HEPATIC REACTIONS TO THERAPEUTIC AGENTS[1,2]

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Introduction

During the last decade, large numbers of new, potent, therapeutic agents have been introduced in all fields of medicine, especially in psychiatry and in the chemotherapy of infections. With these advances has come a tremendous increase in the number of cases of liver complications of treatment, so much so that almost the first question asked of the jaundiced patient concerns the nature of previous medication. The elucidation of these cases has proved difficult for various reasons. Many of the hepatic reactions do not affect animals and are not revealed by even the most extensive toxicity tests. The incidence of these reactions in man is often low, so that extensive clinical use of the drug may be necessary before hepatic complications become evident. Therapy is often multiple, especially of the tuberculous or of the psychotic. Often more than one potentially hepatotoxic drug has been given, so that it becomes impossible to pick out the drug at fault.

Many of the drug reactions mimic, in all respects, the picture of acute virus hepatitis. The agent of virus hepatitis has not yet been consistently cultured (1), and this disease cannot be diagnosed by any specific test. There is no susceptible animal for transmission experiments. It, therefore, proves impossible to be sure whether we are dealing with a sporadic virus hepatitis or a hepatitis which has been induced by therapy.

Many of the reported cases of drug toxicity are poorly detailed, and the type of reaction is difficult to determine. This applies particularly to the many cases where adequate histological detail of the liver is not given.

Jaundice may be classified in terms of the major site of involvement in the liver or extrahepatic bile duct (2). Drug reactions may be similarly divided into various categories: (*a*) pigment overload (haemolytic reactions); (*b*) disturbances of hepatic uptake of bilirubin; (*c*) disturbances of bilirubin conjugation; (*d*) competition for biliary excretion; (*e*) direct liver cell inujry; (*f*) hepatitis-like picture; (*g*) steroid-type cholestasis; (*h*) sensitivity-type cholestasis, and (*i*) general hypersensitivity reactions.

Pigment overload (*haemolytic reactions*).—Drugs rarely cause significant haemolytic jaundice. The liver has a great capacity to handle bile pigment, and, even if production reaches the maximum of some 1500 mg daily (six times normal), serum bilirubin levels rise only to about 2 to 3 mg per 100 ml.

[1] The survey of literature pertaining to this article was concluded July 1, 1964.

[2] The following abbreviations are used: BSP (bromsulphalein); DDT (1,1,1-trichloro-2,2-*bis*(*p*-chlorophenyl)ethane); INHA (isonicotinic acid hydrazide); PAS (*p*-aminosalicylic acid); SG-OT (serum glutamic oxaloacetic transaminase); and T_m (maximum hepatic clearance).

The usual example given, of haemolytic jaundice following drug administration, is phenylhydrazine which has a direct toxic effect on the erythrocyte and was formerly used for the treatment of polycythaemia. Various drugs are capable of initiating the formation of (drug-dependent) autoantibodies. A drug erythrocyte complex is thought to act as an antigen (3). This is usually part of a general hypersensitivity reaction. Such drugs include *p*-aminosalicylate, phenacetin, and quinine (4, 5).

Disturbances of hepatic uptake.—Disturbances of hepatic uptake are characterised, theoretically, by an increase in serum unconjugated bilirubin, by a retention of unconjugated bromsulphalein, and by no difficulty in the excretion of the conjugated substances. Examples of drugs causing such a reaction are male fern extract and the antifungal agent X5079C.

Male fern extract.—The active components of extract of male fern (dryopteris filix mas) consist of various phloroglucinol derivatives. Treatment with the extract readily produces a reversible increase of serum unconjugated bilirubin and also increased bromsulphalen (BSP) retention (6). In a few cases, the effect is sufficiently marked to result in jaundice and a marked and conspicuous decrease of the excretory function of the liver. Serum glutamic pyruvic transaminase and alkaline phosphatase values remain normal. Haemolysis has been excluded. Since all bilirubin and most BSP are excreted in the bile in a conjugated form, one might imagine a specific effect on conjugation. This is rather unlikely, for the conjugation mechanisms differ, bilirubin being conjugated with glucuronic acid and BSP with glutathione. The most probable explanation is that the uptake of pigments from the blood by the liver cells is transiently decreased. The effect was particularly great in a patient with constitutional hyperbilirubinaemia (Gilbert's disease), a condition where decreased uptake of bilirubin by the liver is postulated.

X 5079C.—This new antifungal agent is effective against systemic mycosis. The exact formula has not yet been determined, but it is known to be a polypeptide, pyrogen free, and soluble in water. Preliminary studies in man revealed an abrupt rise in BSP retention soon after the administration. Abnormal values persisted throughout treatment but fell promptly to normal when therapy was discontinued. Further observations were made in the dog and it was shown that the drug interferes with the uptake of BSP by the liver but does not inhibit the excretion of BSP conjugates into the bile (7, 8). Serum bilirubin. alkaline phosphatase, and serum glutamic oxaloacetic transaminase (SG-OT) values did not change.

