BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 19 1962

JAUNDICE*

BY

SHEILA SHERLOCK, M.D., F.R.C.P., F.R.C.P.Ed.

Royal Free Hospital, London

This lecture was founded in 1880 by Mrs. Bradshaw in memory of her husband, Dr. William Wood Bradshaw, who had practised in Reading and who had died 14 years previously. I quote from Sir Rickman Godlee, who gave the companion lecture to the Royal College of Surgeons in 1907: "The simplest method of securing a limited immortality is that which involves the periodical mention of the name of a beneficiary by speakers or lecturers. As long as the Royal Colleges of Physicians and Surgeons exist, and 3% consols bring in any income, and as long as men can be found to deliver lectures, so long must the name of Dr. Bradshaw be twice annually revived in London."

My lecture endeavours to interpret jaundice in the light of recent advances in bile-pigment metabolism. Emphasis is laid on the subject as a clinical problem and on newer techniques that can be applied to its diagnosis. The particular problem of cholestasis—that is, failure to secrete bile into the duodenum—is considered in particular detail.

Bile-pigment Metabolism

The precise pathway of breakdown of haemoglobin first to biliverdin and then, after reduction, to bilirubin is not yet clear (Lemberg and Legge, 1949; Gray, 1957; Klatskin, 1961) (Fig. 1). Bile pigments are the only waste-products formed. The released iron is stored in the liver; the globin enters the protein pool of the body and is available for the manufacture of new haemoglobin; approximately 300 mg. of bilirubin is formed daily. Radioisotope studies, using ^{15}N-labelled glycine, suggest that some bilirubin is formed from sources other than worn-out red blood corpuscles (London *et al.*, 1950). This proportion may increase under pathological conditions; for instance, in pernicious anaemia. This bilirubin might come from other haem pigments such as myoglobin or the cytochromes, from destruction of erythrocyte precursors in the bone-marrow, or as a by-product of haemoglobin synthesis (Klatskin, 1961).

Bilirubin is transported to the liver in the bloodstream attached to serum albumin (Gray and Kekwick, 1948; Martin, 1948). The process by which it is taken up into, passes through, and leaves the liver cells is very complex and little understood.

It has been known for many years that bilirubin, in its passage through the liver, was converted from a lipid soluble pigment to one soluble in water. The post-hepatic pigment, present in bile and sera of patients with obstructive jaundice, gives an immediate red colour with diazotized sulphanilic acid (*direct-reacting bilirubin*) whereas the pre-hepatic pigment, present in sera of patients with haemolytic jaundice, requires the addition of alcohol before the diazo reaction can take place (*indirect-reacting bilirubin*) (van den Bergh and Muller, 1916). The chemical process in the liver which converts one type to the other has only been discovered in the last decade. Cole *et al.* (1954) used reverse-phase partition chromatography to demonstrate three pigments, independent of protein, in jaundiced serum. One, bilirubin, corresponds to the pigment reacting indirectly in the van den Bergh reaction; the other two, pigment 1 and pigment 2, give a direct reaction. Further observations show that both bilirubin and pigment 1 are present in the serum of the hepatectomized dog and hence are of extrahepatic origin. Billing and Lathe (1956) showed that pigment 1 consisted of bilirubin monoglucuronide and that pigment 2 consisted of bilirubin diglucuronide. At the same time Schmid (1956) obtained similar results and Talafant (1956) observed that β-glucuronidase converted direct-reacting pigment to bilirubin.

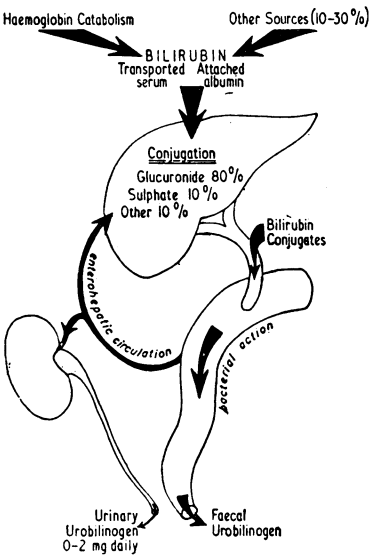

FIG. 1.—Bile-pigment metabolism.

Bilirubin is insoluble in water and is maintained is solution in serum only by linkage to albumin. Alcohol in the diazo reaction acts as a solvent for bilirubin and allows the reaction to proceed (Klatskin and Bungards, 1956; Lathe, 1956). Bilirubin cannot pass the glomerular membrane into the urine. This explains the absence of bilirubinuria in haemolytic jaundice.

The direct-reacting bilirubin glucuronides are formed by conjugation in the liver. They are increased in the serum in obstructive and hepatocellular jaundice, and

*Bradshaw Lecture delivered to the Royal College of Physicians of London on November 23, 1961.

being water-soluble are excreted in the urine. In obstructive jaundice the monoglucuronide is increased more than the diglucuronide. This process of conjugation, however, does not seem to be the only one, for 10 to 15% of the direct-reacting pigment in human bile is alkali-stable, suggesting it is not a glucuronide of bilirubin (Billing *et al.*, 1957). Isselbacher and McCarthy (1959) showed that about half of this may be conjugated as a sulphate and the rest, possibly, as a carboxyl-linked methyl or glycine conjugate.

The conjugation of bilirubin takes place in the microsomes of the liver cell as a result of the action of the enzyme glucuronyl transferase with uridine diphosphate glucuronic acid as the glucuronyl donor (Fig. 2) (Grodsky and Carbone, 1957; Schmid *et al.*, 1957; Lathe and Walker, 1958a).

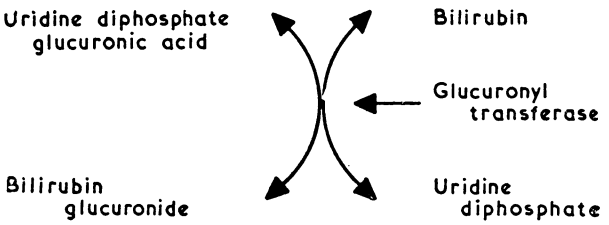

FIG. 2.—The conjugation of bilirubin by the liver as a glucuronide.

On reaching the intestine the conjugated bilirubin is converted by bacteria to stercobilinogen. This is absorbed from the intestine into the portal venous system and so taken back to the liver, where it is re-excreted into the bile (*entero-hepatic circulation of bile pigments*). This process has been confirmed in the rat, using ^{14}C-labelled bilirubin (Lester *et al.*, 1961). It is remarkable, if this is so, that stercobilinogen has never been identified in bile. Presumably some metabolic change takes place in the stercobilinogen molecule before it is re-excreted. The very small amounts of absorbed stercobilinogen not re-excreted by the normal liver (less than 4 mg. daily) passes into the general bloodstream and is removed in the urine as urobilinogen. This amount does not give the usual qualitative tests for urobilinogen.

