JAUNDICE

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Jaundice or icterus, is the yellow colouration of the skin by bile pigment. It is only clinically visible when the serum bilirubin concentration exceeds about 2 mg. per 100 ml. and artificial light adds considerably to the difficulty in detecting mild degrees. Since bile pigment has an affinity for elastic tissue, skin, ocular sclera and blood vessels which contain many elastic fibres become particularly yellow.

Bilirubin is almost all derived from destruction of the haemoglobin of erythrocytes in the reticulo-endothelial cells of bone marrow, spleen and liver. Recent isotopic studies, however, have shown that 10-15 per cent. is derived from some source other than the haemoglobin of mature erythrocytes, and that this is possibly haematin or protoporphyrin (London *et al.*, 1950). The bilirubin is transported to the liver attached to the serum albumin (Klatskin and Bungards, 1956).

Bile Pigments in Serum

The van den Bergh reaction has traditionally been used to distinguish two types of bilirubin in serum, indirect (which has not passed through the liver cells) and direct (which has passed through the liver cells). Controversy has existed whether the different speeds of diazotization in the van den Bergh reaction are due to two different pigments, to different attachments to serum proteins or to the presence of a catalyst in the serum. The differences do not depend on protein binding in the serum for electrophoretic studies show that direct and indirect reacting pigments are both attached mainly to albumin (Martin, 1948; Gray and Kekwick, 1948); neither can a catalyst be demonstrated in the serum. The situation has been clarified by the work of Cole, Lathe and Billing (1954) who used the technique of reverse phase partition chromatography to demonstrate three pigments in jaundiced serum which are independent of protein. 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 by Bollman (1956) show that both

bilirubin and pigment 1 are present in the serum of the hepatectomized dog and hence are of extra-hepatic origin. Billing (1955) has shown that in obstructive jaundice and hepatitis the proportion of pigment 1 in the serum is greater than that of pigment 2 or bilirubin. She suggests that, in liver disease, in addition to obstruction preventing excretion of pigment into the bile there is also an impairment in conversion of bilirubin to pigment 1 and of pigment 1 to pigment 2. The practical significance of these observations has yet to be clarified although in the future the better diagnosis of jaundice may follow the measurement of the various bilirubin fractions.

The bilirubin then passes through the parenchymal cells of the liver into the biliary passages and so into the intestines. Andrews (1955) has put forward an interesting new hypothesis of the secretion of bile pigment by the liver. He suggests that pigment is first metabolized by the liver cells but that the enormous canalicular system in the liver not only transports bile pigment but also excretes direct reacting bilirubin and alkaline phosphatase through its walls. This is by no means proved but, if it were so, some of the obscure instances of obstructive-type jaundice occurring with patent extrahepatic ducts might be explained. They could be functional disturbances of the bile canaliculi analogous to functional disturbances of the renal tubules.

In the intestine the bilirubin undergoes bacterial reduction by the intestinal flora to stercobilinogen which is colourless and then to stercobilin which is orange-yellow in colour (Watson *et al.*, 1954). Some stercobilinogen is absorbed from the intestines and re-excreted into the bile. The very small quantity of absorbed stercobilinogen not re-excreted passes into the general blood stream and is removed in the urine as urobilinogen and further reduced to urobilin (Fig. 1).

The van den Bergh reaction has little practical diagnostic value. Although usually indirect in haemolytic jaundice, a direct component is found when the serum bilirubin level exceeds about

NORMAL BILE PIGMENT METABOLISM

UROBILINOGEN AND STERCIBILINOGEN ARE CHEMICALLY IDENTICAL

FIG. 1. *By courtesy of Blackwell Scientific Publications Ltd., Oxford.*

3 mgm./100 ml. and biphasic reactions also occur in both hepatocellular and obstructive jaundice.

