Drug-Induced Disorders Vol. 1
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A comprehensive survey of the literature on adverse drug reactions up to January 1985

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Volume 2: The Elderly
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FOREWORD

If any apology be needed for devoting this first monograph on 'Drug–Induced Disorders' to the liver, then it must surely start from the fact that the liver is and remains a fundamental, fascinating mystery, for the toxicologist and the physician no less than for the layman. Its very name is in many a language tied to that of life itself, but without a full understanding of the role which it actually plays in sustaining that life or its involvement in disease. *'Meum fervens difficili bile tumet jecur'* ('My liver is in a tumult, burning not to be restrained'), wrote Horace, viewing the liver as the seat of the passions (1). The Dutchman who has 'something on his liver' merely has a problem which he needs to discuss. For the ancients, the state of the liver of a slaughtered animal served as an omen, and for centuries after that the human liver was reputed to be the seat of courage. Much of these beliefs persists somewhere in the languages of Europe, mixed with metaphor and misunderstanding. The Frenchman who has 'les foies' is in a dilemma; but the Englishman who proclaims himself 'liverish' and hastens to take his daily dose of 'liver salts' is in all likelihood merely constipated by an indigestible diet.

As medical knowledge has advanced, the solution of one mystery surrounding hepatic structure and function has as a rule merely exposed several others, with the liver's enzymatic chemistry alone now filling entire volumes. The writer of an elementary handbook of physiology who once described the organ as a 'chemical factory of vast complexity' (and left it at that) put the matter in a nutshell in which some, in their bafflement, are only too content to leave it.

Because so little has been understood of the functions of the liver, there has been a corresponding lack of understanding of its dysfunction, despite a wealth of careful observation. 'In cases of jaundice,' wrote Hippocrates in the fifth century before Christ, 'it is a bad symptom when the liver becomes indurated' (2). Twenty–five centuries later with microscopy to hand, Friedrich Theodor von Frerichs (1819–1885) in his *Clinical Treatise on Diseases of the Liver* was able to provide a detailed picture of the morbid changes in that organ in a wide range of disorders: '...the cirrhosis which occurs in syphilitic patients is often accompanied by amyloid degeneration of the spleen and kidneys, and sometimes of the liver and the mucous membranes of the intestines. The cachexia attains a high grade at an early period. In addition to this, the remains of syphilitic inflammation are found in the liver; the gland is divided into lobes by bands of areolar tissues penetrating more or less deeply into its sub-

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stance, whilst the cirrhotic induration is restricted to isolated masses... In cases where chronic inflammation, originating in the capsule or in the diaphragm, attacks the glandular substance, I have observed the portal vein or the hepatic vein implicated to a great extent, the glandular parenchyma at different places uniformly indurated, and the outer surface lobulated...' (3).

It is not entirely clear when the adverse effect of a drug on the liver was identified for the first time; it may well have been in a report by Bang who in 1774 first hinted at the possibility of a link between arsenic – then much in vogue both as a drug and a cosmetic – and chronic liver disease (4). In 1860 a case of severe fatty liver was ascribed to intoxication with phosphorus and a range of previously published cases was reviewed. Nevertheless, such observations remained incidental and they were hardly followed up. Though fatal chloroform poisoning was recognized in 1847, when Sir James Young Simpson published his classic description of its anesthetic properties (5), another half century was to pass before it was shown that in fact hepatic complications could occur. Many of the hepatotoxic effects of drugs in use in the first half of the twentieth century long remained unrecognized, though incidental discoveries continued to be made; in 1923, Worster–Drought first described idiosyncratic hepatic injury in a patient who had taken cinchophen (6), whilst the first cases of drug–induced intrahepatic cholestasis (involving arsphenamine) were reported in 1940 (7). On the other hand, oxyphenisatine was in use as a popular laxative for 4 decades and on a massive scale before a report from Reynolds and his colleagues in 1971 (8) provided a clue that its use could lead to chronic active hepatitis; by an odd quirk of circumstance, 'Carter's Little Liver Pills' – long based upon oxyphenisatine – thus finally came to merit their name, though perhaps not in the manner contemplated by their originators.

