Target Organ Toxicology Series

Toxicology of the Liver

Editors

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Foreword

The *Target Organ Toxicology* monographs have evolved from the need for periodic review of the methods used to assess chemically induced toxicity. In each monograph, experts focus upon the following areas of a particular organ system: (1) a review of the morphology, physiology, biochemistry, cellular biology, and developmental aspects of the system; (2) a description of the means routinely used to assess toxicity; (3) an evaluation of the feasibility of tests used in the assessment of hazards; (4) proposals for applying recent advances in the basic sciences to the development and validation of new test procedures; (5) a description of the incidence of chemically induced human disease; and (6) an assessment of the reliability of laboratory test data extrapolation to humans and of the methods currently used to estimate human risk.

Thus, these monographs should be useful to both students and professionals of toxicology. Each provides a concise description of organ toxicity, including an up-to-date review of the biological processes represented by the target organ, a summary of how chemicals perturb these processes and alter function, and a description of methods by which such toxicity is detected in laboratory animals and humans. Attention is also directed to the identification of probable toxic chemicals and the establishment of exposure standards which are both economically and scientifically feasible, while adequately protecting human health and the environment.

Robert L. Dixon
Editor-in-Chief

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We are indebted to the National Institute of Environmental Health Sciences, the Society of Toxicology, and the community of academic and federal scientists for the symposia upon which this set of monographs is based. The successful efforts of Joseph R. Borzelleca and Perry J. Gehring in initiating and coordinating the symposia are greatly appreciated.

Preface

Liver injury induced by chemicals has been recognized as a toxicologic problem for close to a century. It was recognized early that "liver injury" is not a single entity, that the lesion observed depends not only on the chemical substance involved and the site affected, but also on the period of exposure. Some forms of liver injury are reversible while others lead to permanent changes.

In the last 25 years, a great deal of scientific knowledge has been acquired regarding the various forms of liver injury. The feature that is most striking during this period is the truly multidisciplinary nature of the approaches utilized: the physiologic, biochemical, and ultrastructural characteristics of hepatotoxicity all have been pursued. In many instances, the advances are the result of collaborative efforts on the part of investigators of diverse scientific training.

The modern toxicologist must be aware of the evolution of knowledge in this area and this book attempts to present the current "state of the art" as comprehensively as possible within the limited confines of a single volume. This book is arranged in four sections. The first part deals with the morphologic and biochemical characteristics of different forms of liver injury. The second section describes some newer techniques that can be applied to the evaluation of hepatotoxicity. This is followed by a third section which concerns itself with newer concepts regarding biochemical events that are fundamental to an understanding of the toxic phenomenon. Finally, the last section deals with the perplexing problem of hepatocarcinogenesis, its detection, and its repercussions.

This book is written primarily for toxicologists who have a need to enlarge their knowledge of chemically induced hepatotoxicity. Scientists and graduate students in related disciplines should find this a valuable textbook of basic information that will also be useful for their general comprehension of the problems associated with this particular toxic response.

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Contents

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Chemical Hepatic Injury and its Detection

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Chemical injury to the liver has many facets. Those to be discussed in this chapter include the nature and sources of hepatotoxic agents, the circumstances of exposure to them, the nature of the injury, and the mechanism for the hepatotoxic effects. The methods most suitable for the detection of chemical injury depend on the nature of the injury and on the circumstances in which its presence is being determined.

NATURE OF HEPATOTOXICANTS

A large number of chemical and biological agents can induce hepatic injury (Table 1). Some hepatotoxicants are products of plants or fungal or bacterial metabolism. Some are minerals. Many are products, by-products, or wastes of the chemical or pharmaceutical industry (115,170).

All agents that can produce hepatic injury might be defined as hepatotoxicants. It is customary, however, to designate agents as either true or idiosyncrasy-dependent toxicants. Those that can damage the livers of most recipients among a variety of species are called *true*, (intrinsic, predictable) hepatotoxicants. Agents that produce hepatic injury only in unusually susceptible humans are designated as *idiosyncrasy*-dependent, (nonpredictable) toxicants (Table 2).

EXPOSURE TO HEPATOTOXIC AGENTS

Chemical hepatic injury is encountered in a variety of circumstances (Table 3). Some natural toxicants, such as the peptides of *Amanita phalloides*, the pyrrolizidine alkaloids, and the toxicant of the cycad nut are taken as food or as folk medicine, in ignorance of their toxicity (4,17,20,62,70,76,89,97,115,151,170). Others such as mycotoxins, are ingested because climatic conditions and cultural practices in some parts of the world favor their presence as unsuspected food contaminants (20,76,77,99,115,170).