Types of Jaundice

Theoretically jaundice could arise in three ways, by increased breakdown of haemoglobin—haemolytic jaundice, by obstruction of the bile passages—obstructive jaundice, and by failure of the liver cells to excrete bile—hepato-cellular jaundice. In practice, however, jaundice is usually of mixed type. In predominantly haemolytic jaundice, for instance, there is a secondary hepato-cellular component related to the anaemia. The jaundice of portal cirrhosis although mainly hepato-cellular is contributed to by diminished survival of erythrocytes. The jaundice of acute virus hepatitis, although mainly hepato-cellular, is also due to intra-hepatic distortion and obstruction of minute bile channels. Even jaundice following total obstruction to the common bile duct soon acquires a lesser hepato-cellular component due to the secondary changes in the liver cells when the bile ducts are obstructed. These considerations explain the frequent apparent fallibility of liver function tests and the clinical anomalies which may add to the diagnostic confusion.

TABLE I.

CLASSIFICATION OF JAUNDICE

Hepato-cellular

- Acute—virus hepatitis { serum infective
- Chronic—cirrhosis (portal or post-necrotic)

Obstructive

- With extrahepatic obstruction { carcinoma of the ampulla
choledocholithiasis, etc.
- Without extra-hepatic obstruction { acute drugs { P.A.S.
chlorpromazine
organic arsenicals
methyl testosterone
butazolidine
chronic ('primary biliary cirrhosis')
malignant deposits in liver

Haemolytic

- congenital
- acquired

N.B. Reticulosis
Uraemia
Cirrhosis
Blood transfusion

Congenital hyperbilirubinaemia ± unidentified pigment in liver cells.

Clinical Management of the Jaundiced Patient

History

Antecedent dyspepsia or a previous attack of biliary colic suggests choledocholithiasis. Pro-

gressive failure of general health and weight loss favours a carcinomatous aetiology. If the patient has had any injection in the preceding six months, the diagnosis is serum hepatitis until disproved; injections include Mantoux testing, BCG vaccination, tattooing, as well as blood or plasma transfusions. Absolute anorexia with aversion to smoking suggests virus hepatitis. The rate of onset of jaundice is important; in virus hepatitis the patient becomes jaundiced rapidly, often in a matter of hours, and the colour quickly deepens. Obstructive jaundice is slower in its beginnings. Persistent mild fluctuant jaundice suggests portal cirrhosis or haemolytic jaundice and in these patients the stools are well coloured. Biliary colic should be noted and the back or epigastric pain of pancreatic carcinoma.

Examination (Table 2, Fig. 2)

Anaemia and weight loss are noted, also the depth of jaundice. A hunched-up position in bed suggests pancreatic carcinoma. The skin should

be observed carefully. Bruising may indicate prothrombin deficiency, purpura, often axillary or on the forearms, is not uncommon with the thrombocytopenia of portal cirrhosis. Other signs of chronic hepato-cellular disease include vascular spiders, palmar erythema, white nails (Terry, 1954), disappearance of secondary sexual hair and gynecomastia. Parotid swellings and Dupuytren's contractures are often found in cirrhotic patients who are alcoholic (Summerskill and Davidson, 1956). Scratch marks on the skin suggest obstructive jaundice and in chronic obstruction the patient may show melanin pigmentation, clubbing of the fingers, xanthomata on eyelids, extensor surfaces and palmar creases with hyperkeratosis related to vitamin A lack. Pigmentation and ulcers on the shins are found in congenital haemolytic jaundice. Malignant deposits in the skin should be noted. Search is made for any primary growth.

TABLE 2

Examination	Significance
Nutrition	
Poor	Cirrhosis. Cancer.
Obesity	Gall-stones.
Anaemia	Haemolysis. Cancer. Cirrhosis.
Search Primary Tumour	Lung, Breast, Stomach, Colon, Thyroid, etc.
Lymphadenopathy	Cancer. Reticulosis.
Skin	
Depth Jaundice	Mild—Haemolytic. Green—Prolonged obstruction.
Vascular spiders	Hepato-cellular jaundice.
Melanosis	Prolonged biliary obstruction.
Xanthomata	" " " "
Scratch marks	Biliary obstruction.
Bruises	Prothrombin deficiency.
Purpura	? Cirrhosis.
Sexual hair	Absent cirrhosis.
Pigmented shins	Congenital spherocytosis.
Ankle oedema	Cirrhosis. Inferior vena caval obstruction.
Tumour deposits	Cancer.
Hands	
Palmar erythema	Cirrhosis.
Clubbing nails	Biliary cirrhosis, portal cirrhosis.
White nails	Cirrhosis.
Periumbilical veins	Cirrhosis.
Ascites	Cirrhosis, cancer.
Liver	
Very large	Cancer. Obstructive jaundice.
Impalpable	Cirrhosis.
Tender	Cirrhosis. Fulminant hepatitis.
Splenomegaly	Hepatitis.
	Cirrhosis, Hepatitis, Haemolytic.
Gall-Bladder	
Palpable	Extra-hepatic biliary obstruction.
Tender	Cholecystitis.
Fetor Hepaticus	Portal-systemic encephalopathy (hepato-cellular jaundice).
Confusion	
'Flapping' Tremor	
Exaggerated Reflexes