Disturbances of bilirubin conjugation.—The best example of a drug which interferes with bilirubin conjugation is the antibiotic novobiocin. An increase in serum unconjugated bilirubin level may rarely follow its administration to the adult. It has, however, been held responsible for a threefold increase in the incidence of severe neonatal jaundice in infants (9), and an effect on bilirubin metabolism has been suggested (10). In rat liver broken-cell preparations, a direct effect of novobiocin on the enzyme glucuronyl transferase

has been demonstrated (11). The effect, therefore, seems to be mainly on the microsomes. To illustrate the complexity of the problem, novobiocin acts not only on conjugation but also on the excretion of bilirubin from the liver cell (12).

Competition for biliary excretion.—The cholecystographic agents are good examples of drugs having such an action. In 1961, Bolt, Dillon & Pollard (13) noted that the oral administration of the cholecystographic medium, bunamiodyl, resulted in mild hyperbilirubinaemia in the majority of patients to whom it was given. Bromsulphalein retention was also increased.

The effect is also produced by other iodinated cholecystographic agents such as iodopanoic acid (Telepaque) and iodipamide (Cholografin) (14). All of these substances can be shown to reduce the maximum hepatic clearance (Tm) of bilirubin in rats (14). This effect does not come from inhibition of uptake of bilirubin by the liver cells, for the livers of the animals receiving bunamiodyl contain more bilirubin than do controls. It seems unlikely to be only an effect on conjugation for, although iodopanoic acid and bunamiodyl are excreted as ether glucuronides, this does not apply to iodopamide. The effect is believed by Billing and co-workers to come from competition of iodopanoic acid and iodipamide with bilirubin for excretion by the liver cells. Other substances whose excretion is dependent on a rate-limited process will no doubt be shown to compete with bilirubin in the same way. The site of competition is unknown, but, as it is almost entirely unconjugated bilirubin that accumulates in the blood, it seems likely that it is in the microsomes and not in the bile canaliculus that the competition occurs. The block may be in the release of bilirubin from the microsomes.

The antibiotic rifamycin (a large molecule which is excreted in the bile at a concentration of 2000 times that of the plasma) may have a similar effect (15).

Direct Liver Cell Injury

Disturbance of hepatic function resulting from poisons acting directly on the liver has long been known and has proved to be a popular experimental tool for the investigation of liver injury. Hyperbilirubinaemia due to hemolysis, disturbances of uptake or conjugation, or competition for excretion does not result in clinical, biochemical, or histological evidence of liver damage. In the present group, hepatocellular necrosis, maximal centrizonally and without much inflammatory reaction is seen; fatty change is also usual. Electron microscopy of liver biopsies shows widespread changes in the cells which persist for several weeks after the intoxication (16). Hepatic metabolism seems to be generally affected, especially mitochondrial function, with diminution of energy production and disturbances of enzyme function, generally. Other organs are poisoned in company with the liver, the most prominent being the kidney and the brain. In fact, renal failure is the usual cause of death.

Carbon tetrachloride is known to alter mitochondria with destruction of the enzyme activity necessary for energy production in the cell (17). A

direct physical attack on the endoplasmic reticulum is suggested (18). A more indirect relationship between carbon tetrachloride and liver injury must be considered. Cervical cordotomy has been reported to protect rats dramatically from the typical hepatotoxicity produced by a single dose of carbon tetrachloride (19, 20). The carbon tetrachloride is said to exert its hepatotoxic effects indirectly via the sympathetic nervous system, resulting in an intense release of catecholamines (21). This catecholamine release causes vasoconstriction in the liver, localised reduction in hepatic blood flow, and anoxic changes. Such a hypothesis does not account for the effects observed with carbon tetrachloride in the isolated perfused rat liver (22). More recently it has been noted that the protection afforded by spinal cord transection at C7 was not complete (23). Further work suggests that the protection is related to the hypothermia resulting from the surgery (24). The lowered metabolic rate mollifies the hepatoxic effects of the carbon tetrachloride.

Antihistaminics can afford protection against this type of liver injury (25, 26).

Tetracyclines also have a direct toxic affect on the liver. Autoradiography shows that the liver and kidney concentrate and retain tetracycline to a greater degree than other organs (27). The tetracycline can be shown by fluorescent techniques to localise in mitochondria (28) and to have an adverse effect on enzyme systems in the liver (29, 30, 31).

When the tetracyclines were introduced, reports of hepatic changes following their use soon appeared. Increase in liver fat followed administration of 2 g oxytetracycline or chlortetracycline per day (32, 33). Fine fatty change in the liver has also been reported after tetracycline. Seven of 14 patients with serious infections were treated orally and intravenously with large doses of chlortetracycline and showed clinical evidence of liver abnormalities; at autopsy, three had fine cytoplasmic fatty change in the liver (34). It is difficult to be sure how much the changes were due to the antibiotic and how much to the underlying serious infection.