The stercobilinogen which is not absorbed (about 300 mg. daily) gives the faeces their brown colour. On exposure to the air, urobilinogen and stercobilinogen are oxidized to the chemically identical substances urobilin and stercobilin.

Theoretically, jaundice, an increase of bilirubin in the blood, might arise in four different ways (Fig. 3). Firstly, there might be an increased load of bile pigment on the liver cell. Secondly, there might be a disturbance in the process by which bilirubin diffuses into the cells from the sinusoids and is actively transported to the microsomes for conjugation. Thirdly, there may be defects in the actual conjugation process. Finally, the bilirubin is concentrated and taken to the cell membrane opposite the canaliculus for excretion into the bile. Difficulties might arise in this canalicular transport or indeed there might be obstruction in the large bile channels before the pigment reaches the intestine. Disturbances in the mechanisms of uptake, transport, conjugation, and biliary excretion are probably responsible for all forms of jaundice, although in most instances knowledge is insufficient to pinpoint the exact defect concerned in any individual patient. In this lecture I will attempt to analyse clinical jaundice in

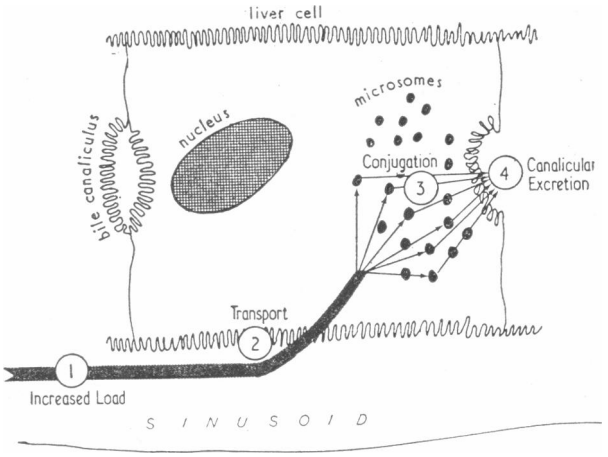

FIG. 3.—Jaundice could theoretically result from (1) an increased load of bilirubin, (2) defective uptake and transport within the liver cell, (3) defective conjugation in the hepatic microsomes, (4) defective canalicular excretion or a mechanical block in the bile-duct system.

terms of these four steps. It must always, of course, be remembered that no clinical example is ever simple and that in many instances more than one process will be involved.

Increased Bilirubin Load (Fig. 4)

Haemolytic Jaundice.—In haemolytic states haemoglobin is released from the red cells in excessive amounts, increasing from the normal of 6.25 g. to as much as 45 g. daily (Crosby and Akeroyd, 1952). Consequently there is greater formation of bile pigment, the increase

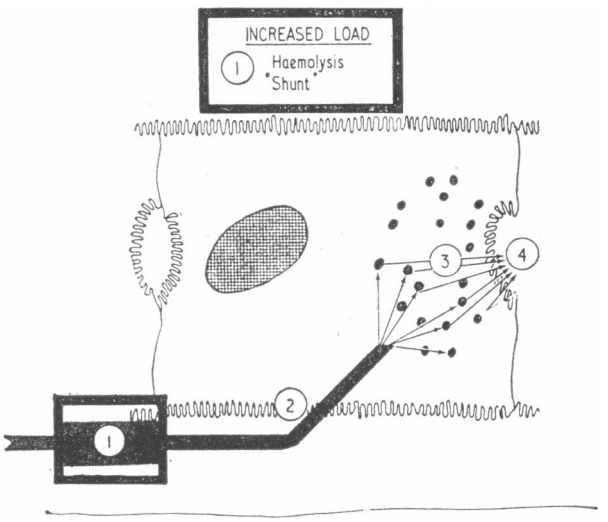

FIG. 4.—Jaundice due to increased bilirubin load.

being mostly in the unconjugated bilirubin, less than 15% being direct reacting (Tisdale *et al.*, 1959). The small amounts of conjugated pigment may arise through renal conjugation of bilirubin (Grodsky and Carbone, 1957) or by regurgitation into the plasma from increased amounts in the bile (Klatskin, 1961). Even if production of bile pigment reaches its maximum of 1,500 mg. daily (six times normal) serum bilirubin rises only to about 2–3 mg./100 ml. This is because of the great capacity of the liver to handle pigment, the amount excreted increasing proportionately to the square of the concentration in the serum (Klatskin, 1961). If patients with haemolytic jaundice show serum bilirubin values greater

than 4–5 mg./100 ml. there is probably the additional factor of hepatocellular dysfunction. Anaemia itself will, of course, depress liver function.

Non-haemolytic Overproduction.—Israels *et al.* (1959) described four cases, three in one family, in which jaundice was predominantly due to unconjugated bilirubin in the serum. Increased urinary and faecal urobilinogen levels were out of proportion to ascertainable haemolysis and persisted after splenectomy. Excess bilirubin production from sources other than the mature circulating red blood cell was postulated and the condition called "shunt hyperbilirubinaemia." Klatskin (1961) thinks that the bilirubin might have come from haemoglobin of erythrocytes and younger red cells destroyed in the bone-marrow before reaching the peripheral circulation. Equally, as these patients showed many of the features of congenital spherocytosis, it is difficult to be certain that this is not an atypical variant of this syndrome.

Disturbance of Bilirubin Transport (Fig. 5)

Here the defect lies in the transport of bilirubin from the serum to its site of conjugation in the liver cells. The best example seems to be Gilbert's disease, which is the commonest form of familial non-haemolytic jaundice. This is probably inherited as a dominant, mild intermittent jaundice being noted from childhood. Deepening jaundice is associated with malaise, nausea, and often discomfort over the liver. These symptoms have never been explained but often lead to a mistaken diagnosis of virus hepatitis. There are no other abnormal physical signs; the spleen is not palpable. The serum total bilirubin level rarely exceeds 3 mg./100 ml. Bile is absent from the urine. Liver histology is normal. The serum bilirubin level is unaffected by corticosteroid therapy (Eanet and Brick, 1955).

Arias and London (1957) postulated a deficiency of the enzyme glucuronyl transferase from the liver in Gilbert's disease. This seems unlikely, as conjugated bilirubin predominates in the bile and faecal stercobilinogen is normal (Schiff and Billing, 1959). Moreover, various substances such as menthol (Foulk *et al.*, 1959), salicylamide (Barniville and Misk, 1959), and N-acetyl-*p*-aminophenol (Schmid and Hammaker, 1959) can be conjugated as glucuronides in normal fashion.

