87 Jaundice

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Definition

Jaundice is the yellow color of skin and mucous membranes due to accumulation of bile pigments in blood and their deposition in body tissues. Jaundice should be distinguished from *cholestasis*, which refers to a decreased rate of bile flow. Depending on the clinical situation, jaundice and cholestasis may coexist or each may exist without the other. Although many sources confidently say that jaundice can be recognized when the serum bilirubin rises to 2 to 2.5 mg/dl, experienced clinicians often cannot see a yellow skin coloration until the serum bilirubin is at least 7 to 8 mg/dl.

Jaundice must be distinguished from yellow or green skin color resulting from carotenemia or quinacrine ingestion. Eating large quantities of green and yellow vegetables, tomatoes, or yellow corn may result in excess carotene intake. The resultant yellow skin color is differentiated from jaundice by the absence of yellow color in mucous membranes and sclerae, the normal urine color, and the accentuation of yellow-brown carotenoid pigment in the palms, soles, and nasolabial folds. Quinacrine, commonly used for treatment of giardiasis, may produce a yellow skin color, but the urine remains normal. Serum bilirubin levels are normal in patients with yellow skin caused by carotenemia or quinacrine.

Technique

The majority of jaundiced patients may be diagnosed by careful and meticulous history and physical examination. These may either give the diagnosis directly or, at the least, direct diagnostic efforts toward appropriate paths.

History

Assessment of constitutional symptoms often provides the first clue to the mechanism of jaundice. Anorexia, nausea, emesis, or weight loss appearing within 2 weeks prior to onset of jaundice suggests hepatitis or biliary obstruction secondary to gallstones. The same symptoms occurring continuously for more than 2 weeks prior to the appearance of jaundice suggest a malignant biliary obstruction, chronic hepatitis, or toxin exposure (especially alcohol). Recurrent brief episodes of anorexia, nausea, or emesis extending over months to years, especially when accompanied by right upper quadrant abdominal pain, implicate gallstones.

The *mode of onset* of jaundice often provides the pathophysiologic basis, if not the specific diagnosis at its root. Jaundice appearing over a few days to a week implies hepatitis, whether drug or toxin induced, viral or bacterial (i.e., leptospirosis). Jaundice appearing over the course of weeks implies a subacute hepatitis or extrahepatic obstruction due to malignancy, gallstone, chronic pancreatitis, or stricture in the common bile duct. Jaundice of fluctuating intensity implicates gallstones, ampullary carcinoma, or possible drug hepatitis. A past history of jaundice, although potentially unrelated to the immediate problem, may implicate chronic hepatitis, cirrhosis, benign recurrent intrahepatic cholestasis, or a genetic nonhemolytic hyperbilirubinemeia (i.e., Gilbert's or Dubin–Johnson syndrome) as the cause.

Symptoms associated with jaundice often provide a diagnosis. Abdominal pain frequently accompanies jaundice, and its character may point to a specific diagnosis. Although hepatocellular jaundice is usually painless, a dull ache or "heavy sensation" in the right upper quadrant may attend acute hepatitis of any cause. Pain associated with alcoholic hepatitis, especially when accompanied by fever, jaundice, and leukocytosis, may be sufficiently severe to simulate an acute surgical abdomen (Mendenhall, 1982). Right upper quadrant abdominal pain occurring episodically over months to years, and especially when radiating to the right scapular area, right shoulder, or around the upper abdomen and back in a girdle distribution, suggests gallstones. Persistent epigastric or right upper quadrant pain possibly radiating to the back suggests carcinoma of the head of the pancreas.

Fever frequently accompanies jaundice caused by acute hepatitis, although it usually lasts no more than a few days. Fever associated with chills usually points to biliary obstruction, especially due to stones or stricture and, less frequently, to malignancy.

Generalized pruritus usually points to biliary tract obstruction as the cause of jaundice. Recent onset localizes the level to the large ducts (i.e., neoplasm) or canaliculi (intrahepatic cholestasis, most commonly due to drug toxicity). A long-standing history of pruritus extending over months to years in a middle-aged woman suggests primary biliary cirrhosis as the culprit. However, pruritus may occasionally occur with viral hepatitis too.