Hepatotoxic chemicals also may be ingested as accidental contaminants of food. This phenomenon is illustrated by the epidemic of "Epping jaundice" in England caused by contamination of a large supply of flour with 4,4′-diaminodiphenyl-

TABLE 1. *Types of hepatotoxic agents*[a]

- Inorganic agents
  - Metals and metalloids
    - Antimony, arsenic, beryllium, bismuth, boron, cadmium, chromium, copper, iron, lead, manganese, mercury, gold, phosphorus, rare earths, selenium, tellurium, thallium
  - Hydrazine derivatives
  - Iodides
- Organic agents
  - Natural
    - Plant toxicants
      - Albitocin, cycasin, cytochalasin, icterogenin, indospicine, lantana, ngaione, nutmeg, pyrrolizidines, safrole, tannic acid
    - Mycotoxins
      - Aflatoxins, cyclochlorotine, ethanol, luteoskyrin, ochratoxins, rubratoxins, sterigmatocystins, griseofulvin, sporidesmin, tetracycline and other antibiotics
    - Bacterial toxicants
      - Exotoxins *(C. diphtheria, Cl. botulinus, Str. hemolyticus)*,
      - Endotoxins
      - Ethionine
  - Synthetic
    - Nonmedicinal
      - Azo compounds
      - Haloalkanes and haloolephins
      - Haloaromatic compounds
      - Nitroalkanes
      - Nitroaromatic compounds
      - Organic amines
      - Phenol and derivatives
      - Various other organic compounds
    - Medicinal agents
      - (Over 100 drugs used for treatment and diagnosis) (See Table 6)

[a]Agents listed in this table vary considerably in their potential for causing hepatic injury.

methane (72), and by the huge outbreak of hepatic disease and porphyria in Turkey, caused by the ingestion of wheat to which hexachlorobenzene had been added, as a fungistatic (138).

Domestic exposure to hepatotoxicants also may result from the accidental or suicidal inhalation or ingestion of known toxicants (e.g., CCl_4, elemental phosphorus, or copper salts) or of large overdoses of medicinal agents (e.g., acetaminophen, ferrous sulfate) (24,70,134,170). The chief means of exposure to a known hepatotoxicant in the Western world, is, of course, through the intake of excessive amounts of ethanol.

Hepatotoxic agents have been encountered in industrial operations (e.g., chlorinated hydrocarbons, nitroaromatic compounds, nitrosamines, inorganic arsenicals, vinyl chloride) (18,57,70,115,116,156,158,170). Agents with known hepatotoxic potential are now used with increased caution, and the improved industrial hygiene seems to have led to a reduced incidence of hepatic injury. Among the industrial

TABLE 2. *Features that distinguish intrinsic hepatotoxicants from those that produce hepatic injury as idiosyncratic reactions*

Basis for hepatic injury	Characteristics			
	Experimental reproducibility	Dose-dependence	Incidence in humans	Latent period
Intrinsic hepatotoxicity[a] (True, predictable hepatotoxic agents)	Yes[b]	Yes	High[c]	Often short and relatively uniform
Idiosyncratic reaction[a] (Nonpredictable hepatotoxic agents)	No[d]	No[d]	Low	Often long and quite variable

[a]Terms preferred by this author. Terms in parentheses are those of other authors.
[b]May apply only to some species.
[c]Depends on dose.
[d]When due to metabolic idiosyncrasy, may be reproducible experimentally in specially manipulated models as in studies by Mitchell et al. (96) with isoniazid, with some evidence for dose dependence.

TABLE 3. *Circumstances of exposure to hepatotoxic agents*

- Toxicological
  - Domestic
    - Accidental or suicidal exposure
    - Ingestion as folk medicine, food, or toxic contaminant of food
    - Exposure to toxic agent as form of drug abuse
    - "Autogenic" (synthesis in gastrointestinal tract of nitrosamines ethionine, lithocholate)
  - Occupational
    - Routine exposure to toxic agents
    - Accidental exposure
  - Environmental
    - Pollution, food or water, pesticides, industrial pollution
    - Pollution of atmosphere (hypothetical hepatotoxic hazard)
    - Natural hepatotoxicants
  - Experimental
- Pharmaceutical
  - Iatrogenic
  - Self-medication

by-products and wastes and pesticides that contaminate the environment there are known hepatotoxicants (115,170), although the magnitude of the hepatotoxic threat remains to be defined.