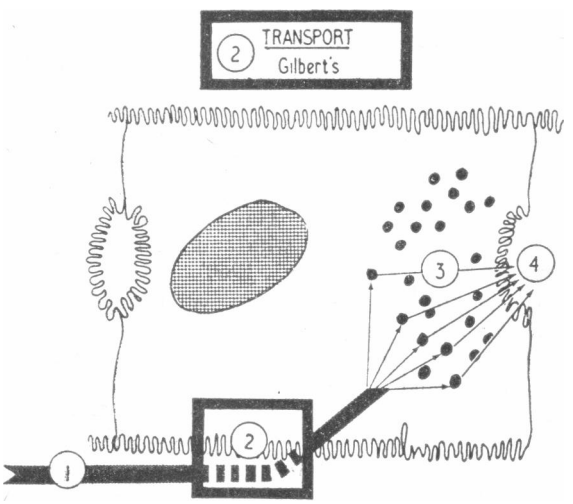

FIG. 5.—Jaundice due to disturbances of intracellular bilirubin transport.

Schmid and Hammaker (1959) believe that the primary defect may be related to the mechanism responsible for bilirubin transport from plasma to the site of conjugation in the liver cell. Billing and Williams (1961, unpublished observations) have indeed found a defect in the uptake of bilirubin by the liver in patients with Gilbert's disease. Since unconjugated bilirubin is insoluble at the *p*H of plasma (Overbeek *et al.*, 1955) and tightly bound to plasma proteins (Klatskin and Bungards, 1956) such transport may be extremely important.

It is probable that Gilbert's disease is not a single entity but represents a number of different conditions. The frequent recognition of such cases after a clear-cut attack of hepatitis may not be pure coincidence. Post-hepatitis hyperbilirubinaemia may be one variant of the disease.

Disturbances of Bilirubin Conjugation (Fig. 6)

Enzyme Deficiency.—The best example of this is probably the neonatal jaundice particularly common in premature infants and formerly referred to as "physiological." This was originally thought to be due to

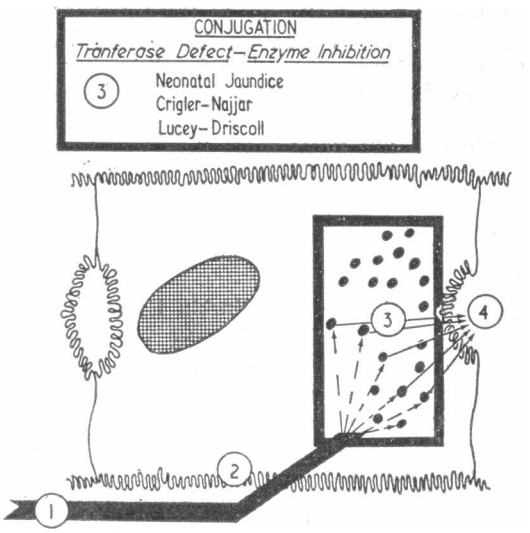

FIG. 6.—Jaundice due to disturbances in the conjugation of bilirubin.

haemolysis of immature foetal erythrocytes. The newborn infant produces bilirubin at a rate approximately three times that of the adult (Mollison, 1948). This cannot be the whole explanation, for those with the highest serum bilirubin levels excrete least bile pigment in the stools, suggesting difficulty in hepatic excretion rather than haemolysis. The newborn liver is undoubtedly immature in its handling of bilirubin. The enzymes glucuronyl transferase and uridine disphosphate glucuronic acid dehydrogenase, which conjugate the pigment, are deficient in the foetus and gradually increase in the first few days of life (Brown *et al.*, 1958). This explains why jaundice is more frequent and deeper in the premature infant. Circulating unconjugated bilirubin, which is lipid-soluble, is increased, and if great enough can lead to

bilirubin poisoning of the brain and the clinical picture of kernicterus.

A deficiency in the enzymatic conjugation of bilirubin by the hepatic microsomes can also be found in the severe, and very rare, Crigler–Najjar (1952) type of hyperbilirubinaemia (Arias and London, 1957). Sufferers also develop kernicterus. The unfortunate Gunn strain of congenitally jaundiced rats also lack the bilirubin glucuronyl transferase enzyme and these animals have proved particularly useful in the study of bilirubin metabolism (Carbone and Grodsky, 1957; Schmid *et al.*, 1957; Lathe and Walker, 1958a).

Enzyme Inhibition.—Lathe and Walker (1958b) have found that the serum of pregnant women and of newborn infants contains a substance which inhibits the conjugation of bilirubin by rat-liver slices. Some steroids act similarly, and an inhibition of the conjugating enzymes in the liver by a steroid produced during pregnancy has been suggested. The clinical importance of such enzyme inhibition may be slight, as sera from babies with neonatal jaundice do not show a greater inhibition of conjugation than those without jaundice. However, a type of congenital hyperbilirubinaemia studied by Lucey and Driscoll (quoted by Arias and Wolfson, 1960) might well have a similar basis. These authors noted a deep jaundice due to unconjugated bilirubin in successive children of certain apparently normal mothers. In the survivors jaundice disappeared within a month. All the usual causes of neonatal jaundice were excluded. Arias and Wolfson (1960) found that sera from these babies and from their mothers inhibited conjugation of bilirubin in rat-liver slices three to five times more than sera from normal infants and mothers. This type of jaundice again might be due to a steroid produced in excess by certain mothers during pregnancy and which inhibits the hepatic conjugation of bilirubin.

Disturbances of Bilirubin Excretion

Here the difficulty lies in the pathway between conjugation in the microsomes in the hepatic cells and entry of bilirubin into the duodenum. The abnormality may be broadly divided into two categories. Firstly, intrahepatic cholestasis where the difficulty lies between the microsomes and the main bile-ducts (Fig. 7), and, secondly, extrahepatic cholestasis where there is obstruction to main bile-ducts.

A good example of the intrahepatic variety is the Dubin–Johnson type of hyperbilirubinaemia. This chronic, benign, intermittent jaundice is seen in young people (Dubin and Johnson, 1954; Sprinz and Nelson, 1954; Dubin, 1958) and is often familial (Beker and Read, 1958; Wolf *et al.*, 1960). The circulating pigment is conjugated so that bile pigment is found in the urine. The main diagnostic point is in the liver, which macroscopically is greenish black "black liver jaundice" (Bynum, 1957). In sections the liver cells show a brown pigment (probably a lipofuscin), which does not contain either iron or bile (John and Knudtson, 1956) and which appears to be identical with the brown "wear and tear pigment" seen in various diseased states. Alternatively, it has been suggested that the pigment is melanin (Bynum, 1957), which has been found in the urine and in the spleen of a patient with this syndrome (Wegmann *et al.*, 1960).