It does, however, seem probable that large doses of tetracycline do have deleterious effects on the liver; this is emphasized by a recent dramatic paper by Schultz and co-workers (35). Six patients, four pregnant and two postpartum, were treated for acute pyelonephritis with large doses (1.5 to 6 g intravenously; sometimes with oral therapy also) of tetracycline. Jaundice was noted on the third to fifth day. Deepening icterus, azotaemia, acidosis, and shock were followed by death five to 13 days after tetracycline therapy was begun. Autopsy showed fine droplets of fat involving all parts of the liver lobules. The renal tubules also showed fatty change. The hepatic and renal toxicity were clearly related to excessive doses of tetracycline. The usual therapeutic dose of tetracycline does not cause significant hepatic damage.

Tannic acid.—In 1942, Wells, Humphrey & Coll demonstrated that the liver necrosis often observed at autopsy in fatal burn cases was not due to

toxemia but to the absorption of tannic acid through burned skin surfaces (36). Animal experiments confirmed the injurious effect of tannic acid on the liver (37, 38). This treatment for burns has now been abandoned.

Tannic acid, however, is often added to barium sulphate enemata used for radiological examination of the colon to improve the definition of the mucosal pattern. It may also be used in the enemata for preparation of the barium examination (39). Tannic acid is known to be absorbed from the gastrointestinal tract (38) and can indeed be absorbed from the colon (39). It can thus exert a toxic effect on the liver.

In 1963, McAlister and co-workers (39) reported the deaths of three children from acute hepatic necrosis following enemata containing tannic acid in a concentration of 0.75 percent. In one case, a positive reaction with Nessler's reagent was obtained with unfixed liver. This test is not specific for tannic acid, although neither normal nor diseased human livers show a positive reaction in the absence of tannic acid. This report was followed by one from Canada of five cases of fulminating liver failure: in four of these, tannic acid was the sole potential hepatotoxin; in the fifth case, halothane anesthesia had also been administered (40). Symptoms of vomiting and abdominal pain appeared late in the same day or early the next morning after the enema. In the next 24 hr, irritability and drowsiness passed into a terminal phase of jaundice and coma. The patients survived for one to five days. Autopsies in four cases showed generalised haemorrhages and a marked centrizonal degeneration and necrosis. Peripheral cells of the lobules survived; the cellular reaction was minimal. The picture did not resemble that of acute virus hepatitis.

Many thousands of enemata containing tannic acid are given and the complication must be very rare. Nevertheless, its existence makes desirable the withdrawal of tannic acid-containing preparations from solutions used for barium-enema examination.

Chlorophenothane (DDT).—This popular insecticide, in large doses, is very toxic to the liver, causing fatty change and hepatocellular necrosis (41, 43). More chronic administration results in fatty inclusions in liver cells which disappear when stopping the drug. Cirrhosis is not a sequel.

The population of western countries consumes about 0.2 mg per day DDT as additives in food, particularly in butter (42). The quantity, however, is unlikely to have deleterious effects on the liver (44).

Other therapeutic agents.—In most instances, the therapeutic dose is well below the hepatotoxic one. Cytotoxic drugs may cause damage to the liver cells or else affect vascular changes in sinusoids and central hepatic veins. Urethane (45) rarely causes hepatic failure which may be related to an effect on capillary permeability in the liver. Prolonged treatment is said to cause centrizonal fibrosis with subsequent development of ascites (46). 6-Mercaptopurine has been reported to cause hepatitis, shown by nausea and an enlarged liver (47).

Accidental ingestion of large quantities of ferrous sulphate has been followed by hemorrhagic necrosis of the portal zones of the liver (48).

Hepatitis-Like Picture

This reaction is virtually indistinguishable clinically, biochemically, or histologically from ordinary acute virus hepatitis. Since there is no specific diagnostic test for this common virus infection and the agent has not yet been conclusively identified, the possibility of a coincident and unrelated virus hepatitis must always be considered. Activation of latent hepatitis virus by the drug has also been suggested by not proven.

Hydrazine drugs.—Iproniazid is a good example of a drug associated with a hepatitis-like picture. Orginally introduced in 1952 for the treatment of tuberculosis, this monoamine oxidase inhibitor was later used in the treatment of mental disorders, especially depression, and intractable angina pectoris. Soon, however, patients were reported to be developing acute hepatic necrosis while receiving the drug (49–53). The incidence is very low. The complication seems unrelated to total dose and may appear as late as 20 days after the cessation of therapy (51). It may be more frequent after a second course of treatment. The preicteric period of gastrointestinal symptoms, resembling those of acute hepatitis, is followed by jaundice associated with pale stools and dark urine and an enlarged tender liver. Biochemical tests indicate hepatocellular damage. In those patients who recover, maximum serum bilirubin levels are reached after 2 to 3 weeks. The most seriously affected show a shrinking liver and die of liver failure. The mortality may be as high as 20 percent.

Pathological changes in the liver are virtually indistinguishable from those of acute virus hepatitis. Electron microscopy shows damage to the endoplasmic reticulum, the part of the cell most concerned with protein synthesis and drug metabolism (54).

