THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

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A knowledge of the 'natural history' of bilirubin is essential for the clear differentiation of the different types of jaundice. Bilirubin is a breakdown product of haemoglobin, manufactured by the reticulo-endothelial system mainly in the spleen and bone-marrow but also in any other organs or tissues of the body where reticulo-endothelial tissue occurs. The haemoglobin molecule consists of a porphyrin fraction linked to globin and iron and it is the porphyrin which is converted into bilirubin via heme (haematin). The bilirubin passes from the spleen, bone-marrow, etc., in the blood stream, to the liver where it is passed through the parenchymatous cells of the liver and into the bile capillaries. (During its passage through the liver cells it is altered in a way to be referred to later.) The bilirubin now passes out of the liver in the bile, and in the gut is reduced to urobilinogen (also called stercobilinogen). Further oxidation converts the urobilinogen (stercobilinogen) into urolibin (stercobilin) which gives the characteristic brown colouration to the faeces. Oxidation of bilirubin to biliverdin may occur and in certain conditions the faeces may be green for this reason. Part of the urobilinogen is re-absorbed from the gut and is carried back in the portal vein to the liver where most of it is re-excreted in the bile but some passes through the liver eventually reaching the kidneys and is excreted in the urine.

The following points need special emphasis :—

1. The bilirubin found in the reticulo-endothelial tissues is different from the bilirubin which passes into the bile capillaries and hence into the gut. These two bilirubins are sometimes called pre-hepatic (or haemobilirubin) and post-hepatic (or cholebilirubin). The chemical difference between the two is not known but the conversion of the former into the latter occurs during passage through the parenchymatous cells of the liver.

2. Pre-hepatic bilirubin is normally present in the blood (0.2-0.4 mgm.), is not excreted by the kidneys, and therefore never appears in the urine, and it gives an indirect van den Bergh reaction.

3. Post-hepatic bilirubin is found in the blood only when obstruction of the biliary passages occurs, it is readily excreted by the kidneys when present in the blood stream, and it gives a direct van den Bergh reaction.

4. Urobilinogen is found in normal urine (in traces) and is increased in the urine when there is an excess of it in the bowel.

5. Bile salts are found in the urine when post-hepatic bilirubin is also present and at no other time.

Applied Physiology of Bilirubin

(a) *In haemolytic states.* If excessive haemoglobin destruction occurs in the body an excess of pre-hepatic bilirubin is formed. The liver excretes a larger amount of post-hepatic bilirubin than normally, more urobilinogen is therefore present in the gut and the faeces are thus darker than normally. Owing to the large amount of urobilinogen in the faeces more is absorbed into the portal vein and more escapes being re-excreted by the liver and passes into the general blood stream to be excreted eventually by the kidneys. An excess of urobilinogen therefore occurs in the urine. Some of the pre-hepatic bilirubin reaching the liver fails to pass through the liver cells and becomes converted into post-hepatic bilirubin, passing instead into the general blood stream and causing a rise in the amount present with subsequent development of icterus.

(b) *In obstructive conditions.* When obstruction to the outflow of bile occurs, post-hepatic bilirubin and bile salts are absorbed from the bile into the general blood stream. Icterus of the skin appears and bilirubin and bile salts appear in the urine. The amount of pre-hepatic bilirubin formed of course remains the same. As no bile is reaching the gut, no urobilinogen and urobilin is found in the gut, so the faeces are pale and devoid of pigment.

(c) *In toxic conditions* affecting the liver. Under these conditions the liver cells undergo cloudy swelling and the endothelium of the bile capillaries also swells. The swelling of the liver cells compresses the bile canaliculi and the bile capillaries so that obstruction to the free outflow of bile occurs and the post-hepatic bilirubin contained therein is absorbed into the blood stream.

At the same time, because of the toxic condition of the liver cells, some of the pre-hepatic bilirubin is not absorbed and passed into the biliary system so that this bilirubin also appears in the blood stream in excessive amounts.