There may be difficulty in excreting the contrast media used for intravenous cholangiography. Serum alkaline phosphatase values are sometimes raised. A rather similar picture of chronic familial non-haemolytic jaundice with conjugated bilirubinaemia was first described by Rotor *et al.* (1948) from the Philippines. This resembles the Dubin–Johnson syndrome closely,

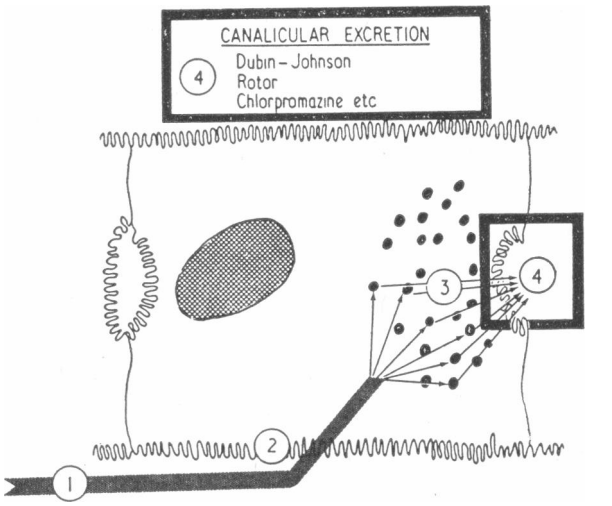

FIG. 7.—Intrahepatic cholestatic jaundice due to disturbances in the excretion of bilirubin into the bile canaliculi.

the main point of difference being the absence of brown pigment from the liver cells. In this syndrome the serum alkaline phosphatase level is low (Schiff *et al.*, 1959).

In both the Dubin–Johnson and the Rotor types a diagnostic pattern is seen in the bromsulphthalein (B.S.P.) excretion test. After an initial fall in serum level the B.S.P. rises so that the value at 210 minutes exceeds that at 45 minutes (Mandema *et al.*, 1960). Bilirubin tolerance shows a similar pattern, with an initial fall of the injected, unconjugated bilirubin followed by a sustained rise of the conjugated pigment (Billing and Williams, 1961, unpublished observations). This suggests normal conjugation of B.S.P. or bilirubin but re-entry of the conjugated material into the bloodstream because of difficulties in transport into the biliary canaliculi. Indocyanine green, a synthetic dye which is unconjugated by the liver, gives a similar tolerance test to that found with B.S.P. or bilirubin (Caesar *et al.*, 1961), confirming that difficulties in conjugation are not concerned.

Since the amount of pigment in the liver of patients with the Dubin–Johnson syndrome may be very variable, it is possible that the Rotor type is in fact a variant of the Dubin–Johnson one. This is supported by the appearance of liver biopsies with and without pigment in the same family (Wolf *et al.*, 1960).

The Dubin–Johnson and Rotor syndromes are rare and of importance mainly to those investigating bile-pigment metabolism. Practically, they must be diagnosed accurately, so that sufferers may be reassured that they are not suffering from serious liver disease; unnecessary invalidism is thus prevented. Of greater importance is the recognition that the complete picture of obstructive jaundice may be seen without obstruction to main bile-ducts. The most important clinical advance in the study of jaundice during the last decade has been the recognition of intrahepatic cholestasis and of its multiple aetiology.

Intrahepatic Cholestasis

In some patients the clinical and biochemical picture of obstructive jaundice is encountered in the presence of patent main bile-ducts (Popper and Schaffner, 1959). These patients itch, are usually afebrile, and suffer no pain The liver is only slightly enlarged and is not tender. The faeces are pale and fatty but rarely acholic. The urine contains bilirubin and variable quantities of urobilinogen.

Biochemically, levels of serum conjugated bilirubin, alkaline phosphatase, total cholesterol, and conjugated bile salts are increased. Electrophoretic separation of the serum proteins shows an increase in the $alpha_2$ and beta components. The sero-flocculation tests are negative and serum transaminase values only moderately increased.

Needle biopsy of the liver shows, basically, only the picture of bile stasis in Kupffer cells, in liver cells, and in the bile canaliculi, and maximally in the centrizonal areas. Active reduplication of bile-ducts in the portal zones, so characteristic of extrahepatic biliary obstruction, is not seen. Bile necrosis is absent. There is no evidence of specific involvement of cholangioles, the minute channels joining the bile canaliculi in the lobule with the ductule in the portal zone, and the lesion should not be termed a cholangiolitis.

The mechanism of acute intrahepatic cholestasis is obscure. The lesion could be in the unidirectional transport system of the liver cell allowing reflux of bile from the canaliculi into the blood. Such disturbances can occur in liver cells showing no histological abnormality (Hanzon, 1952).

The lesion could be in the bile canaliculus itself. Electron microscopy has shown a distortion and sparsity of the microvilli lining these channels in some cases of intrahepatic cholestasis (Schaffner and Popper, 1959).

It is possible that some toxic substance is produced in the bile which damages the canalicular membrane. Antibodies against the cytoplasm of ductule cells have been demonstrated in some instances of liver disease (Paronetto *et al.*, 1961). The antigenic material may also be present in bile. This suggests disturbed immunity in some instances.

An increased permeability of ducts in the portal zone has been suggested (Watson and Hoffbauer, 1946). Such abnormalities might allow increased reabsorption of water from the bile.

Obstruction of the bile channels by infiltrates in the portal zones seems most unlikely to be causative, as many conditions—for instance, leukaemia or sarcoidosis in which such lesions are prominent—are not associated with jaundice.

Cholestatic Drug Jaundice

Whatever the actual mechanism within the liver, the aetiology of intrahepatic cholestasis is multiple. The most frequent association is with the administration of certain drugs. About 1% of patients receiving chlorpromazine develop an intrahepatic obstructive jaundice, usually within four weeks of starting the drug and unrelated to dosage. The condition is mostly mild, recovery taking place within one to four weeks. Occasionally jaundice is more prolonged and there are records of 22 patients in whom icterus lasted more than three months (Read *et al.*, 1961). In these chronic cases the clinical picture may simulate primary biliary cirrhosis. The onset, however, is more explosive and serum cholesterol and alkaline phosphatase levels are very high from the outset. In every instance, moreover, clinical recovery ensues with the passage of time. Biochemical and histological changes in the liver may, however, persist after clinical recovery, and the patients have not been followed long enough to be certain whether these will be progressive or permanent.

The mechanism of chlorpromazine jaundice remains uncertain. An allergic reaction to chlorpromazine has been suggested by the time of onset in relation to drug administration, the occasional appearance one to two weeks after the drug has been stopped, the association with fever and rashes, the blood and hepatic eosinophilia, and the leucopenia. Eleven patients who had recovered from chlorpromazine jaundice were given the drug again. Six showed a recurrence, two abnormal biochemical values, one prodromal features without jaundice, and two no change (Hollister, 1957). Others have given the drug again without the reappearance of jaundice (Elkes and Elkes, 1954) and patients have recovered while still receiving chlorpromazine (Dickes *et al.*, 1957). Electron microscopy has shown abnormalities in the microvilli lining the biliary canaliculus in this condition as in other forms of cholestatic jaundice (Popper and Schaffner, 1959).