Other hydrazine-type monoamine oxidase inhibitors have been reported to cause a similar type of hepatic reaction. These include pheniprazine (55, 56), isocarboxazide (57), phenelzine (56), and phenoxypropazine. Monoamine oxidase inhibitors, such as trancyl promine, which are not hydrazines have not been incriminated. Other hydrazines, however, such as pyrazinamide (58), have caused this type of jaundice.

Isonicotinic acid hydrazide (*INHA*) must be considered in more detail. In dogs, long-term administration of INHA results in fatty change in the liver and jaundice (59). This effect, however, has not been confirmed in clinical trials in man when therapeutic doses are involved (60, 61, 62). Even when massive, suicidal amounts of the drug are taken, jaundice has been reported in only one case after an injection of 8.65 g (63). However, sporadic cases of icterus occurring during routine therapeutic use of the drug have been reported, the first in 1953 (64–67); the numbers are still small, compared with the enormous amount of INHA that is used; only nine cases have been reported up to 1962 (65).

The presenting picture is of a febrile reaction developing usually within

the first 4 wk starting treatment, but may develop within up to 7 wk (65). The dose is in the usual clinical range of 150 to 400 mg daily. Eosinophilia is seen occasionally. The few reports of the hepatic histology during the acute episode suggest an acute hepatitis-like reaction (67), and liver biopsies taken later in the illness are compatible with a healing virus hepatitis (65). Biochemical tests of liver function also suggest hepatocellular damage.

Eight of the 9 reported cases had evidence of hypersensitivity to the other major antituberculous drugs, seven being PAS (65). In each instance, the liver damage was proved to be due to the INHA. All except one case presented with one or usually two of the triad of fever, rash, and eosinophilia. These findings strongly suggest a hypersensitivity mechanism. Isoniazid is a hydrazine derivative and bears a close chemical similarity to iproniazid (1-isonicotynl-2-isopropylhydrazine), a drug which may cause a hepatitis-like reaction in the liver. On the other hand, the reaction to isoniazid is not marked by fever, rash, or eosinophilia, and associated drug hypersensitivity is not present (67).

In view of the small number of reported cases of INHA hepatotoxicity and the absence of knowledge concerning the mode of action of the hydrazines as a whole in causing liver damage, a definitive statement of the mechanism cannot be given at the present time.

Ethionamide (α-ethyl-thioisonicotamide) is a derivative of isonicotinic acid, used in the treatment of tuberculosis. At least nine cases of jaundice have been reported following its use (68–73). The icterus is presumably of hepatocellular type, for in one patient the serum glutamic oxaloacetic transaminase level exceeded 1000 units. The jaundice has recurred when the drug is given again (68).

In 1956, halothane was introduced into anesthetic practice and accepted enthusiastically. Originally, because of the similarity of halothane to chloroform, hepatotoxic effects were anticipated. Preliminary trials, however, showed that biochemical tests of liver function were not more frequently abnormal after halothane than after other anesthetics such as cyclopropane or ether (74, 75, 76). The first report of possible hepatotoxicity came in 1958 (77, 78) but the real spate of publications has been in 1963, following the publication, in January, of the paper of Brody & Sweet (79) and, in March, of papers by Lindenbaum & Leifer (80) and Bunker & Blumenfeld (81). In all, since the drug was introduced, 19 papers have reported hepatotoxic effects in 39 patients, in 17 of whom the condition was fatal (77–95). There are 14 other, unpublished cases, six of them fatal (96, 97). It does seem probable, therefore, that halothane is, on rare occasions, associated with hepatic damage.

By and large, the type of hepatotoxicity ascribed to halothane seems to be hepatitic. It is more frequent after multiple exposures, 28 of the 39 reported cases (72 percent) having received the drug more than once. Pyrexia develops after the anesthetic and is usually maximal at about 5 days. Sometimes it is associated with a rigor. The liver is tender. Jaundice develops usually 1 or 2 wk after the anesthetic but sometimes within only a

few days. The serum transaminase values are greatly elevated. After variable periods of excitement and vomiting, the patient either recovers or passes into coma and dies. Postnecrotic cirrhosis may be a sequel (98). The hepatic histology is indistinguishable from acute virus hepatitis, even to the extent of acidophil bodies; fatty change is not prominent. A good example is the patient reported by Tygstrup (90). In July, 1961, a 54-year-old woman was given halothane on three occasions, twice for carotid angiography and once for craniotomy. After the second anesthetic she became febrile, and seven days after the third anesthetic she developed jaundice. Liver biopsy showed a histological picture indistinguishable from virus hepatitis. In May, 1963, she was given halothane again for carotid angiography and craniotomy. Eight days later she again became jaundiced and a liver biopsy showed a picture of acute virus hepatitis. Tygstrup remarked that cases like this are probably the best obtainable approximation to a provocative test with halothane in man.