Causes of Icterus

1. *False icterus.* (a) Icterus or jaundice is often diagnosed when it is not present. Perhaps the commonest error is to mistake the yellowish pallor present in severe anaemia for jaundice. Examination of the conjunctivae or, in doubtful cases, an icteric index estimation, will soon resolve the difficulty.

(b) Staining of the skin may be present and even of the conjunctivae in various conditions when the level of bilirubin in the blood is normal. Carotinaemia due to excessive ingestion of carotin, and mepacrine administration are two common causes of apparent jaundice which should always be considered.

2. *Physiological icterus.* This occurs normally after birth but disappears in a few days. It is due to the destruction of a proportion of the infant's red blood cells consequent upon the cessation of placental respiration. A mild degree of jaundice may also occur following infarction of the lungs, severe bruising of the tissues, etc., where extravasated blood is converted into bilirubin.

3. *Obstructive jaundice.* Any cause of obstruction to the outflow of bile from the liver or bile ducts will lead to jaundice. A stone or worm in the common bile duct, extrinsic or intrinsic carcinoma blocking the bile duct, or fibrous tissue compressing or strangling the main bile duct or some of its tributaries will all lead to jaundice of the obstructive type. Congenital obliteration of the bile ducts is a rare type.

4. *Toxic or infective jaundice.* (a) In recent years infective hepatitis has been the commonest cause of this type of jaundice. In this condition, the parenchymatous cells of the liver are attacked by a virus leading to swelling and poor functioning of the cells. The bile capillaries are compressed by the swelling, and the endothelium of the bile capillaries also swells leading to further obstruction of the lumen of these vessels. A small amount of bile, however, does reach the common duct in most cases and this bile may become very thick and inspissated and lead to further obstruction of the passages, and a persistence therefore of jaundice when the liver condition itself is returning to normal. Steps should therefore be taken in this disease to keep the biliary passages drained, e.g., mag. sulph. each morning.

(b) Serum jaundice has acquired considerable importance recently and every jaundiced patient should be carefully questioned as to the administration of blood, serum, or other intravenous injections during the previous three months. Again a virus is the responsible agent and its identity with the virus of infective hepatitis is probable though not proved.

(c) Many poisons may affect the liver, leading to jaundice. Chief among these are chloroform, phosphorus, trinitrotoluene, arsenic, etc. It must not be forgotten that sulphonamides can act as liver poisons, but probably only in susceptible individuals or in patients with previously abnormal livers. Acute yellow atrophy has been observed and reported several times after sulphanilamide.

(d) Jaundice may occur during the course of many acute infective processes. To mention a few, Weil's disease, yellow fever, glandular fever, pneumonia, etc.

5. *Haemolytic icterus.* This arises whenever excessive haemoglobin destruction occurs.

(a) Physiological jaundice of the new born has been mentioned above.

(b) Icterus gravis neonatorum. This is a severe type of haemolytic anaemia caused by haemaglutinins arising in a Rhesus negative mother in response to antigens from a Rhesus positive foetus.

(c) Congenital haemolytic icterus (acholuric jaundice). The familial incidence and increased fragility of the red cells, together with splenomegaly and jaundice make this one of the easier conditions to recognize.

(d) Acquired haemolytic icterus. There are many varieties of this condition. In some cases a definite chemical compound can be incriminated, such as lead, phenylhydrazine, potassium chlorate, sulphonamides, arsenicals and benzene derivatives. In other cases micro-organisms such as the malarial parasite, Clostridium welchii, etc., may be causative, and in others no cause can be found and these are usually referred to as ' Lederer's acute haemolytic anaemia.' The jaundice of pernicious anaemia is also haemolytic in origin.

(e) Incompatible blood transfusion is usually obvious with other associated symptoms.