An essentially similar picture can complicate therapy with other phenothiazine derivatives such as promazine ("sparine") (Kemp, 1957; Waitzkin, 1957), prochlorperazine ("compazine") (Weinstein *et al.*, 1959; Mechanic and Meyers, 1958), trifluoperazine ("stelazine") (Kohn and Myerson, 1961), or pecazine ("pacatal") (Mitchell *et al.*, 1957). It can also complicate treatment with non-phenothiazine drugs such as arsphenamine (Hanger and Gutman, 1940), *para*-aminosalicylic acid (Lichtenstein and Cannemeyer, 1953), thiouracil (Gargill and Lesses, 1945), chlorpropamide ("diabinese") (Reichel *et al.*, 1960), ectylurea ("nostyn") (Hochman and Robbins, 1958), carbasone (Radke and Baroody, 1957), and nitrofurantoin ("furadantin") (Ernaelsteen and Williams, 1961).

Another type of cholestatic drug jaundice may complicate therapy with certain steroids of which methyltestosterone was the first described (Werner *et al.*, 1950; Foss and Simpson, 1959). Other steroids reported to cause this type are anabolic agents such as norethandrolone ("nilevar"; 17α-ethyl-19-nortestosterone) (Dunning, 1958; Heaney and Whedon, 1958; Kory *et al.*, 1959; Schaffner *et al.*, 1959), methyl estrenolone (17α-methyl-19-nortestosterone) (Peters *et al.*, 1958), methandienone ("dianabol"; Δ^1-17α-methyltestosterone) (Wynn *et al.*, 1961); and an ovulation inhibitor norethisterone (17α-ethynyl-19-nortestosterone). "Enavid" ("conovid"), also used as an inhibitor of ovulation, contains norethynodrel, a C17 alkylated C19 steroid, and has been reported to cause bromsulphthalein retention (Marquardt *et al.*, 1961). These substances are all active when given orally and are all C17α-alkyl substituted testosterones; this suggests the importance of a substitution in this position for icterogenic action (Fig. 8). Testosterone propionate, without this configuration, does not cause jaundice, neither does nandrolone ("durabolin") a 19-nor compound; these substances must be given by injection (Fig. 9). A similar type can also complicate treatment with non-steroidal substances, including methimazole (Shipp, 1955) and sulphadiazine.

This type differs from chlorpromazine-type jaundice in two respects. The condition is a non-sensitivity one and abnormalities of bromsulphthalein tolerance, if not frank cholestatic jaundice, will develop in *every* patient receiving the drug for a long enough time in sufficient dosage (Heaney and Whedon, 1958; Kory *et al.*, 1959). This is in keeping with the observation that methyltestosterone or norethandrolone given to jaundiced patients for the relief of itching constantly raises serum bilirubin values (Lloyd-Thomas and Sherlock, 1952; Sherlock, 1958, 1959). Secondly, the portal zone cellular reaction is absent and the liver lesion is one of simple cholestasis with slight hepato-cellular change. Alterations in the microvilli of the bile canaliculi have been seen by electron microscopy (Schaffner *et al.*, 1960).

The clinical picture of the jaundice is essentially the same as for chlorpromazine, although it usually follows some months' administration; it can, however, develop after only one to two weeks' therapy. Chronic jaundice has not been reported in this group.

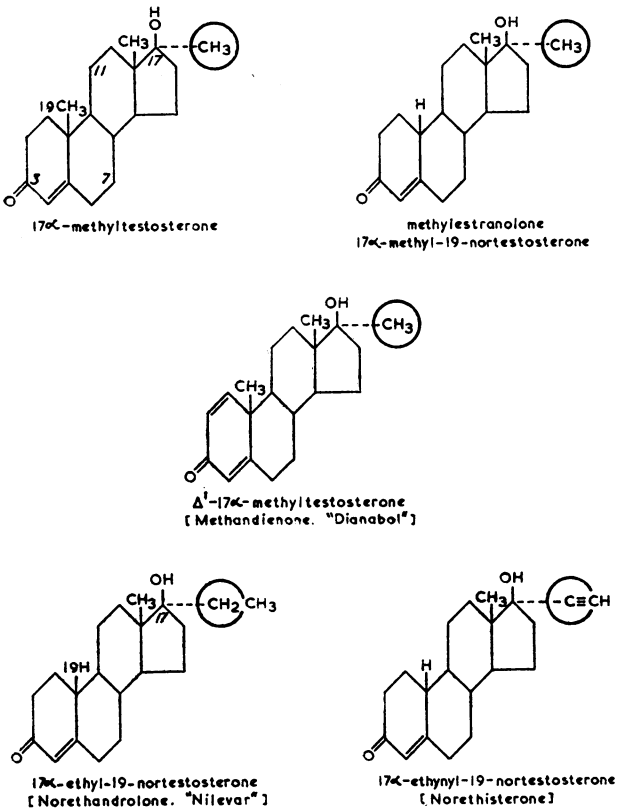

FIG. 8.—Structural formula of orally active steroids reputed to be associated with non-sensitivity cholestatic jaundice. Note alkyl substitution in C17 position.

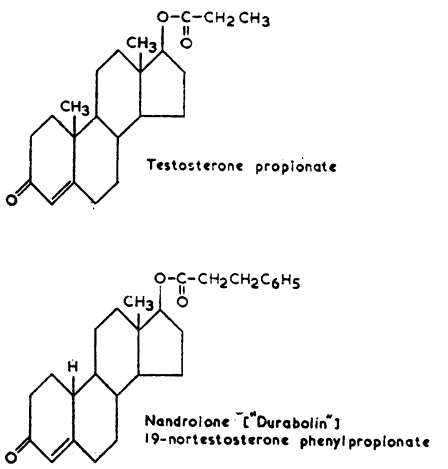

FIG. 9.—Anabolic steroids, active parenterally, which have not been reported in association with cholestatic jaundice.

Other Types of Intrahepatic Cholestasis

The next group are distinguished by showing, in addition to cholestasis, abnormalities within the hepatic cells. Here there is presumably some mechanical or metabolic difficulty with the cell in the transport of bilirubin into the canaliculi. Acute cholestasis, for instance, may complicate acute virus hepatitis. The onset is acute, but within three weeks the picture becomes one of obstructive jaundice (Shaldon and Sherlock 1957; Dubin, 1959). Jaundice persists for 8 to 29 weeks and recovery is complete. Acute fatty liver of the alcoholic may present as obstructive jaundice (Phillips and Davidson, 1954; Ballard *et al.*, 1961). Here the cholestasis is presumably due to obstruction to the canaliculi by the enormously distended fatty liver cells.

