which may be the reason that kernicterus does not occur in conjugated hyperbilirubinaemia.

**Cholestasis**

Cholestasis may be defined as stagnation of bile within the intrahepatic or extrahepatic biliary tree. Biochemically, there is retention of conjugated bilirubin, bile salts, and alkaline phosphatase; morphologically, there is at least dilatation of biliary canaliculi and loss of their microvilli, and later accumulation of bile pigment in the canaliculi (bile plugs). The mechanism underlying the canicular lesion is unknown, though a variety of hepatic diseases may cause it. Similar cholestasis has been produced by the administration of some bile salts, such as lithocholates, which are relatively insoluble and may precipitate in the canaliculi; hence qualitative changes in the metabolism of the bile acids could be important.

Bile can be secreted against a hydrostatic pressure, and is composed of at least two fractions, to which excreted molecules are added. The first, produced by the liver cells, closely follows the secretion of the bile salts; the second (which may be secreted by the smaller biliary passages), is produced independently of the bile salts, but its production is increased by the hormone secretin. The rates of excretion of bilirubin or bromsulphalein and other dyes are not constant, but increase as the volume of bile increases. Furthermore, drugs such as phenobarbitone which induce the synthesis of hepatic microsomal enzymes, also often increase the size of the liver, bile flow, and the biliary excretion of substances such as chlorothiazide and TCG which are not metabolized by hepatic enzymes. Conversely, drugs such as oestrogens and the fungal steroid icterogenin which produce cholestasis also decrease bile flow.

Many other steroid drugs, especially if their carbon atom 17 is substituted, produce cholestasis. A few women develop a similar jaundice while taking the contraceptive pill, and of the two components of the pill the oestrogen, rather than the progestogen, is probably the cause of this reaction—which is observed more commonly in Scandinavia and Chile than elsewhere. Some of these women also develop itching and cholestatic jaundice in the last trimester of successive pregnancies, when the high levels of oestrogen are probably the cause. Though the mechanism of this steroid cholestasis is unknown, in the rat oestrone may increase the permeability of the biliary tree to fluid and reduce the flow of bile.

**Classification of Jaundice**

Any classification of jaundice is difficult. The first consideration is whether unconjugated or conjugated bilirubin predominates in the blood, the latter being much the commoner cause of jaundice. Thus massive haemolysis will overload the normal capacity to excrete bilirubin and occasionally ineffective erythropoiesis may be a cause of jaundice. These are prehepatic causes of unconjugated jaundice (see Table).

The second group, hepatic causes of unconjugated jaundice, includes impairment of uptake of bilirubin, as may occur in Gilbert's syndrome or after the administration of a few drugs such as flavaspidic acid (male fern extract). The conjugation of bilirubin may be inadequate in the Crigler-Najjar syndrome, in normal neonates, and possibly in children born to the rare women who have high serum levels of $\alpha_1$, $\beta_2$-pregnandiol or of the Lucey–Driscoll factor.

Hepatic causes of conjugated jaundice are the commonest group. In the rare Dubin–Johnson syndrome, there is an isolated abnormality of bilirubin secretion, while in intrahepatic cholestasis due to primary biliary cirrhosis in its early stages, intrahepatic biliary atresia, or steroid drugs secretion of all biliary constituents is held up. In drug or viral hepatitis and in cirrhosis there may be multiple defects, including haemolysis, impaired transport, and cholestasis due to widespread damage to the liver cells.

Posthepatic or extrahepatic obstructive jaundice may be due to factors such as gallstones, carcinoma of the pancreas, etc.

**Medical Aspects of Investigation and Treatment**

ROGER WILLIAMS† M.D., F.R.C.P.

In the past year exciting advances in the detection of the elusive hepatitis virus have been reported. Other interesting recent developments include classification of chronic hepatitis; the treatment of some varieties of this condition by immunosuppressive agents; the use of enzyme inducing agents in treating unconjugated hyperbilirubinaemia. A better appreciation of the functional disturbance in chronic cholestasis, and of the value of immunological tests and of percutaneous transhepatic cholangiography in its differential diagnosis has led to a more rational approach to management.