Arthritis or urticaria appearing within a month of onset of jaundice and disappearing shortly before the onset points to hepatitis B virus infection (Alpert et al., 1971). Arthritis may also accompany or precede autoimmune hepatitis (Golding et al., 1973). True arthritis may also accompany hemochromatosis, although this disease rarely causes jaundice (Bassett et al., 1980). Bone pain simulating joint pain may accompany any long-standing cholestatic condition due to vitamin D depletion and calcium deficiency.

The jaundiced patient requires thorough documentation of all recent *drug and toxin exposures*. After asking for a list of the patient's drugs, the physician should specifically ask about pain relievers, tranquilizers, and birth control pills or other estrogens that the patient may forget to mention. Chemicals, especially organic compounds used occupationally or at home, may be hepatotoxins. Alcohol intake should be documented, preferably by estimating the number of grams or ounces of alcohol imbibed per day rather than the number of drinks consumed. Alcohol abusers are often reluctant to tell the truth about their habit, and the physician

may need to talk to the patient's spouse, other family members, or friends to obtain a complete picture.

Potential contact with hepatitis viruses and other infectious agents should also be determined. This involves asking about contacts with other icteric or potentially hepatitic patients, recent transfusions, needle or narcotic use, and ingestion of raw shellfish. Recent foreign travel to areas of poor sanitation carries a risk of exposure to hepatitis A virus or *Entamoeba histolytica*. The homosexual male is at high risk for development of hepatitis A or B infection (Keeffe, 1986). Occupational exposure to barnyard animals, slaughterhouses, or stagnant water may implicate leptospirosis. A patient who is immunologically compromised is a potential target for cytomegalovirus or herpes virus infection, while work in an institution (i.e., prison, day care center) or health care facility may implicate hepatitis A or B virus infection. A young icteric individual with a sore throat and rash may have infectious mononucleosis. A patient with bacterial sepsis due to a wide variety of bacteria may have jaundice without cholangitis or biliary obstruction (Gottlieb et al., 1986).

Surgical history, whether recent or remote may be implicated in the cause of jaundice (Lamont and Isselbacher, 1973). Within the first three postoperative weeks, jaundice may be due to a variety of problems that include: (1) increased bilirubin load related to hemolysis of transfused erythrocytes (especially stored blood), resorption of hematomas or hemoperitoneum and rarely to hemolysis of the patient's erythrocytes due to G-6PD deficiency, drug reactions or malarial parasites in transfused blood; (2) impaired hepatocellular function, which may be related to administration of halogenated anesthesia agents, exposure to other hepatotoxic drugs, sepsis, or hepatic ischemia associated with preoperative or intraoperative hypotension or hypoxia; and (3) extrahepatic biliary obstruction, which may be secondary to inadvertent surgical injury to the common bile duct or occasionally to an unsuspected biliary calculus or to cholecystitis. Biliary tract surgery in the remote past may have produced a biliary stricture, although these are usually clinically evident within 2 years of operation. When investigating a case of jaundice potentially related to surgery, it is important to examine the operative record for transfusion, anesthesia, x-rays, drugs, and potential hypotension or hypoxia, as well as the surgeon's dictated note of intraoperative events and his visual and palpation impression of the patient's liver, biliary tree, and pancreas.

Other systemic conditions may have complications related to the liver. For example, patients with inflammatory bowel disease are predisposed to primary sclerosing cholangitis, cholangiocarcinoma, chronic hepatitis, cirrhosis, and hepatic amyloid. If a significant section of terminal ileum has been involved by or resected for Crohn's disease, the patient may also have gallstones (Allan, 1983; Warren and Kern, 1983). Cystic fibrosis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency and other hereditary metabolic diseases with prominent hepatic effects (i.e., galactosemia, hereditary fructose intolerance, and tyrosinemia) all may be complicated by cirrhosis (Alagille and Odievre, 1979). Systemic lupus erythematosus sometimes directly affects the liver (Runyon, LaBrecque, and Anuras, 1980). Acutely or subacutely decreased hepatic oxygenation of any cause may simulate the hepatic manifestations of viral hepatitis.