The detection of such problems remains almost as problematical as it ever was. In the early 1960s there was much reason to think that reports of hepatic dysfunction were heralding the untimely end of the oral contraceptives, but the dimensions of the problem proved – perhaps fortunately – to be less than was first supposed. By contrast, the lamentable history of benoxaprofen (9) serves as a reminder that even with current methods of drug regulation and adverse reaction monitoring we are not capable of predicting even serious liver damage in subpopulations, detecting it rapidly enough when it occurs, or even agreeing after the event on what has actually happened. There is no reasonable doubt that the community is going to be faced with analogous problems again and again, particularly where special risk groups or interactions are concerned.

The widespread and largely unrecorded use of herbal preparations, often alongside prescribed medicines, introduces a new element of risk which it proves extraordinarily difficult to measure or define; certainly the plant world is a rich source of hepatotoxins, some of which have found their way into the herbalist's shop; a number of such preparations

have also been found to contain inorganic arsenic and mercury, thus reintroducing two ancient problems which orthodox medicine wisely set aside long ago. In a community in which the understandable desire for freedom in self-treatment and self-indulgence inevitably involves risks which escape any form of organized surveillance, one will have to be prepared for unpleasant surprises from time to time. Just as we still know too little about the hepatotoxicity of many traditional remedies and mixtures thereof, so we are largely in the dark as to the extent to which these may render a liver more susceptible to damage by prescribed drugs. Precisely the same problem arises with respect to other hepatotoxic influences to which society chooses to expose itself, notably alcohol. The effects of various patterns of alcohol intake on the liver are extremely well known, but the pattern of alcohol intake – now an increasing social problem in both East and West – has changed drastically in the course of 20 years; the degree to which these sometimes delectable but inevitably noxious habits will accentuate or alter the hepatotoxicity of newer or older drugs is still a matter for debate and study.

Since the predictive value of animal experiments and short-term human studies in matters of safety is limited, there is now a trend to slow the further growth of pre-marketing regulatory requirements, laying greater weight on effective post-marketing surveillance for drug safety. What this in practice means is that after a drug has been released for sale, one will have to follow carefully the reactions to it in a large sample population as well as in various subpopulations. Particular attention will have to be bestowed on those possible risks suggested by animal or early human studies; in the case of possible hepatotoxicity one will also need to examine carefully all that happens in the very young, the very old, and patients with a history of prior liver disease or secondary risk factors.

We cannot ignore the fact that the nature of the risks to which the liver is exposed during drug treatment is changing, and that those risks may alter quite dramatically within the next decade. There was a time, not so very long ago, when virtually every drug in the pharmacopeia acted by virtue of the fact that it was a toxin, inhibiting one system or another and generally several at the same time. With the advent of antibiotics, substitution therapy and releasers we have in part escaped from that situation, but at the same time society has become less hesitant to tinker with much more subtle processes which it claims to understand. The difficulty is, of course, that we do not understand any of them fully. As we proceed to inhibit enzymes, manipulate genes and influence bodily processes in a host of other ingenious ways we are bound to create unpleasant surprises, and the liver is too involved in life processes to escape risk.

The watcher for adverse reactions is not by nature a pessimist or, yet the scaremonger who he is sometimes made out to be; whether he likes the description or not, he is really something of a guardian angel. Like Janus, he must look both backwards and forwards. The authors of *Drug-Induced Hepatic Injury* have looked backwards very carefully, re-eval-

uating what has been written before in this field, so as not to perpetuate mere myths and misinterpretations; but they are also very deliberately looking forwards, providing a tool with the help of which it should become simpler to record, disseminate and study more efficiently each new suspicion of drug–induced injury. In that way we may be enabled to distinguish facts from mere fears more effectively, to detect new forms of drug–induced injury earlier before irrevocable harm is done, and to create a rather more solid base of knowledge for the study of this field in the future.