FIG. 2.—Physical signs in the jaundiced patient.

Abdominal examination includes noting the presence of dilated abdominal wall veins suggesting a portal collateral circulation, ascites, liver size, tenderness and palpability of the gall bladder and splenomegaly. Peripheral oedema is recorded.

Essential Investigations

Urine. The most satisfactory sensitive tests for bilirubin are the tablet test (Tallack and Sherlock, 1954) or Fouchet's method. These are indicated for the early diagnosis of virus hepatitis and of drug jaundice, for instance, that complicating chlorpromazine therapy. They may also be used to screen liver function in workers exposed to hepatotoxins. Persistent absence of urobilinogen suggests total obstruction of the common bile duct. Persistent excess of urobilinogen with a negative bilirubin test supports a haemolytic jaundice.

Faeces. Persistent acholic stools confirm extra-hepatic biliary obstruction. The presence of a positive test for occult blood favours ampullary pancreatic carcinoma or may occur in the cirrhotic patient with portal hypertension.

If a careful daily chart is kept of faecal colour and the presence of excess urinary urobilinogen more elaborate investigations may prove unnecessary and many unnecessary laparotomies would be avoided.

Serum Biochemical Tests. The essential minimum is the serum bilirubin and phosphatase levels and one seroflocculation test. The serum bilirubin level confirms jaundice, assesses severity and is used to follow progress. Serum alkaline phosphatase values over 30 King Armstrong units (greater than 10 Bodansky units) strongly suggest biliary obstruction if bone disease is not present. It must, however, be remembered that high values sometimes occur in patients with portal cirrhosis with but slight icterus. Among the numbers available, the choice of seroflocculation tests is an individual one. The zinc sulphate turbidity and the thymol turbidity are a satisfactory combination. These tests, however, do not measure liver function, but reflect mainly changes in the serum globulins, and these correlate with activity of the reticulo-endothelial system. The seroflocculation tests are therefore liable to be positive in diseases such as malaria, infectious mononucleosis or rheumatoid arthritis without indicating disease of the liver cells.

If possible, serum albumin and globulin levels should be measured quantitatively, although in acute jaundice, whatever the aetiology, they may be little changed. In more chronic hepato-cellular jaundice the depression in albumin and rise in globulin is diagnostically useful. Electrophoretic analysis of the serum is performed routinely in the Chemical Pathology Department of the Post-

graduate Medical School and has proved of surprising value. The virtually normal serum albumin with elevated $\alpha_2\beta$ globulins in obstructive jaundice contrasts with the albumin depression and γ globulin elevation of hepato-cellular jaundice.

Haematology. A low total leukocyte count with a lymphocytosis suggests hepato-cellular jaundice, although in very severe virus hepatitis there may be a leukocytosis with increased polymorphonuclears.

Radiology. A chest film is routinely taken to show primary or secondary tumour. A plain film of the abdomen may reveal hepatomegaly or splenomegaly and 10 per cent. of gall stones are radio-opaque. A barium meal may show oesophageal varices and in patients with hepatomegaly due to cirrhosis or secondary cancer the lesser curve of the stomach may be displaced and even rigid. Distortion and altered mobility of the duodenum is seen in carcinoma of the pancreas. Cholecystography is contraindicated, for, even with the newer contrast media, such as biligradin, there is insufficient excretion of the dye into the biliary track to give informative films.