Occasionally infants with neonatal jaundice due to some condition such as hepatic prematurity or haemolytic disease develop the clinical picture of cholestasis. The conjugated serum bilirubin level rises to heights seen in obstruction to main bile-ducts. This is sometimes called the inspissated bile syndrome, jaundice being attributed to obstruction of the biliary tree by viscid bile. It seems more likely that the increase in conjugated pigment in the serum reflects the hepatocellular damage known to occur in severe erythroblastosis (Craig, 1950). The bile plugs in the liver are secondary to the bile stasis rather than its cause.

A further rare type of intrahepatic cholestasis is that which occurs in some pregnant women. Itching is profound, jaundice mild, and the patient recovers when she is delivered (Thorling, 1955; Svanborg and Ohlsson, 1959). The mechanism is unknown.

Finally the chronic condition of primary biliary cirrhosis (chronic intrahepatic obstructive jaundice) (Ahrens *et al.*, 1950; Sherlock, 1959) must be considered. The onset, usually in middle-aged women, is insidious and liver biopsy shows a very gross infiltrative lesion in the portal zones. The mechanism of this chronic intrahepatic cholestasis is quite obscure.

Extrahepatic Cholestasis

In patients with extrahepatic cholestasis conjugated bilirubin regurgitates back into the serum or lymphatics through rupture of bile canaliculi, permeable canals of Hering, or perhaps the liver cells themselves. Late in the course of the illness the serum monoglucuronide and unconjugated bilirubin accumulate in the blood, suggesting that there is indeed impairment of hepatocellular function. Hanzon (1952) showed defective transport through the liver cells in the presence of extrahepatic biliary obstruction and Billing (1955) has postulated failure of conversion of the monoglucuronide to the diglucuronide in this condition.

Electron microscopy shows an abnormality of the microvilli of the canaliculi similar to that seen in intrahepatic cholestasis (Schaffner and Popper, 1959).

Distinction of Intrahepatic from Extrahepatic Cholestasis

The clinical picture and results of biochemical tests of liver function are, in most instances, not diagnostic either of the site of the lesion, whether intrahepatic or extrahepatic, or of its aetiology. Even the most experienced pathologist has difficulty in deciding whether the histological picture seen in the liver is that produced by intrahepatic cholestasis or by a block in the main bile-ducts. There are, however, some helpful clinical pointers in diagnosing extrahepatic cholestasis. These largely depend on the dilatation of the intrahepatic bile-ducts consequent upon a block in a main duct. The liver is therefore always large (hydrohepatosis) in contrast to intrahepatic cholestasis where it is little, if any, increased in size. Fever, rigors, and leucocytosis are due to secondary infection (cholangitis) in the dilated ducts. Pain may be present in the extrahepatic group, never in the intrahepatic.

Liver biopsy may be a helpful method, but too much must not be expected of the pathologist interpreting the sections. Hepatic histology may show multiplication of bile ductules having prominent lumina in the portal zones. Bile ductules in intrahepatic cholestasis are flattened and inconspicuous. The portal zones in extrahepatic cholestasis show a predominantly polymorph infiltration, reflecting the cholangitis. In some patients with cholestatic jaundice due to drugs the portal zone infiltrate may be merely eosinophilic, but this is seen in only a few cases in their early stages. Bile necroses, reflecting rupture of dilated canals of Hering, are diagnostic of extrahepatic cholestasis but are by no means constant. The signs of centrizonal hepatocellular damage, such as feathery degeneration, variation in nuclear size, and hyaline change, are, albeit slight, more frequent in intrahepatic than extrahepatic cholestasis, especially in the early stages.

Two additional methods are useful in the problem case. The patient in whom intrahepatic cholestasis is due to primary hepatocellular disease, particularly acute virus hepatitis, will show a dramatic response to corticosteroid therapy (Shaldon and Sherlock, 1957). Prednisolone, 40 mg. daily for four days, produces a profound fall of the serum bilirubin level. Patients with obstructive jaundice whether mechanical or due to chlorpromazine show little change. The value of this test has been questioned, specific patterns not being found in the various types of jaundice (Chalmers *et al.*, 1956). A fall of serum bilirubin level greater than 8%, however, strongly suggests hepatitis (Summerskill and Jones, 1958), but an equivocal one does not exclude it. If a decrease is achieved, the drug will have to be continued on into convalescence. The fate of the bilirubin disappearing from the blood after prednisolone is obscure. The steroid "whitewash" cannot be accounted for by changes in erythrocyte survival (reflecting changes in haemoglobin katabolism to bilirubin), faecal or urinary urobilinogen output, or urinary bilirubin (Williams and Billing, 1961). It seems possible that the bilirubin undergoes an alternative metabolic pathway.

The other helpful technique is the injection of contrast material directly into the liver (percutaneous transhepatic cholangiography). A bile-duct is readily punctured in patients with extrahepatic cholestasis but not in those with intrahepatic cholestasis. This technique carries a small risk of biliary peritonitis (Nurick *et al.*, 1953), and if the dilated duct is aspirated surgical exploration of the biliary tract should be performed within four or five hours. It is also important to use a flexible plastic tube rather than a rigid needle for exploration, as this lessens the risk of damage to liver (Shaldon *et al.*, 1962) (Fig. 10). If the duct is not encountered easily, mechanical obstruction to major bile-ducts is unlikely. The cholangiogram enables the site of a main block to be located accurately and the surgical procedure planned accordingly. This technique

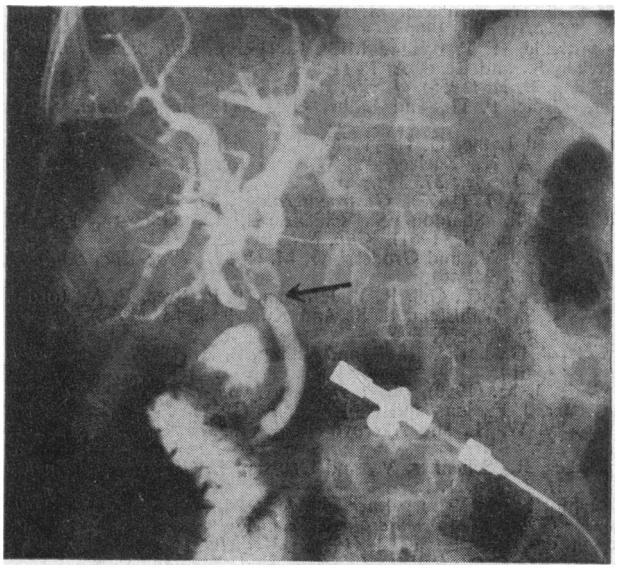

FIG. 10.—Percutaneous transhepatic cholangiogram showing a stricture of the common bile-duct (indicated by arrow) with two filling defects in dilated ducts above. These were shown at operation to be gall-stones.

should only be used when the physician is still in doubt, after careful clinical observation, repeated serum biochemical tests, needle liver biopsy, and if necessary a trial of steroids. A decision to operate must have been made and should be carried out if a duct is punctured.

