Handbuch der experimentellen Pharmakologie

Handbook of Experimental Pharmacology

Volume XVI

Experimental Production of Diseases

Part 5

LIVER

Springer-Verlag Berlin Heidelberg New York

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LIVER

With Contributions by

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With 60 Figures

Springer-Verlag Berlin Heidelberg New York 1976

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ISBN 3-540-07647-6 Springer-Verlag Berlin Heidelberg New York
ISBN 0-387-07647-6 Springer-Verlag New York Heidelberg Berlin

Library of Congress Cataloging in Publication Data. Main entry under title: Experimental production of diseases. (Handbook of experimental pharmacology: New series; v. 16/). Includes bibliographies and index. CONTENTS: pt. 3. Heart and circulation. – pt. 5. Liver. 1. Pathology, Experimental. I. Betz, Eberhard, 1926– II. Schmier, Johannes, 1922– III. Eichler, Oskar, 1898– IV. Series: Handbuch der experimentellen Pharmakologie: New series; v. 16/3, [etc.] [DNLM: 1. Cardiovascular diseases. 2. Pharmacology. QV34 H236 v. 16 pt. 3]. QP905.H3 vol. 16, pt. 3 615'.1'08s [616.07'07'24] 75-28458

Printed in Germany.

Typesetting, printing, and binding: Universitätsdruckerei H. Stürtz AG, Würzburg.

Handbuch der experimentellen Pharmakologie

Handbook of Experimental Pharmacology

Heffter-Heubner New Series

Vol. XVI/5

Springer-Verlag Berlin Heidelberg New York 1976

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Experimental Hepatotoxicity*

HYMAN J. ZIMMERMAN

With 13 Figures

The literature of experimental hepatotoxicity has become so enormous as to overwhelm the effort to summarize the current state of knowledge. Excellent reviews [126, 498, 472, 348, 342, 418, 325, 430, 190, 269, 240, 286, 517, 490, 432] that have been published during the past several decades have assisted the present effort considerably. This review includes a survey of the broad aspects of hepatotoxicity, categorization of types of hepatic injury and discussion of presumed mechanisms followed by a description of the details of the injury produced by a few specific agents. Reference made to hepatocarcinogenicity is restricted to its relationship to hepatotoxicity. The last section contains an analysis of the character of injury according to the source and chemical nature of the individual agents.

A. Introductory Considerations

Chemical hepatic injury includes a number of diverse phenomena. A huge number and variety of compounds have been identified as hepatotoxins of clinical or experimental relevance. Some are found in nature as mycotoxins or other toxic botanical products or as minerals [498, 472, 190, 269, 240, 286, 490, 638]. Others are products of the chemical or pharmaceutical industry, and several (nitrosamines [18], ethionine [140]) may conceivably be produced within the individual animal. They may be as simple as inorganic elements and compounds or as complex as heterocyclic, steroid and peptide [472, 638].

The spectrum of susceptibility to individual agents may extend from substances that injure the livers of almost all individuals in a variety of species to those that produce hepatic damage in uniquely susceptible humans [638]. The hepatic damage may involve mainly the hepatic parenchymal cells, cells of the excretory tree or both [638]. In the case of some hepatotoxic agents, vascular structures are the primary locus of injury [498]. Acute hepatic injury may be translated into chronic liver disease, expressed as cirrhosis or even as carcinoma [472].

A *hepatotoxin* might be defined as any chemical agent that can produce injury to the liver. The term, however, is usually employed to describe agents that are *predictably* toxic to the liver and not those (drugs) that produce hepatic injury unpredictably only in uniquely susceptible humans [472, 269].

* Supported in part by Veterans Administration Research Fund.

Studies of experimental hepatotoxicity necessarily focus on, or begin with, reference to the phenomena of human disease. Accordingly, a glance at the scope of human hepatotoxicity is relevant to the present discussion.

Some natural toxins, like the peptides of *Amanita phalloides* [610, 612], the pyrrolidizine alkaloids [498, 286, 352] and the toxin of the cycad nut [498] are encountered as environmental hazards that are ingested in ignorance of their toxicity or taken as folk medicine [498, 286, 352]. Others, e.g. mycotoxins, are encountered because of climatic conditions in some parts of the world that favor their presence as unsuspected contaminants of food [286].

Hepatotoxic agents that have been employed in industrial operations have proved to be, or are potentially, important sources of liver disease in humans [393, 394]. Most prominent have been the chlorinated hydrocarbons widely used as solvents [394]; although a large number of agents in this category are known. Recently the development of angiosarcoma of the liver, cirrhosis, and of noncirrhotic portal hypertension in workers exposed to vinyl chloride has focused the attention of clinical and experimental hepatotoxicologists on the toxicity of this compound [568].