A *family history* of jaundice, liver disease, or anemia (especially when requiring splenectomy) should be sought. A positive family history of liver disease may implicate the genetically transmitted nonhemolytic hyperbilirubinemias (i.e., Crigler–Najjar, Gilbert's, Dubin–Johnson, or Rotor's syndromes), benign recurrent intrahepatic cholestasis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency or hereditary spherocytosis in the differential diagnosis.

Physical Examination

In most instances, physical examination of the jaundiced patient confirms a diagnosis suspected by history or provides diagnostic proof in its own right. A general examination of the patient furnishes numerous diagnostic clues. At any given level of jaundice, the patient with hepatocellular disease appears more acutely ill than the individual with obstruction. Indeed, unless his course is complicated by cholangitis, the obstructed patient generally does not appear acutely ill at all. The patient's age renders some diagnoses more likely than others. Carcinoma of the pancreas is an increasingly prominent cause of jaundice over 40 years of age. The incidence of hepatitis A virus is greatest in youth, but hepatitis B and non-A, non-B virus infections may occur at any age. Gallstones may uncommonly occur in adolescence but become increasingly common in middle age. A green cast to the jaundice indicates prolonged obstruction, while an orange-yellow color is more compatible with a hepatocellular mechanism. Disorientation, obtundation, or a simple slowing of mental processes such as speech or recall incriminate disturbed hepatocellular function rather than obstruction as a cause of jaundice.

Examination of the *skin* may reveal bruising resulting from disturbed blood coagulation mechanisms. Spider telangiectases are small cutaneous arteriovenous anastomoses that blanch when pressure is exerted on the central point of the vascular complex. They are most liable to appear on the upper body including trunk, arms, hands, neck, and face. Although they may occasionally occur singly in normal people and more commonly during pregnancy, their presence generally indicates chronic hepatocellular disease. Scratch marks confirm a patient's history of pruritus. Decreased axillary and pubic hair and a change from a male to female escutcheon over the genitals suggests cirrhosis. Dupuytren's contracture may also accompany chronic liver disease. Xanthelasma and tuberous xanthomas are fatty deposits appearing on eyelids and over the buttock and extensor surfaces of the extremities respectively and are commonly seen in long-standing biliary obstruction with hyperlipidemia, especially primary biliary cirrhosis.

Auscultation over the liver (including the lower right anterior chest) should be performed prior to manual manipulation of the area. Although abdominal bruits may be found in up to 20% of normal people (Babb, 1973), hepatic bruits, especially those of a harsh quality, are often associated with hepatic malignancy, alcoholic hepatitis, or occasionally with hemangiomas or other vascular lesions. Hepatic friction rubs are usually due to malignancy or inflammatory disease involving Glisson's capsule (Simpson, 1971). Abnormal auscultatory sounds may be better appreciated with the patient standing rather than recumbent.

Palpation of the liver is the single most crucial step in evaluation of the jaundiced patient. An appreciation of its size, surface characteristics, and tenderness are central to understanding the cause of the patient's illness. Liver size should always be expressed in terms of centimeters of total span. This involves determining the position of the lower hepatic border by palpation, percussion, or ballotment and

that of the upper border by percussion and measuring the distance between the two marks. Liver span is dependent on the height and lean body mass of the patient and especially on the percussion technique of the examiner (Castell et al., 1969). However, a "normal" liver span does not guarantee that the organ is functionally or histologically normal. Observer variation regarding liver size can usually be resolved with an objective measurement such as a liver scan. Very large livers are likely to be congested or fatty or to be involved with cirrhosis, neoplasm, or amyloid. A rapidly shrinking liver combined with deepening jaundice and clinical deterioration indicates acute liver failure, usually secondary to a virus or toxin. A hard or nodular liver is probably fibrotic or infiltrated with tumor. Although the normal liver is slightly tender to palpation, unusual hepatic tenderness is often the result of acute hepatitis of any cause, abscess, or rapid hepatic enlargement secondary to vascular congestion or fatty infiltration.