Needle Liver Biopsy. This technique has surprisingly little place in the diagnosis of jaundice, being indicated in only 15 per cent. of patients with this symptom. The technique has its greatest morbidity in the icteric subject, especially if the jaundice is of hepato-cellular type. Prothrombin time must be normal before the puncture and blood must be ready for transfusion if there is complicating intraperitoneal haemorrhage. The hepatic histological pattern is characteristic in the three main types of jaundice, but cannot be relied upon to distinguish obstructive jaundice due to extra-hepatic bile duct obstruction from that occurring without blocked main bile passages.

Haemolytic Jaundice

Investigations should include careful family history with haematological investigation of siblings if possible, haemoglobin level and absolute values, reticulocyte count, blood film for spherocytosis and immature cells, erythrocyte fragility, Coombs' test and bone marrow examination. Occasionally other investigations may be necessary, such as the measurement of the survival of transfused red cells and a quantitative estimation of faecal and urinary urobilinogen. Pigment gall stones may be associated, adding an obstructive element to the jaundice.

The Place of Surgery

It should rarely, if ever, be necessary to resort to operation to diagnose the type of jaundice, although it may be necessary to elucidate the cause. If there is any doubt concerning the diagnosis, it

is better to wait three weeks rather than explore the bile passages of a patient with hepato-cellular jaundice and so run the very real risk of precipitating acute liver failure. The intervening period is occupied by careful clinical observation, daily examination of urine and stools and weekly routine biochemical tests. If there is still doubt, needle biopsy is a usual preliminary to surgery. The patient rarely suffers from the delay. If the diagnosis is virus hepatitis, he will probably be recovering spontaneously; if cirrhosis, the diagnosis should be obvious; and if obstructive, the changes occurring in the liver are essentially reversible. Biliary cirrhosis will not develop in a matter of weeks. If the diagnosis is carcinoma of the pancreas or biliary ducts or metastatic carcinoma, chances of a radical removal are so remote that they are unlikely to be affected by the few weeks' delay. Jaundice is rarely a surgical emergency. When operation is indicated the exploration should be thorough and, if any diagnostic doubt remains, should include operative liver biopsy and operative or post-operative cholangiography.

Medical Treatment

While the stools are acholic dietary fat should be restricted. High protein intake is encouraged provided the patient does not show the features of impending hepatic coma.

Itching is treated by phenol and calamine lotions and by anti-histaminic drugs. If pruritus becomes intolerable, methyl testosterone, 25 mg. daily sublingually, may be given, although this has the disadvantage of increasing the jaundice and causing masculinizing features in women (Lloyd-Thomas and Sherlock, 1952). Prednisolone is also sometimes effective. Hormone therapy should never be given for the transient pruritus associated with acute hepatitis.

When infective cholangitis complicates obstructive jaundice it may be temporarily controlled by tetracycline therapy, although operative relief of the obstruction is essential for permanent cure.

Special Types of Jaundice

It is clearly impossible to describe all the various types of jaundice and examples have been chosen where new developments are being made.

Jaundice in Pregnancy

There is no specific pregnancy jaundice and even in pre-eclampsia or eclampsia jaundice is mild and terminal. The common causes of jaundice in pregnancy are gall stones and virus hepatitis. Choledocholithiasis is common, for the serum and biliary cholesterol levels rise in pregnancy and cyesis is associated with delayed gall bladder emptying. Virus hepatitis is contracted either

through needle punctures in the ante-natal clinic or by close contact with excreta of the patient's other children. In spite of the traditional bad prognosis of virus hepatitis in pregnancy, in most instances the attack does not differ from that occurring in the non-pregnant and the fulminant form ('acute yellow atrophy') is very rare. The patient should be supervised in hospital; termination is usually contraindicated. Miscarriages often occur (four out of 11 in one series) and the foetal mortality is considerable. Foetal abnormalities are unusual and neonatal hepatitis or cirrhosis do not occur (Martini, 1953).

Jaundice in Infancy

So-called 'physiological jaundice' is deeper and most prolonged in premature infants. It is for the most part due to hepatic immaturity and is, therefore, hepato-cellular.