Hepatic injury due to medicinal agents is the facet of hepatotoxicity of most interest to clinicians. There are a large number of drugs that can produce liver damage as the result of a therapeutic misadventure or large overdoses (70,114,170).

Experimental hepatotoxicity is a facet of particular relevance to this volume and one of great importance to human and veterinary medicine (169). It provides models for the study of biochemical, physiological, pathological, pharmacological, and clinical phenomena. It permits studies of accidental and environmental toxicology

TABLE 4. *Morphologic types of toxic hepatic injury*

Type of injury	Agent[d] or comment
Parenchymal	
Acute	
Cytotoxic	
Necrosis[a]	
(1) Zonal	
i. Central	$CC1_4$, acetaminophen, halothane
ii. Mid	Ngaione, furosemide
iii. Peripheral	Allyl formate, albitocin, some drugs
(2) Massive	TNT, Some drugs
(3) Diffuse (panlobular)	Some drugs[c]
(4) Focal	Some drugs[c]
Degeneration (ballooning, acidophilic bodies)	Large number of agents
Steatosis	
(1) Microvesicular	Ethionine, tetracycline, phosphorus
(2) Macrovesicular	Ethanol, MTX
Cholestatic	
Hepatocanalicular ("pericholangitic")	CPZ, erythromycin estolate, organic arsenicals
Canalicular ("bland")	C-17 alkylated anabolic and contraceptive steroids
Chronic	
Cirrhosis	
Macronodular	CCl_4
Micronodular	CCl_4, AF
Congestive ("cardiac" type)	PA
Biliary	CPZ
Steatosis	Ethanol, MTX
Chronic necroinflammatory disease	See Table 11
Neoplasm	
Carcinoma	
(1) Hepatocellular	AFB_1, CCl_4, PA, azo dyes, DMN
(2) Cholangiocellular	Rare (thorotrast)
Adenoma	Anabolic and contraceptive steroids
Sarcoma	DMN (some species)
Angiosarcoma	Vinyl chloride, Thorotrast, inorganic arsenic
Vascular	
Hepatoportal sclerosis	
Venoocclusive disease	PA
Peliosis hepatis[b]	Anabolic and contraceptive steroids
Hepatic vein thrombosis	Contraceptive steroids

[a]Degenerative changes including acidophilic bodies, hyalinization, and ballooning precede necrosis.

[b]*Peliosis hepatis* (see text) may be produced as acute lesion by phalloidin or as chronic lesion by anabolic and contraceptive steroids.

[c]Small doses of toxic agents and drugs can lead to focal necrosis.

[d]TNT = Trinitrotoluene; CPZ = chlorpromazine; DMN = dimethylnitrosamine; PA = pyrrolizidine alkaloids; MTX = methotrexate; AF = aflatoxin.

and screening of individual chemicals and medical agents with potential hepatotoxic effects. Chemical hepatic injury is the foundation of experimental pathology, providing models of known hepatic lesions useful for teaching and study of their pathogenesis. Development of hepatologic diagnostic methods has leaned heavily

on experimental hepatotoxicology. Physiological and biochemical measures of liver disease and function are studied in animals with chemical hepatic injury, prior to using them as tests in humans.

TYPES OF CHEMICAL HEPATIC INJURY

Parenchymal Lesions

Acute

Acute toxic injury may be mainly *cytotoxic*, involving overt damage to hepatocytes; it may be *cholestatic*, involving arrested bile flow with little or no parenchymal injury; or it may be *mixed*, displaying prominent cytotoxic and cholestatic features (Table 4). There is some relationship between the type of hepatotoxicants and the form of injury. Most intrinsic toxicants produce mainly cytotoxic injury, and only a few produce injury that is mainly cholestatic (Table 5). Many of the drugs that produce hepatic damage in humans as idiosyncratic reactions produce mainly cholestatic injury. Others produce cytotoxic injury, and some produce the mixed pattern (Table 6).

Cytotoxic Injury

This includes degeneration, necrosis, and steatosis of hepatocytes. Degeneration may appear prior to, with, or instead of necrosis.