**Acute and Chronic Hepatitis**

**Role of Australia Antigen**

This antigen was first found by B. S. Blumberg and his colleagues in the serum of an Australian aborigine—hence its name, which gives little indication of its probable association or identity with the virus of infective hepatitis. Characteristically a precipitin reaction occurs when Australia antigen
is mixed in with a specific human antisemur, and a simple immunodiffusion technique may be used to screen blood quickly from large numbers of patients. Various surveys have shown that Australia antigen is rare in the normal North American and European populations (0.1%) and that it is present in 30-80% of patients with infective hepatitis. It is also found in up to 30% of patients with Down's syndrome who are in institutions with a known high incidence of viral hepatitis. It is also found in patients with leukaemia after multiple blood transfusions, where again it is attributed to passage of the hepatitis virus.

In acute infective hepatitis the antigen is present in the serum only transiently during the acute stage, its titre then falling in parallel with the serum transaminase level. As a diagnostic test for acute infective hepatitis the demonstration of Australia antigen is therefore limited, though it should provide valuable information about the spread of the hepatitis virus and the development of anicteric hepatitis in close contacts of the patient. Of more practical importance will be its use to detect carriers of the hepatitis virus among blood donors, so that post-transfusion hepatitis can be prevented.

Several authors have now shown that the transfusion of blood containing the antigen is followed by a higher incidence of serum hepatitis, than when blood from donors not carrying antigen was used. Screening for the antigen should also be of considerable practical value in chronic haemodialysis units, in which there have been outbreaks of hepatitis, with fatalities, affecting both patients and staff. G. C. Turner and G. B. B. White found Australia antigen persisting in the blood in nine of 17 patients on maintenance haemodialysis; six had a history of definite hepatitis and three had had many transfusions. Positive tests were also found in several of the staff during acute attacks of hepatitis, but in these the antigen disappeared from the blood with clinical recovery.

Persistence of the antigen in patients with renal failure may point to an immunological defect. This may also be the reason for the high incidence of Australia antigen in the serum of patients with Down's syndrome and in lepromatous, but not tuberculoid, leprosy. For the individual patient, however, the clinical significance of persistent antigen is uncertain. Liver biopsies in some cases of Down's syndrome with positive antigen have shown chronic hepatitis. Up to 25% of sera from patients with active chronic hepatitis have been found to contain the antigen. In some cases of this condition there is clear epidemiological evidence or a history of contact with acute infective hepatitis at the onset, but the continuation of a chronic histological lesion, the pronounced serum hyperglobulinaemia, and the other features of autoimmune state—such as the L.E. cell phenomenon, antinuclear factor, and antibodies in the serum—have all been thought to have an immunological basis.

Hence the part that persistence of the antigen, as opposed to autoimmunity, plays in the development of the final liver disease remains to be seen. Moreover, in one recent study Australia antigen was found in the serum of a similar percentage of patients with acute hepatic necrosis in whom progression to a posthepatic type of cirrhosis was shown by serial biopsy.

Classification of Chronic Hepatitis

Though it has proved difficult to classify the pathological process in patients with persistent cellular infiltration of portal tracts and biochemical signs of inflammation of the liver, an attempt has recently been made to grade the histological activity of this chronic hepatitis. The hepatitis is said to be aggressive when there is destruction of the limiting plate of parenchymal cells around portal tracts, piecemeal necrosis of groups of cells, and fibrous septa in the parenchyma; or it is persistent when these changes are absent. Histological chronic aggressive hepatitis often corresponds with the clinical diagnosis of active chronic hepatitis (sometimes called lupoid hepatitis), with high serum transaminase and the autoimmune features already mentioned. In this condition the chronic hepatitis and hepatic fibrosis usually progress rapidly to cirrhosis. Chronic persistent hepatitis less often proceeds to cirrhosis.