It has been suggested that halothane jaundice is particularly common after abdominal operations. In fact, only 14 of the 39 reported cases had had an abdominal exploration and in only 7 of these was the biliary tract explored. In the majority of patients, therefore, suppurative cholangitis or residual gall stones cannot be invoked as the cause of the jaundice. The report of Tygstrup (90), above, comes from Copenhagen. The complication has also been noted from Britain (86), Canada (93), France (83), Germany (99), and South Africa (82). It is certainly not, as Heidenberg and others (87) suggested, solely an American disease.

It is not possible to exclude with certainty coincident acute viral hepatitis as the cause of the liver damage. Virus hepatitis, however, is a disease of children and young people, whereas the patients with reported liver damage after halothane are mostly middle-aged or even elderly. Much will depend on whether the reports of possible hepatotoxicity after halothane multiply within the next few months, so making the association with the anesthetic more likely. A problem also exists in excluding other causes of postoperative jaundice such as incompatible blood transfusions, shock, and sepsis. Care must be taken that the halothane "witch hunt" does not lead to false accusations and wrong diagnosis.

The reported mortality of liver damage after halothane is high, 17 of 39 cases (44 percent) being fatal. This is almost certainly too high a figure due to poor reporting of milder cases and emphasis on the more dramatic, severe ones. The same difficulty arises in the case of virus hepatitis: the reported mortality is so high as to be unreasonable.

If the injurious effects of halothane on the liver are of the iproniazid type, they will depend on individual susceptibility. The dose of the anesthetic and the association with other drugs will probably be irrelevant. Morris & Feldman (101) showed that hepatic function after halothane was decreased, particularly if the anesthetic was combined with hypotension or especially with hypercapnia. The authors, however, have not studied a group in which other anesthetics were combined with hypotension or carbon dioxide reten-

tion. Hepatic histology was not available, except in one patient who showed focal necrosis which was not of the hepatitis-like type.

A possible lethal effect of halothane in combination with other therapeutic agents has also been suggested (101). Any effect of promazines seems unlikely, for the jaundice is not of cholestatic type. Possible effects of hepatic arterial constriction due to catecholamines used in combination with halothane have also been suggested. Such a combination might produce centrizonal necrosis but not the focal necrosis and inflammatory changes in the liver described in the reported cases of halothane toxicity.

Cohen and others (100) have isolated a halogenated euthane from commercially available halothane. The relative toxicity remains to be established, but it is acutely toxic to dogs when inhaled in anesthetic concentrations. The concentration of this contaminant is increased when halothane is refluxed in the presence of cooper. Here again, such a toxic material would be unlikely to cause the cellular infiltration and hepatitis-like picture described in association with halothane by so many authors.

Comparison of any possible halothane effect with that reported after chloroform is very difficult. Aspiration needle biopsy was not popular when chloroform was in its heyday. Hepatic histology from chloroform poisoning cases is said to show massive necrosis and fatty change, both of which can be largely post-mortem artefacts. It does, however, seem possible that chloroform can exert an injurious effect on the liver in at least two ways. The first is a direct hepatotoxic one with focal hepatic necrosis and ballooning of the hepatic cells. The hepatic lesions are virtually reproducible in animals by carbon tetrachloride or by chloroform, itself (102). In the more severe cases reported, particularly in obstetric patients who have been vomiting repeatedly, the hepatic necrosis is greater and predominantly centrizonal. Fatty change surrounds the zone of necrosis. Jaundice is inconspicuous.

The so-called delayed chloroform poisoning may be different. Jaundice appears on the second or third postoperative day and rapidly deepens. After delirium and occasional vomiting, tenderness in the liver supervenes, and death may occur on about the fifth day. Massive necrosis and fatty change are said to be gross (102). Gibberd (103), however, notes that the bright-yellow color of the liver may be due more to bilirubin than to fat. Wells (104) also noted that the fatty increase may be more apparent than real. Portal zones, in contrast to the change reported in suspected halothane cases, do not show cellularity but may contain proliferated bile ducts. By analogy with the halothane cases, the condition seems more frequent with multiple exposure to the chloroform. All of Gibberd's (103) three patients had had the anesthetic repeated. The condition is also described with only very small doses of chloroform (102). It is difficult, therefore, to make an exact analogy between the delayed chloroform poisoning as reported in the literature and the suspected hepatotoxic effect of halothane. If chloroform is being used again as an anesthetic, then investigation of patients so treated is indicated.

The relation between halothane and hepatic toxicity is still not certain; further reports may confirm the connection. Such cases must be described in

the fullest possible detail and include, if possible, details of hepatic histology obtained, if indicated, by needle biopsy of the liver. The association between hepatotoxicity and halothane must be extremely rare, certainly not frequent enough to merit abandoning the anesthetic at the present time.

More than one exposure to the agent should be avoided, particularly if the first one was followed by otherwise unexplained postoperative fever. There is no evidence that patients with underlying liver or biliary disease are more susceptible to ill effects from halothane (96, 105).