Splenomegaly is frequently found in the jaundiced patient, although its specific etiology is variable. Splenomegaly without hepatomegaly may result from primary hemolytic disease (especially hereditary spherocytosis) or from portal vein occlusion of any cause. Enlarged spleens commonly result from portal hypertension caused by liver disease or hepatic venous obstruction. In these instances, hypersplenism with hemolysis may contribute to the patient's jaundice. Splenomegaly due to portal hypertension is often associated with ascites and, in later stages, a prominent abdominal venous pattern. An enlarged spleen may also occur in viral hepatitis as a nonspecific reticuloendothelial response to infection. Finally, concurrent hepatomegaly and splenomegaly may not be related as cause and effect, but both may be due to involvement by another process, most commonly tumor (particularly hematologic) or storage disease.

Ascites in the jaundiced patient is an ominous sign, usually signifying severly decompensated cirrhosis with portal hypertension or malignancy studding the peritoneum or invading the liver. Occasionally, ascites may be due to massive or subacute hepatic necrosis or hepatic vein obstruction, but is a rare feature of isolated portal vein occlusion. Bilateral lower extremity edema often accompanies ascites, although the latter frequently occurs without evidence of other fluid accumulation. If bilaterally equal leg edema arises in a jaundiced patient who does not have ascites or cardiovascular-renal disease, carcinoma of the pancreas with inferior vena cava obstruction must be considered. An abdominal venous pattern extending over the anterior abdominal wall in a patient with ascites usually means that the patient has portal hypertension. Occasionally it can indicate an obstruction of the inferior vena cava with collateral flow (Missal et al., 1965). If the venous pattern is secondary to portal hypertension, blood in the vessels will flow away from the umbilicus. If the patient has caval obstruction, blood in the dilated veins will flow superiorly at all levels. An everted umbilicus in a patient with massive ascites indicates chronic abdominal distention and usually means cirrhosis.

Dark *urine* resembling tea, which develops a green foam on shaking, is caused by bile pigment. Its presence excludes hemolysis or a hepatic uptake or conjugating defect of bilirubin metabolism acting alone as a cause of jaundice. The *stool* of patients whose jaundice is due to hemolysis is brown. Patients with mild to moderate hepatocellular jaundice also have brown stools, although as their hepatic excretory ability increasingly fails, their stool may turn a clay color. Patients with obstructive jaundice often have clay-colored stools. A jaundiced patient with a positive reaction for blood in a clay-colored stool suggests carcinoma of the pancreas or ampulla of Vater.

Laboratory Tests

Laboratory tests usually serve to confirm the pathophysiology of jaundice. Sometimes they may demonstrate a specific etiology as well (Chopra and Griffin, 1985).

The complete blood count may provide evidence for hemolysis by demonstrating anemia in a patient without blood loss or a blood smear with spherocytes or other oddly shaped erythrocytes. Hemolysis may be proven via a reticulocyte count, Coomb's test, or other specific tests of erythrocyte enzymes. Leukocytosis and neutrophilia are unusual in viral hepatitis, although common in cholangitis and alcoholic hepatitis. Eosinophilia plus jaundice is suspicious for toxic hepatitis on a basis of hypersensitivity.

A jaundiced patient without urinary bilirubin has either hemolysis or a hepatic defect in bilirubin uptake or conjugation. Marked persistent proteinuria in a jaundiced patient is suspicious for amyloid.

Liver function tests are nonspecific indicators of liver disease. None of them alone provides a sensitive evaluation of liver function. Many of the enzymes tested have potential sources other than the liver. Their interpretation is possible only in the light of a thorough history and meticulous physical examination. Even then, their value is often realized only after serial determinations have been obtained.

Normal *serum bilirubin* concentration is usually no greater than 1.5 mg/dl and is composed primarily of the unconjugated form. Jaundice due primarily to hemolysis or a bilirubin conjugation disorder results in a serum bilirubin whose unconjugated component is at least 85% of the total. Moreover, in the presence of a normal liver, hemolysis alone does not produce a serum bilirubin greater than 4 mg/dl (Berk and Javitt, 1978). A rise in serum bilirubin up to 2 mg/dl per day is compatible with extrahepatic obstruction, but a greater rate of increase suggests hemolysis, hepatitis, or hepatic necrosis. The serum bilirubin of patients with pure biliary obstruction generally does not exceed 30 mg/dl; a greater value indicates that a component of hepatocellular jaundice is present as well.