M.N.G. DUKES

Oudaen, Breukelen, The Netherlands
August, 1984

(1) Horatius: *Odes, Book I, 13.* (2) Hippocrates: *Aphorisms, VI, 42.* (3) Von Frerichs (1858) *Klinik der Leberkrankheiten.* (4) Cited by Zimmerman (1978) *Hepatotoxicity.* Appleton–Century–Crofts, New York. (5) Simpson (1847) *Account of a New Anaesthetic Agent as a Substitute for Sulphuric Ether.* (6) Worster–Drought (1923) *Br. Med. J., 1,* 148. (7) Hanger et al (1940) *J. Am. Med. Assoc., 115,* 263. (8) Reynolds et al (1971) *N. Engl. J. Med., 285,* 813. (9) Dukes (Ed) (1984) In: *Side Effects of Drugs, Annual 8,* p xvii. Elsevier, Amsterdam.

INTRODUCTION

Reports of symptomatic drug–induced hepatic injury often concern idiosyncratic reactions experienced during treatment with therapeutic doses. These may occur at any place and tend to be published at random all over the world. Whereas large and well–designed clinical trials of new drugs – designed to determine their therapeutic effects – are most commonly performed in well–reputed clinics and find their way into prominent medical journals, subsequent reports of idiosyncratic reactions to these same drugs, however well–documented, often appear in secondary journals and inaccessible languages. Some are recorded but not published at all.

On a smaller scale, one of us (B.H.Ch.S.) experiences this problem in his daily work at the Netherlands Center for Monitoring of Adverse Reactions to Drugs. The first and clearest reports of hitherto unknown adverse reactions often originate from small rural hospitals, recalling the old saying that the finest pearls may be found in small and unspectacular shells.

Because of the unpredictability and rarity of many instances of drug–induced hepatic injury our knowledge must often be derived from a small number of well–documented case–histories. Any book on this subject therefore has to devote close attention to a relatively small collection of reports per drug and per group of drugs. In each of these instances, the presence or absence of a causal relationship will have to be carefully assessed, since the pattern is rarely so specific that other causes (e.g. viral hepatitis) can readily be ruled out.

Various iatrogenic epidemics, e.g. hepatic injury due to oxyphenisatine and more recently due to tienilic acid and benoxaprofen, clearly demonstrate that early detection of adverse reactions involving the liver is of the utmost importance. It is an ongoing process which will never cease in view of the continuing flow of new drugs and the increase in experience with those already in use. This book will therefore be updated regularly. It will include mostly published but, where necessary, also unpublished data; both types of data will naturally only be considered for inclusion if they are well–documented.

It is hoped that all those who find this book of value will assist the authors in collating new data by reporting to them cases of suspected drug–induced hepatic injury which may merit inclusion. Such reports should be as well–documented as possible, and we would suggest that they be submitted at the same time to the National Adverse Reaction Monitoring

Center in the physician's country of residence. A form of the type used for such reports – but in this instance including a number of specific entries for matters related to hepatic injury – is reproduced at the end of this volume. Reports submitted to the authors will be regarded as confidential unless and until the reporting physician agrees to the form in which it is to be included in this book. They should be addressed to:

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I. PATTERNS OF DRUG–INDUCED HEPATIC INJURY

Generally speaking, patterns of drug–induced hepatic injury are not very specific, showing characteristics identical to those of non–drug–related injury. However, there are important exceptions to this rule (see Section III: 'Diagnosis and Analysis of Drug–Induced Hepatic Injury').

A short description of known patterns is given below. It is based on the assumption that the reader is familiar with the indications and interpretation of diagnostic procedures. Table 1 gives an overview of the patterns.