Conclusions

It may well be questioned why the mechanism of such a common form of jaundice as that associated with virus hepatitis has not been discussed. In fact, the pattern of bile pigments in the serum in what seems to be a predominantly hepatocellular jaundice is identical with that observed in mechanical obstruction to main bile-ducts (Billing, 1955; Baikie, 1957). This picture must result not only from difficulties in the transport of bilirubin through the hepatic cell and possibly in its conjugation but also from its regurgitation out of bile canaliculi. In addition, patients with hepatocellular jaundice, irrespective of aetiology, show a diminished survival of erythrocytes so that a pigment overload factor is added to those of hepatocellular dysfunction and cholestasis. Here, then, is a disease in which bilirubin overload, difficulty in transport, conjugation, and excretion seem to be contributing to the jaundice. This emphasizes that, however we may attempt to pinpoint the mechanism in any particular patient with jaundice, in the clinical situation we are always faced with a multiplicity of factors that provide a challenge for future work.

I thank Mr. R. R. Phillips, of the photographic department of the Royal Free Hospital, for his help, and also Mrs.

Angela Birbeck for drawing the figures. I am also indebted to many colleagues for their advice and for allowing me to quote from original work, especially Dr. Kathleen M. Barber, Dr. Barbara H. Billing, Dr. Stanley Shaldon, Dr. Roger Williams, and Dr. W. B. Young.