Approximately 20 million anesthetics with halothane have now been given, and, if the complication had been at all frequent, the number of reported cases would certainly have exceeded the 40 or so on record. This observation is, on the whole, borne out by statistical results. In a study at Notre Dame Hospital, Montreal, a survey of 50,000 anesthetics given since January, 1959, was made; at least 35,000 were with halothane and nitrous oxide (105). In only eleven patients had hepatic damage probably followed the anesthetic, 8 occurring after halothane. Seven died, 6 following uneventful halothane nitrous oxide anesthesia, the other following spinal anesthesia. The instance of hepatic deaths was about 1 in 8000 of uneventful anesthetics and about 1 in 3000 for halothane nitrous oxide. More surveys of this nature are needed, preferably on a larger scale and prospective rather than retrospective. This is now being done in various centers in the United States, and the results are awaited with much interest.

Cincophen was the drug originally associated with acute yellow atrophy. In retrospect, the reaction seems to have been a hepatitis-like one, analogous to that associated with the hydrazine drugs or with halothane. Other drugs which are not hydrazines but which are similarly incriminated include metahexamide (106) and zoxazolamine (107, 108).

Steroid-Type Cholestasis

Acute cholestatic drug jaundice of this type was first reported after methyltestosterone (109). The reaction does not involve sensitivity, and all persons receiving the drug develop bromsulphalein retention, if not frank jaundice, if given the drug for sufficiently long periods in sufficient quantities. The jaundice is usually mild and is rapidly reversible when the drug is stopped (110). Light microscopy of the liver shows only mild accumulation of bile in liver cells, canaliculi, and Kupffer cells. Electron microscopy shows variable changes in the microvilli of the canaliculi which may be blunt and sparse (111). These changes are not specific for this type of cholestasis.

The site of the block to bile excretion is unknown. As both bilirubin and bromsulphalein, substances which are conjugated differently, appear in the blood in the conjugated form, it is presumably postmicrosomal and associated with difficulties of transport from the liver cells into the bile. This is supported by the observation of a reduction in the maximum rate of secretion of conjugated bilirubin into the canulated bile ducts of Wistar and Gunn rats after norethandrolone, a similar cholestatic compound (112).

Steroids producing this reaction include methyltestosterone (109, 110),

norethandrolone (113–115), methandrostenolone (116–118), methylestrenolone (119), norethisterone (120), norethindrone (121), and norethynodrel (122). These are all C17 alkyl-substituted compounds of testosterone. This configuration was believed necessary for cholestatic action. However, methylandrostenolone (which lacks a C17 substitution) has also been shown to be cholestatic, and it seems that this is not essential (123). Oral activity of the compound, however does seem to be prerequisite.

Electron-microscopic screening of the potentially cholestatic drugs may be possible in animals. Changes have been described in the livers of rats receiving cholestatic drugs, including anabolic steroids. These include focal bile accumulations, canalicular dilatation with shortening and loss of microvilli, increase in vacuoles and of density in the Golgi zone, and increase in size and number of lysosomes (124). If more than one quarter of the bile canaliculae are altered, then cholestasis may be expected in man. Bromsulphalein tests in rabbits may also be useful for screening (125).

Sensitivity-Type Cholestasis

This type is particularly associated with drugs of the phenothiazine group, of which chloropromazine is a good example. The reaction is unrelated to dose; it can occur after only one 20 mg tablet (126). In 80 to 90 percent of the cases, the onset is in the first four weeks, and in 35 to 50 percent it is between the first and third week of treatment (126). The incidence is low, probably affecting less than 0.5 percent of those receiving the drug (127). If it is given again, the reaction recurs in about 40 percent; if it does not, then hyposensitization or desensitization is postulated (126). The reaction can include a rash, fever, eosinophilia (both blood and tissue), and blood dyscrasias. All these phenomena are hallmarks of a hypersensitivity reaction. The drug is believed to act as a haptene, and the antibodies are thought to remain attached to the tissue cells (128). Administration of the drug may cause an antigen antibody reaction of the surface of the cells to which the antibody is fixed, thereby producing injury within a specific organ—in this case, the liver.

The picture simulates surgical obstructive jaundice. Icterus lasts 1 to 4 wk and recovery is complete (129).

The liver under light microscopy shows cholestasis and, in the portal zones, a marked cellular reaction with mononuclear and eosinophils prominent. The hepatic reaction is not merely a cholestatic one. Even in the ordinary case of chlorpromazine jaundice, a certain amount of damage to liver cells can be noted. 'Feathery' degeneration of liver cells, local cell necrosis with cellular reaction, mild fatty change, anisocytosis, and mitoses are all noted. Ballooned liver cells, peripheral vacuolation, and hyaline deposits may also be seen (130). The damage to the liver is greater than that noted in simple mechanical biliary obstruction. Zelman (131) has also remarked on the liver cell necrosis occurring in chlorpromazine jaundice. Sometimes this is so severe that death occurs from hepatocellular failure (131–132). Electron microscopy also shows marked disturbances in the liver cell (133).

