Regular Review

Diagnosis of jaundice

IAN A D BOUCHIER

Jaundice is a cardinal manifestation of hepatobiliary disease. Any patient found to have a raised serum concentration of bilirubin will be investigated further, since diseases responsible for hyperbilirubinaemia range from the trivial to the grave. The approach to diagnosis relies heavily on three techniques that delineate the anatomy of the biliary tract: ultrasonography, percutaneous transhepatic cholangiography, and endoscopic retrograde cholangiopancreatography. One or more of these investigations will usually provide the basis for diagnosis and further management. Nevertheless, in nearly three-quarters of all jaundiced patients the cause can be discovered from the traditional clinical techniques of history taking, physical examination, and a few simple biochemical tests.

Classification of jaundice

Our understanding of bilirubin metabolism and of the processes of bile secretion improved in the 1960s^{1 2} and led to several "new" classifications of jaundice. The essential issue remains simple: is there a cause which requires surgical intervention or is surgery unnecessary—"medical" jaundice? The distinction is critical. An operation on a patient with hepatocellular disease carries an appreciable morbidity and mortality³; conversely, if surgery is delayed when there is obstruction to bile flow the patient is exposed to the risks of cholangitis, septicaemia, and renal failure.⁴ Unfortunately, routine biochemical tests often fail to distinguish the medical and surgical categories. Jaundice can be classified accurately on a fairly complex scheme depending on the various steps in bile secretion⁵; but for practical purposes the best approach probably remains the simple one based on the physiological types of bilirubin.

Serum bilirubin occurs in two forms, unconjugated and conjugated to glucuronide. Unconjugated hyperbilirubinaemia may be caused by haemolysis and, less frequently, hepatocellular disease. Conjugated hyperbilirubinaemia may arise because of disease affecting the liver cells or from obstruction to the secretion of bile—hepatocellular and obstructive jaundice, respectively. At times, however, the biochemical features of these last two disorders may be identical, and this problem has led to the adoption of the term "cholestasis." Used in a clinical setting cholestasis implies a syndrome in which there is biochemical evidence for obstruction to the secretion of bile: conjugated hyperbilirubinaemia and raised serum values of alkaline phosphatase, gamma-glutamyl-transferase, 5'-nucleotidase, bile salts, cholesterol, and lipo-

protein-X. The cause of cholestasis may lie in the liver or outside it.

Conjugated hyperbilirubinaemia may, then, exist as an isolated phenomenon or as part of the biochemical picture of liver-cell dysfunction with raised serum activities of the liver-cell enzymes alanine and aspartate aminotransferases, or as a manifestation of cholestasis which may be due to intrahepatic or extrahepatic disease.

The assessment of a patient with jaundice depends, too, on an appreciation of its common causes, and these will vary in different circumstances. Gall stones, secondary malignant disease of the liver, hepatitis, cirrhosis, and drug reactions account for most cases of conjugated hyperbilirubinaemia. Haemolysis and Gilbert's syndrome are the main differential diagnosis of unconjugated hyperbilirubinaemia. Over one-fifth of all jaundiced patients will not have a primary disease of the liver and bile ducts,^{6 7} and this important minority will be recognised only when sufficient care is given to a detailed clinical examination.

Clinical examination

Cholestasis is suggested by a history of pruritus, dark urine, and pale stools. Questions should be asked about possible exposure to hepatitis viruses, drugs, alcohol abuse, pain, and fever. Abdominal pain may occur in primary liver cell disorders as well as with biliary-tree obstruction. Backache is a feature of pancreatic disease. Appreciable loss of weight suggests cancer of the pancreas or metastatic liver tumours. Among the drugs frequently responsible for jaundice are chlorpromazine, promazine, amitriptyline, trifluoperazine, imipramine, oral contraceptives, and chlorpropamide; but many others have been implicated. Alcohol abuse causes several syndromes of liver dysfunction, and a careful history of alcohol consumption is essential.

The results of a thorough general examination are often more informative than abdominal palpation alone. Signs apparent on careful inspection that indicate chronic liver disease include palmar erythema, spider naevi, clubbing, white nails, skin pigmentation, bruising, and gynaecomastia. Palpation for liver size, like many other physical signs, does not give reliable results.⁸ In many respects evidence of a reduced liver size is more useful than of enlargement because there are two main causes of a small liver—fulminant liver failure and cirrhosis—and these are easy to distinguish clinically, whereas enlargement of the liver has many causes. One that is hard and

irregular suggests metastatic disease, a suspicion that will be increased by finding a bruit, but identical features may occur in cirrhosis. Splenomegaly is a feature of portal hypertension and therefore cirrhosis. Ascites is a sign of portal hypertension or malignant disease; much useful information can be obtained from a diagnostic tap.

