Today's Treatment

Diseases of the alimentary system

Drug jaundice

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There may be no drug (or chemical) that is entirely free from the risk of causing liver damage, so central is the liver's role in the metabolism of foreign substances. The metabolic processes are diverse and complex, and disposal of a drug is not necessarily synonymous with detoxication, since in some cases—paracetamol, for example—a more toxic substance may be produced. Fortunately, however, the liver has considerable reserve, so that the risk of damage is dependent either on overwhelming doses of drugs (causing hepatic necrosis) or on a relatively uncommon individual hypersensitivity, which may be due to defective enzyme systems and is at present usually unpredictable.

Local environmental factors are also important. Blood flow to the liver, its oxygenation, the state of enzyme activity—for example, enzyme induction—and the competing claims of other substances, such as alcohol and steroid hormones, for metabolic pathways will all affect the response to a drug.

Drugs causing hepatitis or cholestasis or both

Hepatitis	Cholestasis
Monoamine oxidase inhibitors	Phenothiazines
Antidepressants	Benzodiazepines
Anaesthetic agents including halothane	Antihistamines†
Anticonvulsants	Oral hypoglycaemic agents
Barbiturates*	Diuretics†
Antituberculous drugs*	Antithyroid agents
Sulphonamides*	Nitrofurantoin
Anti-inflammatory drugs	Oestrogens
Appetite suppressants	Progestogens
Beta-blockers	
Methyl dopa*	

*May also cause cholestasis.

†May also cause hepatitis.

The detailed classification of drug damage can be found in standard texts. Since jaundice is the usual adverse reaction to drugs, I propose to concentrate on the two syndromes of hepatitis and cholestasis. Generally, the reaction to a particular drug is confined to one or other of these, but a few drugs may apparently cause both types of jaundice: these are indicated in the table, which lists only the better-known examples of drugs associated with jaundice. I shall also consider briefly the important question whether drug damage can lead to chronic liver disease.

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Hepatitis

The clinical picture of drug hepatitis mimics that of other types of hepatitis, though it is sometimes possible to recognise minor differences. The interval between prodromal symptoms and jaundice, and their prominence, is often less than in viral hepatitis, and features of hypersensitivity may be pronounced. Abdominal pain is sometimes particularly severe and is a bad prognostic sign. The course of the illness varies from a minor nuisance to death within a few days from acute hepatic necrosis.

The mechanism of drug hepatitis is unknown but is most likely to be caused by hypersensitivity. The similarity to viral hepatitis has led some people to the view that a latent virus is stimulated by the drug. Nevertheless, spread from person to person is unknown, second attacks have occurred on re-exposure, and the mortality from drug hepatitis (which may reach 30% in certain cases) is considerably higher than that of viral hepatitis. Moreover, jaundice may be predicted with chemically related compounds, as in the case of monoamine-oxidase inhibitors and anti-inflammatory drugs. None of these arguments is conclusive, however, and the answer must await isolation of the viruses or a specific test for drug sensitivity. The practice of monitoring the effect on the liver by measuring serum aminotransferase levels may be misleading since rises often occur at the beginning of treatment, possibly owing to enzyme induction. Once hepatitis is suspected the only safe course is to stop the drug and not to use it again.

Such a practice may lead to difficult problems in management as in the case of antituberculous agents, all of which, except streptomycin and possibly some of the newer drugs (though caution is essential with drugs that have not been in use for long), may cause jaundice. Intermittent use of a drug may increase the risk of hepatitis, an example being the jaundice that follows repeated exposure to halothane. This is not the place to discuss the halothane controversy, but, while most cases of postoperative jaundice in which halothane has been given can be explained on other grounds, there is a small residue in which no factor other than halothane can be implicated.

Most drug hepatitis is not dose-related. This is not so with paracetamol, which together with carbon tetrachloride and a few other poisons is a direct hepatotoxin causing acute necrosis. Doses above 15 g are invariably accompanied by liver cell damage, and in severe cases the kidneys, gastrointestinal tract, and brain may also be implicated, a feature of hepatic necrosis from whatever cause. Acute necrosis has also followed inhalation of solvents by glue sniffers.

Cholestasis

The second type of reaction resembles obstructive jaundice both clinically and biochemically. It is caused by intrahepatic

cholestasis and cannot be distinguished from mechanical obstruction, although severe pruritis is more likely to be caused by drug cholestasis.

Cholestatic jaundice is a hypersensitivity reaction, so its occurrence and frequency are unpredictable. It may occur after a few doses of a drug or after years of treatment; vanish or persist after stopping the drug; disappear while treatment continues; and does not always recur when the offending drug is given again. If jaundice occurs with one member of a group of drugs—for example, phenothiazines—it is likely with others. Once obstruction is complete it may take months for jaundice to subside, so that the diagnosis is questioned and operation may be undertaken, with disastrous results. In spite of the equivocal nature of drug cholestasis and its generally benign nature, the wisest course is to stop the drug and avoid its use in the future.

