomycin N-Diazoacetylglycine hydrazide Puromycin Methotrexate (also causes cirrhosis) Cause necrosis Calvacin[c] Mithramycin[c] Urethane[c] Cyclophosphamide Chlorambucil 6-Mercaptopurine[c]		
Miscellaneous agents	Tannic acid[c] Trimethobenzamide Tripelennamine Oxyphenisatin Phenazopyridine	Carbamazepine	

[a] Direct hepatotoxin.
[b] Possibly indirect hepatotoxin.
[c] Indirect hepatotoxin.
All other agents apparently depend on host idiosyncrasy, either hypersensitivity or metabolic abnormality.

that arise in mitochondria [e.g. glutamate dehydrogenase(GDH), mitochondrial isoenzymes (GOT-II, MDH($_M$)], endoplasmic reticulum [e.g., liver monoesterase (LME), glucose-6-phosphatase (G-6-Pase)] and, conceivably, lysosomes.

Employment of serum enzymes as markers of hepatic injury requires awareness of the relative specificity of an enzyme test as a reflection of hepatic disease (Table 4) and knowledge of the mechanisms that can lead to altered enzyme levels in the serum (Table 5) and of the relationship between known hepatotoxic states and elevated enzyme levels.

Table 4. Groups of serum enzymes according to their levels in experimental or clinical hepatic disease.

Group	Enzymes[a]	Obstructive jaundice and intrahepatic cholestasis	Acute necrosis	Chronic diseases	Diseases of other organs[b]
I	AL PH, 5'N, LAP,GTP	Markedly increased	Increased	Increased	±
II A	GOT, MDH, LDH, ALD	Increased	Markedly increased	Increased	Increased
II B	GPT, ICDH, GDH	Increased	Markedly increased	Increased	Increased
II C	OCT, SDH, LDH$_5$, guanase, F-P-ALD, arginase	Increased	Markedly increased	Increased	±
III	CPK	Normal	Normal	Normal	Increased
IV	CHE	Normal	Decreased	Decreased	±

[a] AL PH = alkaline phosphatase; 5'N = 5' nucleotidase; LAP = leucine aminopeptidase; GTP = glutamyl transpeptidase; LDH, = isoenzyme of lactate dehydrogenase; CPK = creatnine phosphokinase; CHE = cholinesterase; MDK = maleate dehydrogenase; ALD = fructose diphosphate aldolase; GPT = glutamate pyruyate transaminase; ICPH = isocitrate transferase; SDH = sorbitol dehydrogenase; F-P-ALD = fructose monophosphate aldolase.
[b] I = insignificant or minimal change.

Table 5. Mechanisms for abnormal serum enzyme levels.

Increased levels
Increased release due to
Necrosis
Increased permeability without necrosis
Increased production and release
Decreased disposition
Decreased levels
Decreased production

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