Mild and transient elevation of serial liver enzyme levels without

TABLE 1 *Patterns of drug-induced hepatic injury*

Acute		
	Hepatocellular	A. Steatosis
		B.1. Degeneration
		2. Necrosis
		C. Granulomas
	Cholestatic	A. Puré cholestasis
		B. Cholestatic hepatitis
Chronic		
	Hepatocellular	A. Steatosis and fibrosis
		B. Lipid storage disease
		C. Chronic persistent/active hepatitis
		D. Cirrhosis
	Cholestatic	A. Chronic intrahepatic cholestasis
		B. Biliary cirrhosis
Vascular disorders		
	A.1. Veno-occlusive disease	
	2. Occlusion of large hepatic veins	
	B. Sinusoidal dilatation/peliosis hepatis	
	C. Hepatoportal sclerosis, perisinusoidal fibrosis	
Tumors		
	A. Hepatocellular adenoma	
	B. Hepatocellular carcinoma	
	C. Cholangiocarcinoma	
	D. Angiosarcoma	

symptoms and histological signs of injury is not uncommon after starting drug therapy. It is uncertain whether this reflects minimal injury to the hepatocyte or enzyme leakage without injury. Although usually without clinical significance, a follow-up in such cases is advised since it may precede symptomatic hepatic injury in a number of patients.

ACUTE

HEPATOCELLULAR

A. Steatosis (e.g. methotrexate, tetracycline, alcohol, valproic acid etc.)

Fatty change of hepatocytes involves either small droplets without displacement of the nucleus (microvesicular, e.g. tetracycline, valproic acid) or large globules displacing the nucleus to the cell border (macrovesicular, e.g. methotrexate). Inflammatory cells are often scanty but may be present when necrosis coexists. Steatosis may predominate in the centrilobular (e.g. alcohol) or periportal (e.g. ethionine) region. Sometimes fatty cells coalesce to form fatty cysts, resulting in lipogranulomas.

Biochemical alterations depend on the degree of steatosis and (if present) necrosis. Aminotransferase and alkaline phosphatase levels may be normal but are mildly/moderately raised in most cases of acute toxic steatosis. Hypolipemia and hypocholesterolemia are present. Acute steatosis may present with acute hepatic failure (coagulation disorders etc.).

Symptoms may show the same spectrum of severity as in necrosis (see below). Immunoallergic manifestations are absent. Acute steatosis may have a rapidly fatal course (e.g. tetracycline).

B.1. Degeneration (e.g. many hepatotoxic drugs in low doses)

Hepatocellular unrest is seen with bi/trinucleation, mitotic figures, ballooning and acidophilic bodies; there is minimal infiltration, mainly by mononuclear cells.

Mild elevation of liver enzymes (ALAT/ASAT, alkaline phosphatase etc.) may occur.

Clinical symptoms are usually absent; sometimes there are vague, non-specific complaints.

B.2. Necrosis (many drugs, e.g. paracetamol, methyldopa, halothane, isoniazide etc.)

Necrosis varies in severity (focal/massive) and pathogenesis (toxic/idiosyncratic) determined by type of drug, status/localization of metabolizing enzymes and individual susceptibility. Necrosis is mainly zonal, but rarely massive in the toxic form. In the idiosyncratic form, necrosis is

diffuse (immunoallergy?) or zonal (metabolic variant?). Necrosis may also vary in localization: although mostly centrilobular (Zone III, Rappaport; e.g. paracetamol), necrosis may predominate in the midzonal (furosemide overdose, rats) or periportal region (e.g. $FeSO_4$). Severe necrosis may cause bridging (central–central/central–portal/portal–portal) often with collapse of the reticular framework. Massive necrosis is caused mainly by idiosyncrasy, not toxicity. In immunoallergic hepatitis, necrotic sites and portal areas are infiltrated by mononuclear cells, which sometimes have a granulomatous appearance. Toxic injury may give a less densely, more neutrophilic infiltrate. Although eosinophilic infiltration is not highly specific, it is often associated with an immunoallergic pathogenesis. Necrosis around the central vein may result from severe hypotension or congestive heart failure, in the latter accompanied by edema, extravasation of blood and dilated sinusoids.

The extent of necrosis is usually paralleled by an equivalent rise in serum aminotransferase levels, although a sudden decline indicates hepatic failure when accompanied by a sharp rise in serum bilirubin and prolongation of the prothrombin time. Alkaline phosphatase and bilirubin levels in serum are less markedly elevated. Hypoprothrombinemia is frequent. Many other liver enzymes are elevated (e.g. γ–glutamyl transferase, 5–nucleotidase etc.). No markers of viral hepatitis are present. Eosinophilia in the blood may indicate an immunoallergic pathogenesis. In intoxication, blood levels of drug/metabolites confirm a causal relationship.