It is usual to distinguish two groups of cholestatic drugs. The first are those such as the phenothiazines in which histological changes are characterised not only by cholestasis but also by spotty “degenerative” changes in liver cells and portal tract infiltration, especially with eosinophils. The presence of liver cell damage may account for the fact that fatalities have occurred in this group. By contrast, the second group, in which bile stasis only is seen on liver biopsy, appear to be relatively benign. This so-called “steroid jaundice” was first recognised with methyl-testosterone and has since come to be associated with anabolic steroids and the pill. It is to some extent dose-related, and my impression is that its frequency has fallen considerably since the introduction of the “low dose” pill. There is, however, an element of hypersensitivity, since it occurs in families and in women who develop itching and jaundice during pregnancy. If jaundice is going to result from the pill it will do so during the first few

cycles. Possibly other cholestatic drugs should be avoided in such women: one of my patients developed an identical reaction to diazepam some years after pill jaundice.

Chronic liver disease

As already mentioned, some drugs produce a variety of liver damage. This is particularly true of methyldopa and the fact that it and other drugs—for example, oxyphenisatin—have been associated with chronic active hepatitis raises the important question whether drugs can cause cirrhosis. A few cases of biliary cirrhosis have followed the use of phenothiazines, and it has been suggested that primary biliary cirrhosis—a disease of unknown aetiology—might result from the habit among middle-aged women of taking rejuvenating medicines containing small amounts of testosterone. The pill can occasionally cause hepatic vein thrombosis, with severe abdominal pain; a tender, swollen liver; ascites; and the rapid development of portal hypertension, which if not quickly fatal results in cirrhosis. Hepatic fibrosis and cirrhosis sometimes follow methotrexate treatment of psoriasis and have been reported with other cytotoxic drugs in the treatment of malignant lymphoma.

All these are rather special and isolated examples. There is as yet no evidence that drug usage in general can lead to cirrhosis. Nevertheless, repeated doses of drugs known to be associated with liver damage over a long period could possibly lead to cirrhosis in a susceptible person, in much the same way that alcohol results in cirrhosis. A third of the patients in this country have cryptogenic cirrhosis of unknown cause, and a study of their drug-taking habits might be worthwhile.

Is there any satisfactory explanation for the curious symptom of seeing red intermittently that sometimes occurs after cataract extraction?

I do not know of any satisfactory explanation for the erythropsia that may occur sometimes, though intermittently, after a cataract extraction. In fact, most patients do if anything see more towards the blue end of the spectrum because the cataract has given a yellowing of light so that they tend to see the complementary colour after its removal.

As a member of the “coronary club” my trepidation when prescribing beta-blockers has increased on reading of acute coronary episodes after the sudden withdrawal of propranolol¹ yet the makers of one brand claim in their current advertising that treatment with propranolol reduces the risk of infarction. What does one do?

Propranolol and other beta-adrenergic blocking drugs can greatly reduce myocardial oxygen demand. These drugs may therefore regain a credit balance between myocardial oxygen supply and demand in patients with obstructive coronary artery disease. They achieve this by increasing cardiac efficiency in the true engineering sense and not through coronary dilatation. When exercise is carried out at a slower heart rate, with a lower blood pressure, and with a reduced velocity of ejection of blood from the left ventricle, an impaired coronary blood flow may be sufficient for the reduced need. Unfortunately, obstructive coronary disease is by its nature progressive and even with the help of a drug angina may reappear or become more limiting. In this case the sudden withdrawal of propranolol will almost inevitably induce an “overdraft” and precipitate severe angina at rest, infarction, or death. Such severe consequences of withdrawal of the oxygen-sparing effect of propranolol are to be anticipated in some patients. Treatment with beta-blockers probably reduces the risk of infarction, although this is difficult to prove. What does one do? Beta-blockers should not be stopped when angina gets worse and

should probably never be stopped abruptly. It is not essential to stop propranolol before such investigations as coronary angiography provided atropine is given in the premedication to avoid the increased risk of vagal bradycardia that can be hazardous. Similarly, it is not essential to stop beta-blockers before coronary artery surgery provided an adequate heart rate can be maintained, and it is now routine to install temporary pacing wires at the end of the operation. These wires are used in the early postoperative period to counteract unwanted bradycardia and are pulled out quite simply through the chest wall when they are no longer needed. Even in patients with damaged left ventricular function beta-blockers can be prescribed safely, provided the heart is supported with digitalis and diuretics. The development of angina at rest is a signal for bed rest and continuation of beta-blockers followed by coronary angiography as soon as the rest pain has subsided, as it usually does. Exacerbation of symptoms after sudden withdrawal of an effective drug is not a reason for not prescribing the drug. Rather it provides proof of the drug's efficacy. There is no evidence of a true rebound phenomenon after the withdrawal of beta-blockers: simply re-emergence of symptoms that had not arisen while the patient enjoyed their benefits.

¹ Canadian Medical Association Journal, 1976, 114, 1123.

Claude Bernard, in discussing the constancy of the body fluids, referred to the “milieu intérieur” (?) but in some books the quotation has become “milieu interne.” Is the latter a misrepresentation?

Claude Bernard used the word “intérieur” contrasting le milieu intérieur with le milieu extérieur. In *Leçons sur les Phénomènes de la Vie Communs aux Animaux et aux Végétaux* (Paris, J R Baillière et fils, 1878) he writes “le milieu liquide intérieur formé par le liquide organique circulant qui entoure et baigne tous les éléments anatomiques de tissus.” Both intérieur and interne can be translated as “internal,” interne usually being used in the context of illness or geometry. Bernard, however, preferred intérieur.