REFERENCES

Ahrens, E. H., jun., Payne, M. A., Kunkel, H. G., Eisenmenger, W. J., and Blondheim, S. H. (1950). *Medicine (Baltimore)*, **29**, 299.
Arias, I. M., and London, I. M. (1957). *Science*, **126**, 563.
—— and Wolfson, S. (1960). *Gastroenterology*, **38**, 797.
Baikie, A. G. (1957). *Scot. med. J.*, **2**, 359.
Ballard, H., Bernstein, M. A., and Farrar, J. T. (1961). *Amer. J. Med.*, **30**, 196.
Barniville, H. T. F., and Misk, R. (1959). *Brit. med. J.*, **1**, 337.
Beker, S., and Read, A. E. (1958). *Gastroenterology*, **35**, 387.
Billing, B. H. (1955). *J. clin. Path.*, **8**, 130.
—— Cole, P. G., and Lathe, G. H. (1957). *Biochem. J.*, **65**, 774.
—— and Lathe, G. H. (1956). Ibid., **63**, 6P.
Brown, A. K., Zuelzer, W. W., and Burnett, A. H. (1958). *J. clin. Invest.*, **37**, 332.
Bynum, W. T. (1957). *Gastroenterology*, **33**, 97.
Caesar, J., Shaldon, S., Chiandussi, L., Guevara, L., and Sherlock, S. (1961). *Clin. Sci.*, **21**, 43.
Carbone, J. V., and Grodsky, G. M. (1957). *Proc. Soc. exp. Biol. (N.Y.)*, **94**, 461.
Chalmers, T. C., Gill, R. J., Jernigan, T. P., Svec, F. A., Jordan, R. S., Waldstein, S. S., and Knowlton, M. (1956). *Gastroenterology*, **30**, 894.
Cole, P. G., Lathe, G. H., and Billing, B. H. (1954). *Biochem. J.*, **57**, 514.
Craig, J. M. (1950). *Arch. Path.*, **49**, 665.
Crigler, J. F., jun., and Najjar, V. A. (1952). *Pediatrics*, **10**, 169.
Crosby, W. H., and Akeroyd, J. H. (1952). *Amer. J. Med.*, **13**, 273.
Dickes, R., Schenker, V., and Deutsch, L. (1957). *New Engl. J. Med.*, **256**, 1.
Dubin, I. N. (1958). *Amer. J. Med.*, **24**, 268.
—— (1959). *Gastroenterology*, **36**, 645.
—— and Johnson, F. B. (1954). *Medicine (Baltimore)*, **33**, 155.
Dunning, M. F. (1958). *J. Amer. med. Ass.*, **167**, 1242.
Eanet, M. P., and Brick, I. B. (1955). *New Engl. J. Med.*, **253**, 1062.
Elkes, J., and Elkes, C. (1954). *Brit. med. J.*, **2**, 560.
Ernaelsteen, D., and Williams, R. (1961). *Gastroenterology*, **41**, 590.
Foss, G. L., and Simpson, S. L. (1959). *Brit. med. J.*, **1**, 259.
Foulk, W. T., Butt, H. R., Owen, C. A., jun., Whitcomb, F. F., jun., and Mason, H. L. (1959). *Medicine (Baltimore)*, **38**, 25.
Gargill, S. L., and Lesses, M. F. (1945). *J. Amer. med. Ass.*, **127**, 890.
Gray, C. H. (1957). *Brit. med. Bull.*, **13**, 94.
—— and Kekwick, R. A (1948). *Nature (Lond.)*, **161**, 274.
Grodsky, G. M., and Carbone, J. V. (1957). *J. biol. Chem.*, **226**, 449.
Hanger, F. M., jun., and Gutman, A. B. (1940). *J. Amer. med. Ass.*, **115**, 263.
Hanzon, V. (1952). *Acta physiol. scand.*, **28**, Suppl. 101.
Heaney, R. P., and Whedon, G. D. (1958). *J. Lab. clin. Med.*, **52**, 169.
Hochman, R., and Robbins, J. J. (1958). *New Engl. J. Med.*, **259**, 583
Hollister, L. E. (1957). *Amer. J. Med.*, **23**, 870.
Israels, L. G., Suderman, H. J., and Ritzmann, S. E. (1959). Ibid., **27**, 693.
Isselbacher, K. J., and McCarthy, E. A. (1959). *J. clin. Invest.*, **38**, 645.
John, G. J., and Knudtson, K. P. (1956). *Amer. J. Med.*, **21**, 138.
Kemp, J. A. (1957). *Gastroenterology*, **32**, 937.
Klatskin, G (1961). *Ann. Rev. Med.*, **12**, 211.
—— and Bungards, L. (1956). *J. clin. Invest.*, **35**, 537.
Kohn, N., and Myerson, R. M. (1961). *New Engl. J. Med.*, **264**, 549.
Kory, R. C., Bradley, M. H., Watson, R. N., Callahan, R., and Peters, B J. (1959). *Amer. J. Med.*, **26**, 243.
Lathe, G. H. (1956). *Lancet*, **2**, 683.
—— and Walker, M. (1958a). *Biochem. J.*, **70**, 705.
—— —— (1958b). *Quart. J. exp. Physiol.*, **43**, 257.
Lemberg, R., and Legge, J. W. (1949). *Hematin Compounds and Bile Pigments*. Interscience Publishers, New York.
Lester, R., Ostrow, J. D., and Schmid, R. (1961). *Nature (Lond.)*, **192**, 372.
Lichtenstein, M. R., and Cannemeyer, W. (1953). *J. Amer. med. Ass.*, **152**, 606.
Lloyd-Thomas, H. G. L., and Sherlock, S. (1952). *Brit. med. J.*, **2**, 1289.
London, I. M., West, R., Shemin, D., and Rittenberg, D. (1950). *J. biol. Chem.*, **184**, 351.
Mandema, E., de Fraiture, W. H., Niewig, H. O., and Arends, A. (1960). *Amer. J. Med.*, **28**, 42.
Marquardt, G. H., Fisher, C. I., Levy, P., and Dowben, R. M. (1961). *J. Amer. med. Ass.*, **175**, 851.
Martin, N. H. (1948). *Biochem. J.*, **42**, xv.
Mechanic, R. C., and Meyers, L. (1958). *New Engl. J. Med.*, **259**, 778.
Mitchell, P. H., Sykes, P., and King, A. (1957). *Brit. med. J.*, **1**, 204.
Mollison, P L. (1948). *Lancet*, **1**, 513.
Nurick, A. W., Patey, D. H., and Whiteside, C. G. (1953). *Brit. J. Surg.*, **41**, 27.
Overbeek, J. T. G., Vink, C. L. J., and Deenstra, H. (1955). *Rec. Trav. chim. Pays-Bas*, **74**, 81.
Paronetto, F., Schaffner, F., and Popper, H. (1961). *Proc. Soc. exp. Biol. (N Y.)*, **106**, 216.
Peters, J. H., Randall, A. H., jun., Mendeloff, J., Peace, R., Coberly, J. C., and Hurley, M. B. (1958). *J. clin. Endocr.*, **18**, 114.
Phillips, G. B., and Davidson, C. S. (1954). *Arch. intern. Med.*, **94**, 585.
Popper, H., and Schaffner, F. (1959). *J. Amer. med. Ass.*, **169**, 1447.
Radke, R. A., and Baroody, W. G. (1957). *Ann. intern. Med.*, **47**, 418.
Read, A. E., Harrison, C. V., and Sherlock, S. (1961). *Amer. J. Med.*, **31**, 249.
Reichel, J., Goldberg, S. B., Ellenberg, M., and Schaffner, F. (1960). Ibid., **28**, 654.
Rotor, A. B., Manahan, L., and Florentin, A. (1948). *Acta med. philipp.*, **5**, 37.
Schaffner, F., and Popper, H. (1959). *Gastroenterology*, **37**, 565.
—— —— and Chesrow, E. (1959). *Amer. J. Med.*, **26**, 249.
—— —— and Perez, V. (1960). *J. Lab. clin. Med.*, **56**, 623.
Schiff, L., and Billing, B. H. (1959). *Gastroenterology*, **37**, 595.
—— —— and Oikawa, Y. (1959). *New Engl. J. Med.*, **260**, 1315.
Schmid, R. (1956). *Science*, **124**, 76.
—— and Hammaker, L. (1959). *New Engl. J. Med.*, **260**, 1310.
—— —— and Axelrod, J (1957). *Arch. Biochem.*, **70**, 285.
Shaldon, S., Barber, K. M., and Young, W. B. (1962). *Gastroenterology*. In press.
—— and Sherlock, S. (1957). *Brit. med. J.*, **2**, 734.
Sherlock, S. (1958). *Diseases of the Liver and Biliary System*, 2nd ed. Blackwell, Oxford.
—— (1959). *Gastroenterology*, **37**, 574.
Shipp, J. C. (1955). *Ann. intern. Med.*, **42**, 701.
Sprinz, H., and Nelson, R. S. (1954). Ibid., **41**, 952.
Summerskill, W. H. J., and Jones, F. A. (1958). *Brit. med. J.*, **2**, 1499.
Svanborg, A., and Ohlsson, S. (1959). *Amer. J. Med.*, **27**, 40.
Talafant, E. (1956). *Nature (Lond.)*, **178**, 312.
Thorling, L. (1955). *Acta med. Scand.*, Suppl. 302.
Tisdale, W. A., Klatskin, G., and Kinsella, E. D. (1959). *Amer. J. Med.*, **26**, 214.
van den Bergh, A. A. H., and Muller, P. (1916). *Biochem. Z.*, **77**, 90.
Waitzkin, L. (1957). *New Engl. J. Med.*, **257**, 276.
Watson, C. J., and Hoffbauer, F. W. (1946). *Ann. intern. Med.*, **25**, 195.
Wegmann, R., Weinmann, S., and Rangier, M. (1960). *Rev. méd.-chir. Mal. Foie*, **35**, 95.
Weinstein, A., Alper, B. J., and Dade, J. R. (1959). *J. Amer. med Ass.*, **170**, 1663.
Werner, S. C., Hanger, F. M., and Kritzler, R. A. (1950). *Amer. J. Med.*, **22**, 325.
Williams, R., and Billing, B. H. (1961). *Lancet*, **2**, 392.
Wolf, R. L., Pizette, M., Richman, A., Dreiling, D. A., Jacobs, W., Fernandez, O., and Popper, H. (1960). *Amer. J. Med.*, **28**, 32.
Wynn, V., Landon, J., and Kawerau, E. (1961). *Lancet*, **1**, 69.

The work of the Manchester Committee on Cancer in the field of public education has been honoured by the appointment of the executive officer of its Educational Project, Mr. JOHN WAKEFIELD, as one of the six members of the World Commission on Cancer Control of the International Union against Cancer (U.I.C.C.). His term of office will be for four years between the Eighth International Cancer Congress in Moscow in July, 1962, and the ninth in Tokyo in 1966. The full membership of the Commission is as follows: *chairman*, Dr. R. M. TAYLOR, director, National Cancer Institute of Canada; executive director, Canadian Cancer Society; *members*, Dr. FERNANDO GENTIL (director, Instituto do Cancer, São Paulo, Brazil; Dr. R. GRANT (director of professional education, American Cancer Society); Dr. J. R. Heller (director, Memorial Center, N.Y., U.S.A.); Dr. EINAR PEDERSON (director, State Cancer Registry, Norway); Professor L. M. SHABAD (Academy of Medical Sciences, U.S.S.R.); Mr. JOHN WAKEFIELD (executive officer, Educational Project, Manchester Committee on Cancer).