Corticosteroids and Immunosuppressive Therapy

Corticosteroids should not be used routinely in the treatment of acute viral hepatitis, for, though they may produce a more rapid fall in serum bilirubin, the total duration of illness is not shortened and indeed premature cessation may lead to relapse. Nevertheless, in patients who have developed a prolonged cholestatic phase, administration of prednisone (30 mg. daily) may initiate recovery. The drug should be continued in gradually decreasing doses until the convalescent period. Corticosteroids are also usually given empirically to patients with a fulminating hepatitis and to those following a subacute course.

Steroid therapy may produce dramatic symptomatic and biochemical improvement in patients with active chronic hepatitis, but there has been much discussion about whether it affects the long-term prognosis. In the carefully controlled Copenhagen trial 334 cases of cirrhosis were randomly allocated to prednisone or control groups. The death rate was significantly lower in women without ascites and with a high serum globulin—the group which has most of the characteristics of active chronic hepatitis.

Beneficial effects have also been reported from the immunosuppressive agents—6-mercaptopurine and azathioprine (Imuran)—in active chronic hepatitis. Both these drugs are potentially hepatotoxic and the doses given must be smaller (50-75 mg. daily) than those used in the treatment of non-hepatic disorders. Toxic reactions which may develop within two to six weeks include jaundice, hepatic coma, leucopenia, thrombocytopenia, and a reduced resistance to viral and other infections. For the moment this therapy should be reserved for patients who are not completely controlled biochemically, or who have developed troublesome side-effects of corticosteroids.

Treatment of Unconjugated Hyperbilirubinaemia

Neonatal Jaundice

Phenobarbitone induces the synthesis of many hepatic microsomal enzymes, including the specific bilirubin glucuronyl transferase, and this effect is greater in immature animals. It is also known that phenobarbitone crosses the placenta and is slowly excreted by the neonate. The observation by D. Trolle that babies born to mothers who had been given phenobarbitone during pregnancy had a lower incidence of neonatal jaundice was of considerable importance. Later he reported that giving phenobarbitone to babies after birth would also reduce the severity of jaundice. A controlled trial showed that treating mothers with 60 mg. of phenobarbitone daily during late pregnancy undoubtedly lowered the bilirubin level of their babies.

Though the main factors responsible for neonatal jaundice are probably the late development of the hepatic enzyme glucuronyltransferase, together with the haemolysis which occurs soon after birth, other factors may be concerned, whose importance varies in different parts of the world. In Hong Kong severe neonatal hyperbilirubinaemia is a major problem among the Chinese and a daily dose of 15 mg. of phenobarbitone given to jaundiced babies from the time of admission to a paediatric unit has been found valuable in lessening the need for exchange transfusion. Nevertheless, the value of phenobarbitone therapy in the treatment of neonatal jaundice in Britain is questionable; thus fewer than
1% of low-weight babies born at the Hammersmith Hospital in the last two years required an exchange transfusion. Furthermore, with the wider availability of gamma globulin for rhesus negative mothers the incidence of severe erythroblastosis is likely to show a sharp decline.

As already mentioned, A. J. Levi and his colleagues have described two acceptor binding proteins in the cytoplasm of hepatic cells which may be responsible for the uptake of bilirubin. A delay in the maturation of Y, the major binding protein, was found in fetal and newborn guinea-pigs, and this may be another factor in human neonatal jaundice. They also showed that phenobarbitone induced Y but not the Z protein, so that phenobarbitone may affect bilirubin uptake as well as its conjugation and excretion.

**Congenital Unconjugated Hyperbilirubinaemia**

Phenobarbitone may also be used to lower the serum bilirubin in certain types of congenital unconjugated hyperbilirubinaemia in which glucuronyl transferase activity is reduced. In the most severe form of the Crigler-Najjar syndrome—in which glucuronyl transferase activity is absent—phenobarbitone has no effect. In the less severe form (serum bilirubin levels 8-22 mg./100 ml.) in which the enzyme activity is reduced—phenobarbitone can rapidly reduce the serum bilirubin within a few weeks (Fig. 4). Unfortunately, the dose of phenobarbitone necessary may cause undesirable drowsiness, and dicophane has been found to be equally effective, safe, and free from side-effects. Moreover dicophane has a prolonged action owing to its storage in fat, and a yearly short period of treatment may suffice to keep the patient free of jaundice.