Haemolytic disease of the new-born is the result of Rhesus or A-B-O iso-immunization in the mother. It is characterized by patechiae, hepato-splenomegaly and many primitive red cells in the circulating blood.

In both the above conditions the pigment circulating is bilirubin (reacting indirectly in the van den Bergh reaction), which is increased even to 40 mg./100 ml. These are the only types of jaundice where this pigment achieves such levels and this is presumably due to failure of the liver to convert to pigment 2. Bilirubin has an affinity for nervous tissue, especially the basal ganglia, and is believed responsible for kernicterus, the most dreaded complication of neonatal jaundice (Claireaux, Cole and Lathe, 1953). The height of the serum bilirubin is an important indication for exchange transfusion (Mollison and Cutbush, 1949). The teeth become green, probably due to toxic action of bilirubin on the enameloblasts (Claireaux, Gerrard and Marsland, 1955).

Congenital anomalies of the bile duct are rare causes of neonatal jaundice. The extra-hepatic or intra-hepatic ducts may be affected. Jaundice develops within 10 days of birth and continues unrelentingly until death at age one to four years. Pruritus is troublesome and xanthomas may develop later. Few of these patients are relieved by surgery, although all should be explored.

Hepatitis is frequent in the new-born, and Gellis (1955) has collected 75 instances, including seven families in whom more than one child was affected. Jaundice may appear at birth or develop soon afterwards. The infant is unwell, does not take its feeds, may die rapidly with fulminant hepatitis or recover after a mild illness. After a relapsing course the baby may make an apparent recovery only to appear in childhood with hepatic cirrhosis. Hepatic histology shows an acute hepatitis with

multinucleated liver cells, indicating rapid regeneration, foci of erythropoietic activity and haemosiderosis (Dible *et al.*, 1954). It is thought, although not proved, that this condition is virus hepatitis of serum type transmitted from the mother. It is probably an important cause of cirrhosis, not only in childhood, but also in adolescence and early adult life.

The circulating bile pigment associated with congenital lesions of the bile duct or neonatal hepatitis is mostly of the direct type, has no affinity for nervous tissue, and kernicterus is a very rare complication.

Other rarer causes of neonatal jaundice include galactosaemia and viraemia due to the herpes simplex virus. With the emergence of antibiotic-resistant staphylococci umbilical sepsis with mild jaundice is being encountered again.

Drug Jaundice

There are four possible types of iatrogenic jaundice. Serum hepatitis may be transmitted by the syringe or needle with which the drug is given. Jaundice due to direct toxic action on liver cells is extremely rare and the maximal damage produced by drugs such as gold is usually on the kidney. Similarly, haemolytic jaundice due to such drugs as sulphonamides, phenylhydrazine or to benzene derivatives is very uncommon. An obstructive type of drug jaundice, however, is extremely frequent (Johnson and Doenges, 1956). Drugs causing it include methyltestosterone, organic arsenicals (Hanger and Gutman, 1940), butazolidine, paramino-salicylate, thiouracil, dinitrophenol and the most common is chlorpromazine and this will be described as the prototype.

Chlorpromazine Jaundice

Jaundice occurred in 1.4 per cent. of 7,599 patients treated with the drug (Doughty, 1955). The jaundice appears in the second or third week of therapy or may even start as long as two weeks after stopping the drug. It is preceded by mild malaise, fever, chills and nausea. Anorexia is not so conspicuous as with virus hepatitis. The temperature may rise to 101° . Hepatomegaly is inconstant. The jaundice is of obstructive type, with pale stools, bilirubinuria, raised serum alkaline phosphatase levels, negative seroflocculation tests and often conspicuous itching. Needle biopsy of the liver shows only centrilobular bile retention with a minimal cellular increase in the portal zones with eosinophils conspicuous. The peripheral blood sometimes shows an eosinophilia. The jaundice is usually mild and clears within two weeks of stopping the drug. Occasionally, however, it may persist as long as six months, but with eventual recovery. The only fatalities have been reported

FIG. 3.—Diagram of the biliary system showing the probable site of the lesion in chlorpromazine jaundice.

in patients with underlying chronic liver damage or with a serious concomitant condition, such as carcinoma or congestive heart failure.