The Clinical Features of Jaundice

In all cases of course the history is important. The mode of onset, associated with gastro-intestinal or other symptoms, the occupation of the patient, any loss of weight, the administration of drugs or injections, the family history, etc., should all be elicited. On physical examination, the presence or absence of pyrexia should be noted,

also the depth of the jaundice; in particular a careful examination of the abdomen is essential. The right hypochondrium must be carefully palpated and the size of the liver noted, together with any evidence of tenderness or irregularity of the organ. The epigastrium must be palpated for a possible neoplasm of the stomach and the left hypochondrium examined for splenic enlargement. Glandular enlargement should be looked for and also the presence or absence of anaemia with any associated neurological signs or tongue changes. In all cases the urine and faeces must be examined. The colour of the faeces—whether pale and putty-like, or normal, or darker than normal—and the presence or absence of bilirubin, bile salts or urobilinogen in the urine are the main points to be looked for. Having elicited the history and completed a physical examination, we can in the majority of cases decide if the jaundice is toxic, haemolytic or obstructive in origin. Clinically, therefore, in toxic jaundice there may be a history of drug or chemical poisoning, the temperature is commonly raised, the jaundice is moderately deep, nausea is present, anaemia is slight or absent, the liver is enlarged and tender, the spleen is not palpable, the faeces are pale and the urine is dark and contains bilirubin and, maybe, bile salts. In certain diseases there may be associated signs such as skin haemorrhages or herpes—as in Weil's disease. In obstructive jaundice there may be a history of biliary colic, or loss of weight, or loss of appetite, suggesting either impaction of a calculus, or a neoplasm of the pancreas or stomach. The temperature is normal or subnormal, the jaundice is marked and deepens rapidly, nausea may be absent, anaemia may or may not be present, the liver is usually a little enlarged and may have palpable metastatic carcinomatous masses present in it, the spleen is not palpable and the faeces are pale, with the urine very dark and loaded with bile salts and bilirubin. Itching of the skin is common. In haemolytic jaundice there may be a family history or a history of malaria, drug or chemical ingestion, the temperature is usually raised while haemolysis is occurring, the jaundice is mild and the trunk appears to be more jaundiced than the legs, nausea is absent, anaemia is marked, the liver is usually only slightly enlarged, if at all, the spleen is enlarged, sometimes markedly so, the faeces are dark and the urine is dark, containing an excess of urobilinogen but no bilirubin or bile salts. In acholuric jaundice, ulcers are common on the legs, and in pernicious anaemia there is glossitis and signs of subacute combined degeneration of the cord.

Laboratory aids in differential diagnosis. If the points mentioned above are clearly noted, a case of jaundice can usually be ascribed to one of the three main classes without any laboratory aid. Difficult cases do occur, however, particularly in differentiating between toxic and obstructive jaundice. Indeed, obstruction is a feature of most cases of toxic jaundice and sometimes even laboratory aids do not help in distinguishing the two types and the subsequent history of the case has to be relied on in deciding the final diagnosis. If the jaundice gradually lessens it was toxic in origin, but if it remains deep after a month then obstruction is almost certainly present and laparatomy is advisable to determine the cause. Urine and faeces examination has been dealt with in the clinical section. A complete blood count is always advisable and may give valuable aid. A marked anaemia with increased fragility of the red cells and a reticulocytosis would indicate haemolytic icterus. A leucocytosis also occurs in

SUMMARY OF MAIN DIAGNOSTIC FEATURES IN JAUNDICE

		Obstructive.	*Toxic or Infective.*	*Haemolytic.*
1.	Mode of onset.	Rapid with or without pain.	Gradual, jaundice deepening fairly rapidly.	Gradual.
2.	Nausea.	Slight or moderate.	Marked.	Absent.
3.	Temperature.	Normal.	Commonly raised.	Raised only in acute haemolytic states.
4.	Degree of icterus.	Great.	Slight or great.	Moderate.
5.	State of liver.	Little enlarged, may have metastatic nodules.	Enlarged and tender.	Normal.
6.	Spleen.	Not palpable.	Rarely palpable.	Palpable, often grossly enlarged.
7.	Faeces.	Pale.	Pale.	Dark.
8.	Urine.	Dark, contains bile pigment and bile salts. No urobilinogen present.	Dark, contains bile pigment and bile salts. May be trace of urobilinogen present.	Dark, but contains no bile pigment or salts. Urobilinogen present in excess.
9.	Blood count.	Normal or slight anaemia.	Normal but maybe leucocytosis.	Anaemia with reticulocytosis.
10.	Duration of icterus.	Persists until obstruction is relieved.	Clears usually in less than a month.	May persist for years.