Necrosis may be zonal or diffuse (Fig. 1). Zonal necrosis is found most frequently in the central zone of the lobule, uncommonly in the peripheral zone, and rarely in the mid-zone. The zonality appears to be related to the mechanism of injury (170). The centrizonal necrosis induced by CCl_4 (145,146), bromobenzene (121), and acetaminophen (94,95) appears to be a consequence of the centrizonal concentration of the enzyme system responsible for the conversions of the agents to hepatotoxic metabolites. The necrosis in the peripheral zone produced by allyl formate has been attributed to the location in that zone of the enzyme system that converts the compound to its toxic metabolite (123). Midzonal necrosis produced by ngaione is attributable to the midzonal accumulation of its toxic metabolite (141).

The necrosis due to idiosyncrasy-dependent hepatic injury in most instances is not zonal. The lesion usually consists of diffuse degeneration with multiple small areas of necrosis, not unlike the lesion of viral hepatitis (170). When severe, diffuse injury may lead to widespread destruction (massive or submassive necrosis).

Steatosis can be produced by a large number of toxic agents (Table 5). Two main types can occur. Some agents (e.g., tetracycline) produce *microvesicular* steatosis; i.e., the fat droplets are small, there are many in each hepatocyte, and the nucleus remains in the center of the cell. Other substances (e.g., ethanol, methotrexate) lead to *macrovesicular* steatosis; i.e., there are individual large fat droplets within each cell which displace the nucleus to the periphery (58,137,170).

TABLE 5. *List of some agents that produce hepatic necrosis, steatosis or cholestasis in experimental animals*

	Site of necrosis[a]					
	CZ	MZ	PZ	M	Steatosis	Cholestasis
Acetamide	−	−	−	−	+	
Acetaminophen	+	−	−	−	−	
Aflatoxins	+	−	+	+	+	
Albitocin	−	−	+	−	−	
Allyl compounds	−	−	+	−	−	
α-Amanitin	+	−	−	−	+	
Aniline	−	−	−	+	−	
ANIT	(+)	(+)	(+)	−	−	+
Anthrapyrimidine	+	+	−	−	−	
Antimony	−	−	−	−	+	
Arsenic (inorg.)	+?	−	+	−	+	
Arsenicals (org.)	+	−	−	+	−	
L-asparaginase	−	−	−	−	+	
Azacytidine	−	−	−	−	+	
Azaserine	−	−	−	−	+	
Azauridine	−	−	−	−	+	
BAL[b]	−	−	−	−	+	
Barium salts	−	−	−	−	+	
Beryllium	−	+	−	−	−	
Bile acids	−	−	−	−	−	
Bleomycin	−	−	−	−	+	
Borates	−	−	−	−	+	
Botulinus toxin	+	−	−	−	−	
Bromobenzene	+	−	−	−	(+)	
Bromotrichloromethane	+	−	−	−	+	
Carbon disulfide	−	−	−	−	+	
CCl_4	+	−	−	−	+	
Chlorobenzenes	+	−	−	(+)?	(+)	
Chloroform	+	−	−	−	+	
Chloroprene	+	−	−	−	+	
Chlorinated biphenyls	(+)	−	−	+	+	
Chloronaphthalenes	(+)	−	−	+	+	
Chloropropane	+	−	−	−	+	
Chromates	−	−	−	−	+	
Cytochalasin B	−	−	−	−	−	+
4,4′-diaminodiphenylmethane	−	−	−	−	−	+
4,4′-diaminodiphenylamine	−	−	−	−	−	+
Dichloroethylene	−	−	−	−	+	
Dichloropropane	+	−	−	−	+	
Dimethylhydrazine	−	−	−	−	+	
Dioxane	+	−	−	−	−	
Dioxins	+	−	−	(+)	−	
DDT	+	−	−	−	+	
Diphtheria toxin	+	−	−	−	−	
Dimethylnitrosamine	+	−	−	−	+	
Dinitrobenzene	+	−	−	−	+	
Dinitrophenol	−	−	−	(+)	+	+
Dinitrotoluene	−	−	−	(+)	+	
Divinyl ether	+	−	−	−	−	
Ferrous sulfate	−	−	+	−	−	