Hepatotoxins encountered in domestic settings include not only the botanical and mycotoxins cited above, but also various chemical agents to which exposure occurs by inhalation or ingestion, as the result of carelessness or during suicidal attempts, or because of accidental contamination of food by toxic chemicals [280, 497]. Contamination of flour by the hepatotoxic chemical 4′,4-diaminodiphenylmethane recently led to a curious epidemic of jaundice in Epping, England [280]; and contamination of wheat with hexachlorabenzene (employed as a fungistatic) led to a severe outbreak of hepatic porphyria in Turkey several decades ago [497]. A unique form of hepatotoxicity has become a matter of at least theoretical concern in recent years. The demonstration that certain preserved fish may contain nitrosamines [483, 309], and that nitrosamines may be formed by intestinal bacteria in experimental animals which ingest food preserved with nitrites [18], has led to the concern with this possible mode of human exposure to the hepatotoxicity and hepatocarcinogenicity of dimethylnitrosamine [631]. (See Section on Dialkylnitrosamines.)

B. Historical Aspects

Hepatotoxicity has been the subject of experimental study for over 100 years. In 1866, NOTHNAGEL [389] first produced hepatic injury in dogs by the administration of chloroform, 18 years after the first deaths in patients anesthetized with that agent [81], and over two decades before a report (1889) [565] that showed "delayed" chloroform poisoning to include severe, acute liver disease. Studies by ROSENBAUM in 1882 [469] on the effects of inorganic phosphorous and arsenic on hepatic glycogen, and by ZIEGLER and OBOLONSKY in 1888 [637] on experimental arsenic poisoning, mark the only other contributions to experimental hepatotoxicity prior to the present century; although hepatic injury had been recognized in a fatal case of phosphorous poisoning as early as 1860 [198].

By the turn of the century, experimental hepatotoxicity began to be employed as a tool to study problems encountered in human or veterinary medicine. Between

1900 and 1910 systematic studies, conducted in Canada [406] and Australia [170], confirmed the etiologic role of plants of the Senecio and Heliotropum family in liver disease of grazing cattle and sheep [352]. At about the same time a series of thoughtful studies [581, 396, 547, 218, 604, 605, 606, 395] on the toxicity of $CHCl_3$ for experimental animals and on the role of dietary [395] and other modifying factors [218, 604, 605, 606] were undertaken. Some of these [218, 604, 605, 606, 395] reports are now among the classics of experimental hepatotoxicity. Interest in the experimental toxicity of the related compound, CCl_4 came only during the third decade of this century when the use of the agent as a vermifuge led to unexpected liver disease and death in humans [527, 360]. During the intervening half-century, CCl_4 has been subjected to an enormous number of studies [126, 472, 348, 430, 190, 269, 240, 432] as a model for the study of hepatic disease and as an experimental cause of necrosis.

By the end of the first quarter of the 20th century, a number of hepatotoxic agents had become clearly identified as the result of experience with disease in humans and domestic animals and of experimental observations [126, 638]. Experimental hepatotoxicity was at first descriptive in its thrust, defining the forms of injury that some chemical agents induce, demonstrating differential susceptibility of various species and attempting to define age, sex and dietary factors that modify susceptibility. The descriptive phase continued until the mid-forties. The fifth and sixth decades of this century, comprised an era of pathophysiologic approach to experimental toxicity. During the mid-fifties studies began to be directed at the subcellular and molecular basis for chemical hepatic unjury [430]. The unravelling of the enzyme mechanisms for the metabolism of foreign compounds and of the phenomenon of enhancement ("induction") of this mechanism during this period has clarified the mechanisms of hepatotoxicity [430, 432, 347, 146]. In turn experimental hepatotoxic states have been of value in the study of the enzymatic machinery of the endoplasmic reticulum [146].

Most attention by clinicans to chemical hepatic injury during the past 50 years has focused on the type induced by medicinal agents. From the midpoint of the 19th century until the fourth decade of this century, the recognized hepatotoxins included chloroform, carbon tetrachloride, inorganic phosphorous and arsenical compounds encountered accidentally or occupationally [126, 638] and some botanical hepatotoxins of interest to animal husbandry [352]. Iatrogenic hepatic injury was restricted to instances of hepatic necrosis after chloroform anesthesis or after ingestion of CCl_4 employed as a vermifuge, or of hepatic necrosis or cirrhosis induced by inorganic arsenicals [638]. Such agents were, accordingly, removed from clinical use. In 1923, the first report [633] of an instance of hepatic injury induced by a drug (cinchophen) apparently innocuous for most exposed individuals, appeared. By the mid-thirties several hundred cases had been reported [398]; and the development of hepatic disease as the result of unique susceptibility to a drug was recognized [638]. During the intervening half-century many others drugs have been incriminated in the production of liver damage [418, 269, 639]. Relatively few of these have been found to be toxic for experimental animals and the mechanism of injury has been the subject of inference, speculation and hypothesis [638]. Nevertheless, some drugs that are not ordinarily considered hepatotoxic for experimental animals can be shown to produce injury in experimental settings [638, 368].