An allergic aetiology is supported by the eosinophilia, but the drug has been exhibited again after recovery with no recurrence of jaundice (Garmany, May and Folkson, 1954).

The site of the lesion seems to be in the cholangioles (Fig. 3), but its nature is unknown. Strangulation by the slight exudate in the portal sinus seems unlikely, as does primary cholangitis. A metabolic anomaly of the cholangiole similar to primary tubular defects in the kidney is possible but not proved. Werner and co-workers (1950) suggested that methyl testosterone jaundice might be due to altered hydration of bile, excessive water being reabsorbed in the canaliculi so that the bile becomes very viscid and blocks the cholangiole. This again seems unlikely, for the number of canaliculi is so great that occlusion of a few by bile thrombi would not be sufficient to produce jaundice.

No special treatment is needed for this type of jaundice. Every jaundiced patient, however, must be questioned about previous medication and, if necessary, confronted with chlorpromazine tablets for recognition. There is a real risk of these patients undergoing surgical operations. A similar picture may sometimes be seen in some patients with virus hepatitis or with Hodgkin's disease and also lead to confusion with extra-hepatic biliary obstruction.

Chronic Intra-hepatic Obstructive Jaundice (Primary Biliary Cirrhosis)

This condition resembles chlorpromazine drug jaundice in being of obstructive type without an extra-hepatic biliary obstruction being demon-

strated. The site of obstruction is presumably in the cholangioles. This is, however, a chronic, incurable disease and drugs have not so far been incriminated in the aetiology. The condition is more frequent in women (10 to 1). It is of gradual onset with mild jaundice and itching; hepatosplenomegaly is constant. Hepatic histology shows bile retention with a florid exudative lesion in the portal zones, which eventually develops to biliary cirrhosis. Serum cholesterol levels may rise very high with the production of xanthomata (xanthomatous biliary cirrhosis). An important distinction from extra-hepatic biliary obstruction is the absence of bouts of cholangitis (rigors, fever, exacerbations of jaundice and itching) and the condition is always painless. Laparotomy with cholangiography is usually needed to prove patency of the extra-hepatic bile ducts. The course is three to 10 years and complications include bleeding duodenal ulcer, oesophageal varices, thinning of the bones (Atkinson *et al.*, 1956) and finally inter-current infection or liver cell failure with ascites and hepatic coma.

Treatment includes control of anaemia, calcium Sandoz, 6 g. daily, and regular intramuscular vitamins A, D and K. Pruritus may need treatment.

Symptomless Jaundice

The problem may arise of the patient who feels well but is intermittently mildly jaundiced. Slight jaundice may continue for some months after virus hepatitis without fibrosis in the liver (Hult, 1950). Alternatively, the patient may have a true post-hepatic cirrhosis. Cholelithiasis is unlikely without symptoms. Congenital spherocytosis (acholuric jaundice) exists in all grades of severity, including the patient who notices only icterus from time to time and is never clinically anaemic. The diagnosis in this latter group is made by family history, splenomegaly, spherocytes in blood smear, reticulocytosis and diminished erythrocyte fragility.

When the above conditions have been excluded, there remains the congenital hyperbilirubinaemias (constitutional hepatic dysfunction). Jaundice, often with mild nausea and languor, occurs intermittently throughout life. This is the only physical sign. Two types are recognized, depending on the presence of excess pigment in the liver. Congenital hyperbilirubinaemia with unidentified pigment in the liver was described by Dubin and Johnson

(1954). The liver biopsy, naked eye, appears black and, microscopically, the liver cells contain a non-iron, non-bile pigment allied to the lipochromes but whose exact nature is unknown. This group also show a slightly raised serum alkaline phosphatase level and the gall-bladder fails to fill on cholangiography. In addition, serum from this type with pigment in the liver, in contrast to that without, shows a high percentage of 'direct bilirubin' and bile appears in the urine. Investigation usually shows that serum bilirubin values are raised in relatives.

Patients with symptomless jaundice demand the most complete investigation and aspiration needle biopsy is usually needed for accurate diagnosis.

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