In Gilber's syndrome there is no evidence that the mild jaundice (serum bilirubin usually less than 5 mg./100 ml.) is harmful, though many patients complain of abdominal pain, nausea, and lassitude—particularly when the serum bilirubin is raised, as, for instance, during infections and other stresses. On these occasions phenobarbitone therapy can be helpful.

**Management of Chronic Cholestasis**

The patient with primary biliary cirrhosis or chronic cholestasis from other causes should be given vitamins A, D, and K parenterally; 100,000 units of vitamin A and D and 10 mg. of vitamin K monthly should be more than adequate. To prevent bone thinning calcium supplements (Calcium Sandoz six tablets daily) should also be given, but even then this may progress. The steatorrhoea of bile-salt deficiency can be helped by reducing neutral fat intake of 30-40 g. daily, and giving additional fat as medium-chain triglyceride, which can be digested and absorbed in the absence of bile salts.

Unless impairment of biliary excretion is complete pruritus can be relieved by oral cholestyramine (Cuemid)—a resin which exchanges chloride for bile acids in the gut and increases faecal bile acid excretion. The normal enterohepatic cycle of bile salts is interrupted and the serum bile acid level falls. But steatorrhoea is aggravated and the powder is unpleasant to take. Between 4 and 12 g. daily is given in divided doses, and since cholestyramine may bind other drugs these should be given at least an hour beforehand.

In advanced primary biliary cirrhosis or in complete extrahepatic biliary obstruction little or no bile salts reach the gut and cholestyramine is ineffective. In such patients norethandrolone (Nilevar) 10-30 mg. daily gives relief. The mechanism is unknown and unfortunately it will increase the jaundice.

**Intrahepatic Cholestasis**

Intrahepatic cholestasis—or the syndrome of an obstructive type jaundice with itching, pale stools, and dark urine but with patent main extrahepatic bile ducts—has several causes (Fig. 5). In clinical practice it is usually not difficult to diagnose whether the jaundice is due to primary biliary cirrhosis or cholestasis.

**Fig. 5.—Main causes of the syndrome of intrahepatic cholestasis (data from Williams).**
worth considering when cholestatic hepatitis is suspected. In such patients the administration of prednisone (40 mg. daily) results, with few exceptions, in a prompt lowering of the serum bilirubin. If this occurs steroid therapy should be continued into convalescence, for otherwise a relapse may occur. In drug cholestasis there is usually little effect. In extrahepatic obstruction the fall, if it occurs at all, is smaller, and there is a prompt return to the initial level on discontinuing prednisone unless the test has happened to coincide with spontaneous relief of jaundice in a patient with an amillary neoplasm or gallstones.

Immunofluorescent Test

This test, which depends on the presence in the serum of a non-organ specific cytoplasmic antibody directed against a mitochondrial antigen, is positive in most patients with primary biliary cirrhosis. Positive reactions are also obtained in about a quarter of patients with active chronic hepatitis or post-necrotic cirrhosis. In main duct obstruction, and in drug or viral hepatitis, positive reactions of low titre are obtained only occasionally (Table II).