Serum alkaline phosphatase derives from liver, bone, placenta, intestinal mucosa, and certain tumors. In most instances, only sources from liver and bone are clinically important. Alkaline phosphatase is often elevated to at least three times the upper limit of normal in patients with jaundice due to intra- or extrahepatic obstruction but is usually less than this figure in hepatocellular jaundice. However, patients with acute alcoholic liver disease may have alkaline phosphatase elevations higher than five times the upper limit of normal without an obstructive component. The enzyme is also frequently elevated in diffuse hepatic infiltration (i.e., tumor, granulomas). An alkaline phosphatase elevated out of proportion to serum bilirubin may mean hepatic infiltrative disease or partial biliary obstruction associated with choledocholithiasis, biliary stricture, chronic pancreatitis, or with malignancy involving only one of the hepatic ducts. In jaundiced women with a long history of hyperphosphatasia and pruritus, a diagnosis of primary biliary cirrhosis is likely (Tornay, 1980). This is confirmed by an antimitochondrial antibody test that is positive in approximately 85% of patients with this condition (Klatskin and Kantor, 1972). Although the test is not specific for primary biliary cirrhosis, it is almost always negative in ex-

trahepatic obstruction, the most important differential diagnostic problem of this disease. Gamma glutamyl transpeptidase, leucine aminopeptidase and 5'-nucleotidase, serum hepatic enzymes used to determine the origin of an isolated alkaline phosphatase elevation, are not useful in the jaundiced patient because the source of the alkaline phosphatase is then obvious.

Transaminases (SGOT and SGPT) are found primarily in liver, skeletal and cardiac muscle, and kidney (Ticktin and Trujillo, 1966). However, SGPT elevations are relatively more specific for liver disease than those of SGOT (Chopra and Griffin, 1985; Ticktin and Trujillo, 1966). Transaminase elevations are common in both hepatocellular and obstructive jaundice, although higher values are generally achieved in the former case. Unexpectedly elevated transaminases due to obstruction are caused by transient mechanisms such as floating gallstones or to sphincter of Oddi spasm. In these instances, the transaminases fall rapidly toward normal over 48 hours. Transaminase elevations associated with hepatocellular jaundice gradually decline over weeks. Interestingly, the SGOT elevation in alcoholic hepatitis is uncommonly higher than 600, while the SGPT is almost always significantly lower than the SGOT. In viral hepatitis both enzymes are often elevated to or higher than ten times the upper limit of normal, and the two are more nearly equal or the SGPT is frequently higher. In general, transaminase elevations greater than 1000 are usually due to viral or toxic hepatitis, decrease in hepatic oxygen supply (i.e., congestive heart failure, hypotension), or Reye's syndrome, and, uncommonly, to metastatic liver disease.

Prothrombin precursor is a protein manufactured by the liver whose full expression of activity in coagulation relies on a vitamin K-dependent carboxylase (Corrigan et al., 1982). The concentrations of circulating prothrombin precursor and fully functional prothrombin may be measured independently. Moderately severe hepatocellular disease results in reduction of both proteins, while extrahepatic obstruction, due to impairment of vitamin K absorption, will cause a fall of functional prothrombin alone. Prognostically, a rise of the precursor concentration indicates return of hepatic synthetic capacity even though the patient's prothrombin time remains abnormal. In practice, the prothrombin time may be prolonged (more than 3 seconds over control) in both hepatocellular and obstructive jaundice. Parenteral administration of vitamin K 10 mg will correct the prothrombin time of the obstructed patient to normal within 24 hours, while that of the hepatocellular icteric patient will improve only partially or not at all. A prothrombin time at least 10 seconds over control in a jaundiced patient and the inability to correct it with vitamin K is a poor prognostic sign.