A general hypersensitivity reaction may, as we have seen, be associated. This group of sensitivity-type cholestatic reactions to drugs cannot, therefore, be easily distinguished from more obvious general hypersensitivity reactions, for instance, to sulphonamides or to para-amino salicylates.

Although the jaundice which complicates chlorpromazine therapy is usually mild and lasts a matter of days, occasionally it may become chronic. Myers and co-workers (134) described a patient in whom xanthomas developed as part of this syndrome. After 13 mo, the patient made a clinical recovery, and liver biopsy showed mainly portal fibrosis. Read, Harrison & Sherlock (130) found records of 17 other patients in whom chlorpromazine jaundice had lasted longer than 3 mo. Two developed skin xanthomas. Read et al. added four patients of their own, in whom the icterus lasted 7 to 36 months. The clinical picture was that of prolonged obstructive jaundice with steatorrhoea and weight loss. Three patients showed xanthomatosis. The biochemical changes included very high serum cholesterol and alkaline phosphatase values commencing early in the illness. The clinical picture may resemble that of primary biliary cirrhosis, but the onset is more acute and a history of receiving the offending drug can be elicited.

In contrast to primary biliary cirrhosis, which is inevitably fatal, clinical recovery ensued in all four patients. Elevated serum alkaline phosphatase and cholesterol levels remained for many months after the jaundice had cleared. The histologic picture in the liver resembles that of primary biliary cirrhosis only in the later stages, when clinical recovery is in progress. The portal-zone infiltration and evidence of liver cell damage are always less in chronic chlorpromazine jaundice than in primary biliary cirrhosis. Although some changes persisted in the liver after clinical recovery, progression to the histologic picture of biliary cirrhosis was not seen.

Two further patients have since been described by Norredam (135). One of these showed diffuse xanthomatosis and xanthomas of bone.

Other cholestatic drugs.—An essentially similar picture can complicate therapy with other phenothiazine derivatives such as promazine (136, 137) or prochlorperazine (138, 139), mepazine (140), or trifluoperazine (141).

Generalized Hypersensitivity Reactions

Such reactions are not uncommon during medication, particularly with penicillin or with sulphonamides. The liver must be involved in any generalized hypersensitivity reaction, but it is rare for this to be overt. The response may be predominantly cholestatic, or may be hepatocellular, or even mixed. It is difficult to classify these reactions. They tend to resemble the cholestatic (promazine) sensitivity type far more than the hepatitic (hydrazine) variety. The promazine reactions may include manifestations of general hypersensitivity, whereas the hydrazine variety never does.

Penicillin.—Hepatitis and jaundice have been reported in a 25-year-old woman who developed a hypersensitivity reaction following treatment with penicillin and streptomycin (142). The penicillin was probably responsible.

Symptoms included shock, pruritis, rash, lymphadenopathy, facial edema, fever, and malaise. The jaundice was of cholestatic type. A needle biopsy of the liver on the eighteenth day showed focal intralobular necrosis of hepatic cells with infiltration by histiocytes and polymorphonuclears. The sinusoids contained eosinophils and the portal zones showed an inflammatory reaction with mononuclears, eosinophils, and neutrophils. A second liver biopsy on the forty-fifth day showed a marked reduction in the inflammatory changes, but centers of unicellular necrosis persisted.

Other similar cases have been reported but in less detail (143, 145). In one interesting case, the reaction to penicillin was granulomatous, lesions being found in liver spleen and kidney (145).

Sulphonamide derivatives.—The liver may be involved in the hypersensitivity reaction. Acute massive hepatic necrosis has been associated with sulphonilamide (146). Sulphadiazine has been reported in association with diffuse hepatic necrosis and extensive fatty infiltration (147). The newer, longer-acting sulphonamide, sulfamethoxypyradazine, has been incriminated (148). The patient developed fever, rash, leukopenia, and signs of hepatic injury 4 days after the last dose of a 37-day course of the drug. Needle biopsy of the liver showed foci of hepatic cellular necrosis with acidophil bodies resembling those seen in acute viral hepatitis. A predominantly mononuclear exudate involved the portal tract, parenchyma and venous radicles. Kupffer cells were swollen and proliferated. Eight weeks later, further liver biopsy showed almost complete restitution to normal structure.

Histological changes in the liver were also noted (149) in a 78-year-old woman developing a hypersensitivity reaction to succinylsulphathiazole or to neomycin (probably the former). A similar histological change was seen in the liver. Fifteen days later, the patient died suddenly of focal interstitial myocarditis. There had been almost complete regression of the inflammatory process in the liver. The patient was not obviously jaundiced, and serum bilirubin levels and flocculation tests had been normal at the time of the liver biopsy.

Esters of macrolide antibiotics.—Esters of erythromycin and oleandomycin (the macrolide antibiotics) have been reported to have untoward effects on the liver.