### Table II.—Incidence of Serum Antibodies in Chronic Liver Disease

<table>
<thead>
<tr>
<th>Incidence of Antibodies (%)</th>
<th>Antinuclear (&gt;1/20)</th>
<th>Smooth muscle</th>
<th>Mitochondrial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active chronic hepatitis</td>
<td>56</td>
<td>67</td>
<td>23</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>31</td>
<td>50</td>
<td>94</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>16</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Main duct obstruction</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

Results of various studies (data of Walker et al.14)

Percutaneous Cholangiography

If the diagnosis is still in doubt and laparotomy is being considered this should be preceded by a percutaneous trans-hepatic cholangiogram. In this technique a fine polyethylene catheter is inserted into the liver under local anaesthesia. If the intrahepatic ducts are dilated from extrahepatic obstruction they are easy to puncture, and the picture obtained after injection of contrast medium will define the site and nature of the obstruction. The technique is particularly useful in showing the presence of strictures or fistulae and in demonstrating the small hepatic duct carcinoma situated in the porta hepatitis, which can be missed even at surgery (Fig. 6 and 7). Once a bile duct has been punctured, there is a risk of a bile leak, and laparotomy should follow within a few hours. In intrahepatic cholestasis the ducts are not dilated and usually bile cannot be aspirated. Unfortunately, occasional patients with partial extrahepatic biliary obstruction do not have dilated ducts, and so, like any test, it is not perfect.

Irreversible liver failure can be precipitated by laparotomy in patients with jaundice due to hepatitis, and a good general rule is not to operate within two weeks of the onset of jaundice, however certain the diagnosis appears, unless there is definite evidence of cholangitis. Moreover, with few exceptions, only palliative operations are possible for biliary obstruction due to carcinoma, and the chances of an operable lesion becoming inoperable during an adequate period of evaluation must be very small indeed.

### Surgical Aspects

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Preoperative Preparation

Two special hazards face a patient with obstructive jaundice undergoing an operation; firstly, bleeding because of prothrombin deficiency, and, secondly, postoperative renal failure. The bleeding diathesis is easily corrected by the administration of a vitamin K analogue given by injection for a few days before operation. It is now recognized that the risk of postoperative renal failure, and indeed deaths from all causes, is directly related to the depth of the jaundice.18

The mechanism of the postoperative renal failure has been investigated both experimentally using the rat and clinically.18 19 Experiments were planned to observe the effect of 60-minute renal ischaemia in jaundiced animals and to compare it with the changes observed in controls. The difference was striking; renal ischaemia was poorly tolerated in the presence of obstructive jaundice and fatal tubular necrosis developed in nine out of 14 animals in this group but in none of the 13 in the control group. A further group of jaundiced animals was studied in whom a manniot diuresis was established just before a period of 60 minutes of renal ischaemia. In this group the amount of renal damage was much less severe and was similar to that observed in the nonjaundiced group.

More recently Gunn rats were used in similar experiments.20 The Gunn rat has a congenital unconjugated hyperbilirubinaemia; after duct ligation the serum bilirubin level remains unchanged, but bile salt retention occurs. Sixty minutes of renal ischaemia produced identical mild changes in the two groups with and without bile-duct obstruction. Thus neither unconjugated bilirubin nor bile salts seem to be responsible for the renal sensitivity to ischaemia in jaundice. The most likely substance seems to be conjugated bilirubin.

Sequential renal function studies were made in 12 patients undergoing upper abdominal surgery,21 and the results were compared with those obtained from 15 jaundiced patients undergoing laparotomy. A greater fall in creatinine clearance was observed in the jaundiced group, which was maximal in the mostly deeply jaundiced patients. In a further seven deeply jaundiced patients a manniol diuresis was initiated just before operation and in these the excessive fall in creatinine clearance was prevented.

Thus on both clinical and experimental grounds prophylactic mannitol should be given to jaundiced patients undergoing surgery—and certainly in all those in whom the serum bilirubin level is over 15 mg./100 ml. Possibly large volumes of intravenous Ringer's lactate or glucose saline solution would have the same effect. Nevertheless, it is less easy to maintain high urine flows with these solutions and dangerous fluid retention may occur;22 whereas mannitol easily breaks through the postoperative antidiuresis and promotes a high flow of dilute urine. No complications have been encountered using mannitol in the following regimen:

- 500 ml. 10% mannitol infused beginning one hour before operation and 5% mannitol given in the postoperative period sufficient to maintain the urine flow above 1 ml./min. for 48 hours. This usually requires 500-1,000 ml. in each 24 hour period.

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