Albumin is synthesized in the liver. Because the protein has a relatively long half-life (approximately 2 weeks), its serum concentration will usually not fall significantly until liver disease has been present for at least 1 to 2 weeks. However, elevated total serum globulins, especially when exhibiting a broad gamma electrophoretic distribution and when unexplained by other chronic inflammatory conditions, are a generally reliable indicator of chronic hepatocellular disease. A serum protein electrophoretic pattern missing an alpha-1 peak suggests alpha-1 antitrypsin deficiency and should be followed by a specific assay for alpha-1 antitrypsin.

Serologic assays for *hepatitis A and B viruses* should be performed in cases of acutely developing jaundice. Hepatitis A virus does not produce chronic liver disease, so only hepatitis B virus serology will be meaningful in patients with chronic hepatocellular disease (Lemon, 1985; Friedman and Dienstag, 1986). Antibody titers against delta agent, Epstein-Barr virus, herpesvirus and cytomegalovirus, and urine culture for cytomegalovirus can also be obtained in selected cases. In special cases, serological tests for leptospirosis, syphilis, and *Entamoeba histolytica* are also available.

Imaging Evaluation

Although a thorough history and physical examination still provide the best clinical diagnostic assessment of the jaundiced patient, new imaging procedures designed to identify biliary obstruction or other potential surgical causes of jaundice (i.e., multiple hepatic abscesses) have proved invaluable. In the past 10 to 15 years, the development of high-resolution ultrasound and computerized tomography (CT) and advanced techniques and equipment for performing percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP), and hepatobiliary scintigraphy (HBS) have revolutionized the investigation of jaundice.

Imaging investigation should start with a chest x-ray and plain film of the abdomen. The former may furnish clues such as cardiac enlargement with pulmonary venous engorgement, mass lesion in the chest, bony erosion of the ribs and spine, pleural effusions, or an elevated right diaphragm. The abdominal film may demonstrate hepatic or pancreatic calcifications or gallstones, approximately 10 to 15% of which are radiopaque.

Abdominal sonography is a valuable screening test in the jaundiced patient (Ferruci, 1979; Meire, 1984). The demonstration of biliary ductal dilation, gallstones, hepatic mass lesion, or an enlarged or abnormally shaped pancreas directs further investigation or therapy. Sonography is noninvasive, readily available in most hospitals, does not involve radiation exposure, and is cheaper than CT or other procedures in which the bile ducts are directly opacified. It may also allow guided biopsy or drainage of lesions in the liver or pancreas. However, sonography may be technically unsatisfactory in up to 40% of cases, primarily due to obesity or to accumulation of bowel gas, which prevents transmission of sound waves. Sonography is frequently more successful at identifying ductal dilation rather than its level or cause, but may also miss early cases of obstruction in which the biliary tree has not had sufficient opportunity to dilate. Finally, the procedure may be difficult to perform in the postoperative patient with surgical wounds, dressings, and drains that prevent close apposition of the sonographic probe to the abdominal wall. Nevertheless, in most patients sonography should be the initial imaging procedure directed at the biliary tree.

Computerized tomography has the advantage of surveying the entire abdomen as well as the hepato-biliary-pancreatic axis (Lee and Evens, 1980; Kreel, 1984). In addition to reliably detecting ductal dilation, CT is superior to sonography in determining the level and cause of obstruction. The pancreas is displayed more reliably and accurately by CT than by sonography. The obese patient and patients with prior biliary-enteric bypass procedures (in whom the bile ducts may not be well seen sonographically) might best be first examined by CT. Like sonography, CT allows accurate guided biopsy or drainage of otherwise inaccessible lesions. CT is technically unsatisfactory in only approximately 2% of cases. It is expensive, however, involves ra-

diation exposure, and is not available at some health care facilities. Optimal interpretation of CT for the jaundiced patient often involves administration of intravenous or oral contrast (to opacify the bile ducts and bowel repectively); some patients may not tolerate these agents due to drug allergy or to abdominal pain or ileus. Residual intestinal barium may also prevent x-ray transmission and create artifact. Although CT usually defines an abnormally shaped pancreas with high accuracy, it may not always distinguish the cause of the misshapen gland (i.e., carcinoma versus chronic pancreatitis). ERCP may then be necessary to complete the evaluation. CT is particularly useful in patients with equivocal sonographic data or a strong suspicion of pancreatic disease or biliary obstruction despite negative sonography. Patients with ductal dilation on sonography or CT whose cause is not identified should be investigated with either PTC or ERCP.