Biochemical tests

Those biochemical tests which suggest hepatocellular damage should be distinguished from those indicative of cholestasis. A serum alkaline phosphatase activity above 30 KA units and aspartate transaminase activity less than 300 IU favour cholestasis, but very high transaminase values may be encountered in extrahepatic biliary obstruction.⁹ Low serum concentrations of albumin and disorders of clotting indicate hepatocellular dysfunction. Lipoprotein-X is an abnormal lipoprotein, rich in lecithin, which appears in cholestatic jaundice and can be measured easily by commercially available kits; its presence does not help to differentiate between intrahepatic and extrahepatic cholestasis.¹⁰ Similarly, the estimation of serum bile acids in the jaundiced patient has not proved to be diagnostically useful despite the simplicity of radioimmunoassays. Their measurement provides little more information than the long-established tests and does not distinguish between the two groups of cholestasis.¹¹

Immunological tests

Most clinicians will have available a number of immunological and serological tests. Hepatocellular disease is accompanied by the appearance of several antibodies, of which one of the most useful is the antimitochondrial antibody. Its presence strongly suggests primary biliary cirrhosis¹² and virtually excludes an extrahepatic cause for cholestasis. High titres of antinuclear and smooth-muscle antibodies suggest chronic active hepatitis. Of great value are the various serological markers of hepatitis B virus infection, HBsAg, HBcAg, and their respective antibodies. Serological tests for hepatitis A virus remain to be developed, whereas those for non-A, non-B infections are showing promise.

Radiology

While the clinician may be able to suggest with a fair degree of confidence the probable cause for the jaundice he will usually wish to establish the diagnosis with greater certainty either by identifying whether or not the bile duct system is dilated or by confirming histologically the presence and nature of hepatocellular disease. Unless the clinical features strongly favour hepatitis or cirrhosis, when a liver biopsy is the definitive diagnostic procedure, the best option is likely to be one or more of the radiological methods for visualising the bile ducts—ultrasonography, percutaneous transhepatic cholangiography, or endoscopic retrograde cholangiopancreatography. Which one is selected will depend on the facilities and clinical skills available. In many respects ultrasonography is the method of choice for the initial evaluation of the patient with cholestatic jaundice. It is quick, non-invasive, and enables a

positive diagnosis to be made in nearly all patients.^{13 14} "Real-time" imaging, which allows visualisation of motion, has added an extra dimension to the conventional B scan. The gall bladder is particularly suited to ultrasonographic analysis—but a finding of stones must not be assumed to exclude malignant disease in the pancreas or bile ducts.¹⁵ The size of the gall bladder is a fickle sign: the normal fasting gall bladder may become appreciably distended, whereas some gall bladders fail to enlarge when there is cancer of the head of the pancreas. Gross dilatation of the intrahepatic radicles produces a very characteristic ultrasonographic appearance, but in long-standing obstruction, when the bile has become inspissated, the pattern may become more difficult to interpret. A further difficulty is the occurrence of minimal dilatation of the duct in some patients with cholangitis. Ultrasonography cannot always show the cause of the bile-duct obstruction. Small gall stones escape detection, and the technique is not accurate in identifying the cause of pancreatic disease. Ultrasonography has the added advantage of providing diagnostic information in hepatocellular disease, with hyperreflectivity as a feature of cirrhosis and fatty liver.

The technique of percutaneous transhepatic cholangiography was improved and simplified by the introduction of the fine-bore 23-gauge Chiba needle. The biliary tree can be outlined accurately and the site and cause of the obstruction identified in all patients with extrahepatic obstruction. Non-dilated intrahepatic bile ducts can be outlined in 80% of cases—a particular advantage in sclerosing cholangitis. Failure to pierce an intrahepatic radicle, however, should not be taken as proof that the ducts are not dilated. Percutaneous transhepatic cholangiography also makes possible either internal biliary drainage with a prosthesis or external drainage. Preoperative external biliary drainage reduces the morbidity and mortality of surgery on the obstructed biliary tree.^{16 17} Percutaneous brush biopsy of obstructing lesions has also been described.¹⁸

Endoscopic retrograde cholangiopancreatography is a most successful technique in expert hands, but it is less easy to perform and more expensive than ultrasonography or percutaneous transhepatic cholangiography. On the other hand, the yield of information is high. The procedure includes endoscopy of the upper gastrointestinal tract, the ampulla of Vater is visualised, and pancreatic juice can be obtained for biochemical and cytological analysis.¹⁹ Endoscopic papillotomy can be performed for choledocholithiasis. Endoscopic retrograde cholangiopancreatography is the method of choice if a pancreatic lesion is thought to be the cause of the bile-duct obstruction, but the distinction between cancer and inflammation remains difficult, and a firm answer usually requires a battery of investigations.²⁰ A plain abdominal radiograph contributes little and intravenous cholangiography nothing to the diagnosis of jaundice.