Symptoms vary depending on severity and susceptibility. They may be absent, mild (malaise, anorexia etc.) or severe (jaundice, bruising). Extrahepatic manifestations may be prominent, both toxic (e.g. renal, CCl_4) and immunoallergic (rash, fever, arthralgia). The latter can also occur as prodromal signs of viral hepatitis, which should be excluded. Sometimes minor hepatic injury is secondary to extrahepatic drug–induced hypersensitivity reactions (e.g. Stevens–Johnson syndrome, myocarditis, pneumonitis). In some cases a picture arises resembling that of infectious mononucleosis with fever, rash, generalized lymphadenopathy and atypical lymphocytes. Mortality of acute hepatocellular necrosis is high. It depends on which drug is responsible and is estimated at 50% for some drugs.

C. Granulomas (e.g. allopurinol, phenylbutazone, sulfonamides)

Drug–induced granulomas usually appear within the first 4 months of therapy, either with mild cellular swelling/cholestasis or without accompanying hepatocellular injury. Occasionally liver injury is more severe. Drug–induced granulomatous hepatitis is often pericholangitic. Granulomas may appear in portal, lobular and pericentral areas invariably accompanied by portal inflammation with lymphocytes, histiocytes, plasma cells and eosinophils; the eosinophils may be very numerous.

Portal granulomas are usually discrete with a surrounding mononuc-

lear infiltrate but may also be part of a diffuse portal inflammation expanding into the lobules. Granulomas are always non–caseating, although occasionally there is central nuclear fragmentation. Giant–cell formation may be marked. Eosinophilic infiltration may be prominent, especially in the early phase. There are no biochemical abnormalities unless hepatic injury is present. The diagnosis can only be made by biopsy.

Granulomas are often non-symptomatic. However, as part of a generalized hypersensitivity reaction, immunoallergic signs and symptoms (e.g. rash, eosinophilia, fever, arthralgia) may be prominent. Disappearance after discontinuation of therapy suggests a drug–induced cause. It is advisable to exclude at least sarcoidosis and infectious causes (especially tuberculosis, schistosomiasis).

CHOLESTATIC

A. Pure cholestasis (e.g. anabolic steroids)

B. Cholestatic hepatitis (e.g. chlorpromazine, erythromycin)

Predominantly centrilobular bile–staining of hepatocytes and bile casts is seen in (sometimes distended) canaliculi. Bile 'lakes' as seen in extrahepatic obstructive jaundice are absent. It may occur without (pure cholestasis) or with minor/moderate hepatocellular unrest/necrosis (cholestatic hepatitis). In the former, inflammatory cells are virtually absent; in the latter there is a mononuclear and eosinophilic infiltrate, rich in the portal zones, moderate at necrotic sites; some bile duct multiplication is often present. A pattern exists characteristic of both acute cholestatic and hepatocellular hepatitis (mixed pattern).

Serum bilirubin, alkaline phosphatase, 5–nucleotidase and γ–glutamyl transferase levels are high while aminotransferase levels are normal or moderately elevated (the latter especially in cases of cholestatic hepatitis). Imaging procedures (e.g. ultrasound, cholegraphic imaging, computed tomography) show normal extrahepatic bile ducts.

Jaundice and pruritus are outstanding features. Cholestatic hepatitis may be accompanied by rash, fever and arthralgia, manifestations that are usually absent in pure cholestasis. Mortality is low (estimated at less than 1%) especially in cases of pure cholestasis. Occasionally, recovery from cholestasis takes a long time ($> {}^1/_2$ year).

CHRONIC

HEPATOCELLULAR

A. Steatosis and fibrosis (e.g. methotrexate, alcohol etc.)

The same pattern is seen as for acute steatosis. If however accompanied

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