haemolytic icterus during the acute stage but in the absence of anaemia a leucocytosis of 15,000 or over would indicate malaria, Weil's disease or suppurative pylephlebitis. The van den Bergh reaction on the serum has rightly gained the most important place in the laboratory diagnosis of jaundice. A prompt direct reaction indicates obstructive jaundice, a biphasic reaction probably toxic jaundice and an indirect reaction, haemolytic jaundice. But too much reliance must not be placed on the test and it must always be interpreted in conjunction with the history and physical examination. In toxic jaundice a prompt direct reaction is often obtained and in obstructive jaundice a biphasic reaction may occur.

Of the other aids to diagnosis little need be said. A cholecystogram may reveal a calculus; blood or urine culture will show leptospira in Weil's disease; blood films will be positive in malaria, etc.

The main diagnostic features in jaundice may be summarized in the foregoing table.

BOOK REVIEWS

DIAGNOSIS IN STERILITY

Edited by EARLE T. ENGLE. Blackwell Scientific Publications. 1947. Pp. 236. Price 25s.

This book chronicles the proceedings of a conference sponsored by the National Committee on Maternal Health, and is concerned with diagnosis only. The conference was attended by every well-known worker in the field of sterility in the U.S.A. The proceedings are presented verbatim and are all the more interesting on this account, and there is a most useful summary of the conference.

Chapters on laboratory examination of semen and the clinical interpretation of such analyses are sound and rational. There are excellent chapters on the value of testicular and endometrial biopsies and the discussion on the interpretation of basal body temperature curves is excellent in every respect.

Most English readers will appreciate the attitude of 'debunking' which has pervaded the conference, and has consequently resulted in a high standard of scientific attainment.

Most British readers will also take heart when they find that during the war years there was no advance in the U.S.A. over the progress maintained in this country in the subject of infertility.

This is a most readable publication with excellent references, and throughout it is illustrated most beautifully by first class photomicrographs.

C.D.R.

DISEASES OF THE NOSE, THROAT AND EAR

By I. SIMSON HALL, M.B., CH.B., F.R.C.P.E., F.R.C.S.E. 4th Edition. E. & S. Livingstone Ltd. Edinburgh. 1948. Price 15s.

This book was first published in 1937 and the fourth edition is now published. This is a measure of its popularity and a comment on the lack of an adequate student's textbook on this subject in the English language. For this book of 440 small pages, approximately 150,000 words, attempts to cover the whole subject including anatomy and treatment and in doing so sacrifices clarity and accuracy. Many examples of this can be given. On page 43 'In other instances a virus infection appears to be the cause' is read in the paragraph on the causation of the common cold. Surely this is an inadequate comment on the part played by the virus. On page 44 in the paragraph on Treatment of Acute Rhinitis this sentence appears, 'If possible the patient is put to bed with a hot drink and a mild laxative, and is nursed in an even temperature (Prescription—Camphor ½ per cent., Menthol ½ per cent., paraff. lig. 1 ounce).' The context in no way clarifies this sentence and the reviewer would not know whether to prescribe this as the hot drink, the laxative or as nasal drops which are not mentioned. On page 114 this sentence appears in reference to frontal sinus operations, 'One of the most convenient places to start the opening is just on the outer edge of the orbital roof, almost above the inner canthus.' This is a strange juxtaposition of inner and outer where they do not have opposite meanings as outer in reference to orbital edge is opposed to deep (not inner as there is no inner edge to the orbit) and inner in reference to canthus is opposed to lateral (or outer).

On the whole the illustrations are good and helpful. A notable exception is Fig. 49 (1) on page 239, which fails to show the falling forwards of the cartilage of Wrisberg and apparent shortening of the paralysed cord in the resting larynx.

It is always easy to criticize adversely a textbook and the preceding examples of defects could be multiplied but there are also many good features in the book and pages 372 and 373 on the local signs of acute mastoiditis should be particularly commended for emphasizing the important points clearly and concisely and omitting nothing important.