Liver histology

Percutaneous liver biopsy using the Menghini needle is safe and has a low complication rate if all the appropriate precautions are taken.²¹ Examination of the specimen will usually identify the cause of cirrhosis and suggest the nature of the hepatitis. The presence of bile-duct obstruction is often said to be a contraindication, but one premier liver unit reported that when biopsy was performed in the presence of dilated ducts there were few serious complications.²² The issue is no longer worth debating, because if there is any clinical or

biochemical evidence of cholestasis the biliary tree should be visualised before deciding whether or not to perform liver biopsy. A biopsy is always indicated in jaundiced patients whose ducts are not dilated.

Other techniques are available to identify the cause of jaundice but many require a particular skill and are not in general use. Various mathematical models have been proposed to identify biochemical patterns of liver disease and the computer has been introduced, but modern radiological techniques have overtaken computer developments.^{23 24} Angiography and laparoscopy²⁵ have given satisfactory results in skilled hands. Radionuclide scanning, in contrast, seems inferior to ultrasonography in the diagnosis of pancreatic disease because of the unacceptable number of false-positive scans. Isotope scanning, however, has a part to play in liver disease, particularly in the diagnosis of primary and secondary neoplasms. Computed tomography gives results comparable with those from ultrasonography but is better able to show the cause of extrahepatic obstruction.²⁶ Its disadvantages are expense and limited availability.

Jaundice in infancy

Infants with persistent jaundice present a particular problem. The important differential diagnosis is between the neonatal hepatitis syndrome and biliary atresia, and less commonly a choledochal cyst. Two essential investigations are the liver biopsy and ¹³¹I-rose-bengal excretion. Faecal excretion of under 10% of injected ¹³¹I-rose-bengal within 72 hours suggests extrahepatic biliary atresia. If these two investigations give equivocal results ultrasonic scanning may help by showing a choledochal cyst. The percutaneous transhepatic cholangiograph may make a contribution to the diagnosis because in extrahepatic biliary atresia the ducts are rarely shown.²⁷

Unconjugated hyperbilirubinaemia

The patient with unconjugated hyperbilirubinaemia is not deeply icteric and serum bilirubin concentrations seldom rise more than 70 μ mol/l (4.1 mg/100 ml). The urine contains urobilinogen but no bilirubin.

Haemolytic syndromes are suggested by the ethnic origin of the patient, anaemia, enlargement of the spleen, and the presence of reticulocytes. Measurement of haptoglobins, haemoglobin electrophoresis, and, on occasions, red cell survival may give useful information. If there is no haemolysis the most likely diagnosis is Gilbert's syndrome; drugs or parenchymal liver disease rarely cause pure unconjugated hyperbilirubinaemia. The diagnosis of Gilbert's syndrome is established by the absence of any clinical features of liver disease and the demonstration that a 400 kcal (1.7 MJ) diet given for three days induces a twofold to threefold rise in the concentration of unconjugated bilirubin.²⁸ Patients with Gilbert's syndrome have reduced bilirubin glucuronyl-transferase activity, but proof of this defect by liver biopsy is seldom necessary. A biopsy may be required, however, to exclude hepatocellular disease.

The diagnosis of jaundice remains an important but frequently taxing exercise for the clinician. Modern technology has not reduced the importance of a careful history and physical examination. Biochemical tests are necessary if only to identify whether or not the jaundice is cholestatic. Ultrasonography has most to offer as the initial radiological test in jaundice, but best management is provided when there is close liaison between clinicians and radiologists to decide which technique is most appropriate for an individual patient.

IAN A D BOUCHIER

Professor of Medicine,
University of Dundee;
Honorary Consultant Physician,
Ninewells Hospital and Medical School,
Dundee DD1 9SY