Erythromycin estolate is the propinoyl erythromycin ester of lauryl sulphate and produces higher and more sustained blood levels than erythromycin base. In 1961, this ester was first reported to cause a cholestatic type of jaundice (150, 151). By 1963, 25 cases had been reported (150–157). Hypersensitivity has been invoked, for the patient may have multiple allergies; the complication is common after multiple exposure to the antiboitic; skin rashes may develop and a peripheral and tissue eosinophilia are frequent (151, 155, 157).

Liver biopsy shows portal zone cellularity, esinophils being prominent (151). Cholestasis and occasional necrosis of liver cells may be seen (157).

The jaundice seems not only to be cholestatic, but also is hepatocellular

as is evidenced by the biopsy findings of liver cell necrosis and the occasionally elevated serum transaminase values and positive seroflocculation tests (155, 157).

Triacetyl oleandomycin has been reported to cause jaundice, believed to be allergic (158, 159). This is supported by the finding in one patient of a fixed drug reaction commonly held to be allergic and the hallmark of drug sensitivity (160). Against the suggestion is the observation of Robinson (161) that an elevated serum glutamic pyruvic transaminase value is found in 10 percent of all patients receiving tricaetyl oleandomycin, and this is more than would be expected with allergy. In a more comprehensive study, more than 50 percent of 50 patients receiving a daily dose of 1 g triacetyl oleandomycin for 2 wk developed impaired bromsulphalein excretion (162). Thirty-six percent manifested elevated glutamic oxaloacetic transaminase levels, 8 percent elevated glutamic pyruvic transaminase level, 10 percent abnormal thymol turbidity tests, and 24 percent abnormal cephalin flocculation tests. These abnormalities were more marked 3 or 4 wk after beginning treatment, and in 2 patients jaundice had developed. In the nonjaundiced patients, the bromsulphalein, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase levels had returned to normal by 1 wk after withdrawal of the drug. The flocculation tests remained abnormal in some patients for as long as 5 wk after administration of the drug had stopped. Administration for 1 day resulted in a prompt rise in the serum oxaloacetic transaminase level in 3 of the 4 patients so tested. These results also cannot be ascribed to hypersensitivity; although the incidence of jaundice was less than 5 percent, which would be consistent with hypersensitivity, the incidence of hepatic dysfunction was considerably higher. For 50 percent of the population to be considered allergic to this drug would hardly be consistent with the usual criteria for hypersensitivity. The recurrence of hepatic dysfunction in 3 of 4 patients given a challenge dose would be consistent with hypersensitivity.

Doubt has also been cast that the reaction to triacetyl oleandomycin is predominantly cholestatic, One patient, recovered from a hepatic reaction with oleandomycin, was challenged with erythromycin estolate, and the serum glutamic pyruvic transaminase rose to 2060 units, suggesting a hepatio cellular type of jaundice (161). Results of other function tests suggest hepatocellular injury, and liver biopsy sections confirm mild cell damage (162).

The liver lesion complicating both erythromycin estolate and triacetyl oleandomycin therapy should be termed 'mixed', being both hepatocellular and cholestatic in type.

Gilbert (163) offers an interesting explanation of the mechanism. In their basic form, erythromycin and oleandomycin do not cause liver damage; they acquire this capacity only by esterification of their desosaline side chains, so haptenizing them.

Other drugs.—The hepatic reaction to *p*-aminosalicylates (PAS) may be predominantly a generalized hypersensitivity reaction. This is shown by a patient who reacted to isoniazid and *p*-aminosalicylates, probably the latter (164). The patient showed urticaria, lymphadenopathy, sweating fever, and,

in addition, myocardial infarction and orthochromic erythrocytes in the peripheral blood. The patient was not jaundiced, the cephalin cholesterol test was positive, serum alkaline phosphatase values were raised, and bromsulphalein retention was found. Needle biopsy of the liver showed infiltration of the portal tracts and sinusoids with mononuclear cells and eosinophils. Hepatic cells showed mild changes. A follow-up biopsy 2 mo later showed only slight round-cell infiltration and nuclear changes. Liver function tests were normal. Alternatively, the reaction to PAS may be predominantly hepatocellular or cholestatic without such an obvious hypersensitivity reaction (165, 166). Death may even occur in hepatic failure (167).

Other drugs associated with this reaction include phenindione (168) and nitrofurantoin (169).

Conclusions

No drug is completely safe. No therapeutic advance can be made without taking risks. Testing of drugs for hepatotoxic effects in animals is not a complete safeguard, for the hepatitic and cholestatic sensitivity reactions will not be revealed. These complications are infrequent and do not affect animals. Clinical trials may fail to reveal hepatotoxicity unless the reaction is particularly common. In most instances, only time with wide usage will tell. Any effective therapeutic agent has its drawbacks. When hepatotoxicity is suggested, certain questions must be asked and if possible answered (170). (*a*) How frequent is it? This involves a national system for recording the side effects of drugs and the cooperation of the clinician in notification. (*b*) How serious are they? Clearly the hepatitic reaction is graver than the steroid one; the hypersensitivity types are intermediate. (*c*) Is there a safe and equally effective alternative treatment, in which case the offending drug may be withdrawn?

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