	Site of necrosis[a]					
	CZ	MZ	PZ	M	Steatosis	Cholestasis
Flavaspidic acid	–	–	–	–	–	+[c]
Flectol H	–	–	–	–	+	
Fluoracetate	+	–	–	–	–	
Furosemide	–	+	–	–	–	
Galactosamine	–	–	–	Dif	(+)	
Hydrazine	–	–	–	–	+	
Hypoglycin	–	–	–	–	+	
Icterogenin	–	–	–	–	–	+
Iodobenzene	+	–	–	+	(+)	
Iodoform	+	–	–	–	–	
Islandicin	+	–	–	–	+	
Lithocholate	–	–	–	–	–	+
Luteoskyrin	+	–	–	–	+	
Manganese compounds	–	–	+	–	–	+
Methyl bromide	–	–	–	–	+	
Methyl chloride	–	–	–	–	+	
Methylchloroform	+	–	–	–	+	
Methylene chloride	(+)	–	–	(+)	(+)	
Naphthalene	+	–	–	–	+	
Ngaione	–	+	–	–	–	
Paraquat	+	+	–	–	–	
Phalloidin	+	–	–	–	–	
Phosphorus	–	–	+	–	+	
P. vulgaris endotoxin	–	–	+	–	–	
Pyridine	+	–	–	–	–	
Puromycin	–	–	–	–	+	
Pyrrolidizine alkaloids	+	–	–	–	(+)	
Rare earths	–	–	–	–	+	
Rubratoxin	+	–	–	–	–	
Safrole	–	–	–	–	+	
Selenium	–	–	–	+	–	
Sporidesmin	–	–	+	–	–	+
Steroids						
C-17 anabolic	–	–	–	–	–	+
Oral contraceptives	–	–	–	–	–	+
Synthalin	–	–	+	–	+	
Tannic acid	+	–	–	–	+	
Tetracycline	–	–	–	–	+	
Thallium compounds	–	–	–	–	+	
Thioacetamide	+	–	–	–	–	
TNT	(+)	–	–	+	(+)	
Toluenediamine	–	–	–	–	–	+
Uranium compounds	–	–	–	–	+	
Urethane	+	–	–	–	–	
Warfarin	–	–	–	–	+	
Xylidine	+	–	–	–	+	

[a]CZ = Central zone; MZ = midzone; PZ = peripheral zone; M = massive; Dif = diffuse.
[b]BAL = British anti-lewisite (Dimercaprol).
[c]Refers to impaired uptake by hepatocyte, rather than true cholestasis.

Necrosis and steatosis comprise the lesion produced by some agents (131) (Table 5). With some of these agents (e.g., CCl_4) the necrosis is more prominent, and with others (e.g., toxic mushrooms, elemental phosphorus), the steatosis stands out more.

Phospholipiodosis is a form of lipid accumulation that has been described (106,144) in patients taking 4,4′-diethylaminophexestrol as a coronary vasoculator and has been reproduced in experimental animals by administration of that and other amphiphilic compounds (82). The lesion consists of enlarged, foamy hepatocytes and Kupffer cells. The foaminess reflects lysosomes packed with phospholipids which have been trapped by the amphiphilic drugs (82).

Cholestatic Injury

Some agents lead to hepatic injury characterized mainly by arrested bile flow with little or no parenchymal damage (70,114,170). This is particularly true of some drugs (Table 6), but cholestasis-producing chemicals can also be found among natural hepatotoxicants, synthetic industrial compounds, and even among the secondary bile acids (Table 5). Putative or known physiologic lesions responsible for the cholestasis are listed in Table 7.

There are two types of drug-induced cholestasis. One type is accompanied by portal inflammation and by evident, although slight, hepatocyte injury. This type has been called *hepatocanalicular* or *cholangiolitic* cholestasis. The other, which is accompanied by little inflammation or hepatocyte injury, has been called *canalicular*, *steroid*, or bland cholestasis (170).

Chronic

A number of forms of chronic hepatic damage can result from continual or repeated injury due to prolonged exposure to hepatotoxic agents, or can be a sequel to an episode of acute injury (171). Several of these lesions are discussed below.

Fibrosis and Cirrhosis

Chronic or repeated hepatic injury leads to an increase in fibrous tissue. When the fibrosis, accompanied by nodular regeneration and parenchymal collapse and by the development of pseudolobules, leads to distortion of hepatic architecture, cirrhosis results. The cirrhosis may be a sequel to prolonged and repeated parenchymal injury, the result of subacute hepatic necrosis, or, rarely, may follow a single episode of necrosis. In general, a single bout of zonal necrosis in experimental animals (e.g., CCl_4 poisoning) even when extensive, is followed by complete histologic restitution in surviving animals (19). When given repeatedly to experimental animals at intervals too short to permit recovery from each dose, CCl_4 can lead to cirrhosis (19). Instances of cirrhosis in humans also have been attributed to occupational exposure to CCl_4 (57,70).