- ¹ Billing BH. Twenty-five years of progress in bilirubin metabolism (1952-77). *Gut* 1978;**19**:481-91.
- ² Forker EL. Mechanisms of hepatic bile formation. *Annu Rev Physiol* 1977;**39**:323-47.
- ³ Harville DD, Summerskill WHJ. Surgery in acute hepatitis. Causes and effects. *JAMA* 1963;**184**:257-61.
- ⁴ Blumgart LH. Biliary tract obstruction: new approaches to old problems. *Am J Surg* 1978;**135**:19-31.
- ⁵ Zimmerman HJ. Intrahepatic cholestasis. *Arch Intern Med* 1979;**139**:1038-45.
- ⁶ Abbott RJ, Carter NW, Clee MD, Bouchier IAD. A study of hyperbilirubinaemia in clinical practice. *Postgrad Med J* 1979;**55**:787-90.
- ⁷ Malchow-Møller A, Matzen P, Bjerregaard B, et al. Causes and characteristics of 500 consecutive cases of jaundice. *Scand J Gastroenterol* 1981;**16**:1-6.
- ⁸ Meyhoff H-H, Røder O, Andersen B. Palpatory estimation of liver size. Within—and between—observer variation. *Acta Chir Scand* 1979;**145**:479-81.
- ⁹ Ginsberg AL. Very high levels of SGOT and LDH in patients with extrahepatic biliary tract obstruction. *Am J Dig Dis* 1970;**15**:803-7.
- ¹⁰ Ritland S. The abnormal "lipoprotein of cholestasis," lipoprotein-X. *Scand J Gastroenterol* 1975;**10**:785-9.
- ¹¹ Bouchier IAD, Pennington CR. Serum bile acids in hepatobiliary disease. *Gut* 1978;**19**:492-6.
- ¹² Munoz LE, Thomas HC, Scheuer PJ, Doniach D, Sherlock S. Is mitochondrial antibody diagnostic of primary biliary cirrhosis? *Gut* 1981;**22**:136-40.
- ¹³ Ferrucci JT Jr. Body ultrasonography. *N Engl J Med* 1979;**300**:590-602.
- ¹⁴ Leopold GR. Ultrasonography of jaundice. *Radiol Clin North Am* 1979;**17**:127-36.
- ¹⁵ Gordon P, Cooperberg PL, Cohen MM. Presence of gallstones is a poor indicator of the cause of obstructive jaundice. *Surg Gynecol Obstet* 1980;**151**:635-6.
- ¹⁶ Nakayama T, Ikeda A, Okuda K. Percutaneous transhepatic drainage of the biliary tract. Technique and results in 104 cases. *Gastroenterology* 1978;**74**:554-9.
- ¹⁷ Ferrucci JT Jr, Mueller PR, Harbin WP. Percutaneous transhepatic biliary drainage. Technique, results, and applications. *Radiology* 1980;**135**:1-13.
- ¹⁸ Mendez G Jr, Russell E, Levi JU, Koolpe H, Cohen M. Percutaneous brush biopsy and internal drainage of biliary tree through endoprosthesis. *AJR* 1980;**134**:653-9.
- ¹⁹ Elias E, Hamlyn AN, Jain S, et al. A randomized trial of percutaneous transhepatic cholangiography with the Chiba needle versus endoscopic retrograde cholangiography for bile duct visualization in jaundice. *Gastroenterology* 1976;**71**:439-43.
- ²⁰ Mackie CR, Cooper MJ, Lewis MH, Moossa AR. Non-operative differentiation between pancreatic cancer and chronic pancreatitis. *Ann Surg* 1979;**189**:480-7.
- ²¹ Perrault J, McGill DB, Ott BJ, Taylor WF. Liver biopsy: complications in 1000 inpatients and outpatients. *Gastroenterology* 1978;**74**:103-6.
- ²² Morris JS, Gallo GA, Scheur PJ, Sherlock S. Percutaneous liver biopsy in patients with large bile duct obstruction. *Gastroenterology* 1975;**68**:750-4.
- ²³ Solberg HE, Skrede S, Blomhoff JP. Diagnosis of liver diseases by laboratory results and discriminant analysis. Identification of best combinations of laboratory tests. *Scand J Clin Lab Invest* 1975;**35**:713-21.
- ²⁴ Wheeler PG, Theodossi A, Pickford R, Laws J, Knill-Jones RP, Williams R. Non-invasive techniques in the diagnosis of jaundice—ultrasound and computer. *Gut* 1979;**20**:196-9.
- ²⁵ Irving AD, Cuschieri A. Laparoscopic assessment of the jaundiced patient: a review of 53 patients. *Br J Surg* 1978;**65**:678-80.
- ²⁶ Morris AI, Fawcitt RA, Wood R, Forbes WSC, Isherwood I, Marsh MN. Computed tomography, ultrasound, and cholestatic jaundice. *Gut* 1978;**19**:685-8.
- ²⁷ Howard ER, Nunnerley HB. Percutaneous cholangiography in prolonged jaundice of childhood. *J R Soc Med* 1979;**72**:495-502.
- ²⁸ Owens D, Sherlock S. Diagnosis of Gilbert's syndrome: role of reduced caloric intake test. *Br Med J* 1973;iii:559-63.