Until recently, *hepatobiliary scintigraphy* had little to contribute to the differential diagnosis of jaundice except in the instance of neonatal hepatitis versus biliary atresia or the occasional need for objective assessment of liver size. However, the development of new radionuclide agents with improved hepatic extraction and biliary excretion, improved imaging techniques, and the application of computer assistance to interpretation of dynamic scans have transformed HBS into an accurate modality for the diagnosis of large bile duct obstruction and may also prove useful in demonstrating intrahepatic cholestasis (Lieberman and Krishnamurthy, 1986). The advantages of HBS include its safety, ready availability in standard nuclear medicine facilities, and its ability to visualize liver and bile ducts despite obesity, bowel gas, rib cage configuration, or serum bilirubin levels up to 30 mg/dl (Weissmann, 1983). When evaluating the patency of the extrahepatic bile ducts by HBS, the scintigraphic image of the liver provides an added advantage to uncover unsuspected abscess or neoplasm. HBS does not have the resolution needed to diagnose specifically gallstones or tumor in the biliary system. Consequently, HBS, when used for uncovering extrahepatic obstruction, provides functional data (i.e., are the ducts normally patent?) but uncommonly furnishes anatomic data (i.e., cause of the obstruction). However, because biliary obstruction may exist for several weeks before the proximal ducts dilate sufficiently to be visualized by ultrasound or CT, HBS may provide a more rapid assessment of biliary patency then is obtainable by other noninvasive means (Kaplun et al., 1985). Demonstration of intrahepatic or extrahepatic obstruction by HBS usually leads to investigation with CT, PTC, ERCP or needle liver biopsy, which usually supply the final diagnosis.

Percutaneous transhepatic cholangiography involves passage of a thin needle into the liver under fluoroscopic guidance and injection of contrast into the biliary tree (Lintott, 1985). The procedure is easily available, its cost is generally less than that of ERCP, and a local anesthetic injection over the right flank is the only sedative or anesthetic medication required. Dilated ducts are opacified in 95 to 100% of cases, but even nondilated ducts are opacified in 60 to 95% of cases. A dilated, obstructed duct may be decompressed percutaneously by passage of a guide wire and cannula through the right flank incision. If the ducts are not visualized or if a nonobstructed biliary tree is found, one can immediately perform a needle liver biopsy through the anesthetized incision in the patient's right side. The patient should have a normal clotting mechanism and intravenous antibiotics should be administered before the procedure to guard against cholangitis and septicemia should an obstruction be revealed. PTC cannot visualize the pancreatic ductal system but can only show the effect of pancreatic compression on the distal common bile duct. Thus, PTC cannot accurately distinguish between obstruction due to pancreatic carcinoma or chronic pancreatitis. Patients allergic to iodinated contrast agents should not undergo PTC.

Endoscopic retrograde cholangiopancreatography is performed by passing a flexible fiberoptic endoscope into the patient's duodenum, inserting a cannula into the pancreatic and common bile ducts and injecting radiopaque contrast into these structures under fluoroscopy (Salmon, 1978). ERCP has the advantage of visualization and potential biopsy of the stomach and duodenum (since the scope is side-viewing, the esophagus cannot be seen). The procedure diagnoses pancreatic carcinoma in at least 90% of cases and can furnish visual (photographic and radiographic) and histologic proof of ampullary tumors. Cytologic smears may be obtained from juice aspirated from the pancreatic and bile ducts or from a brush inserted into these ducts. Finally, the endoscope may be used to place biliary stents or to dissolve or physically remove gallstones from within the biliary tree. However, the procedure is usually expensive and requires considerable endoscopic experience to master. Sedative medications are necessary, prior antibiotics are advisable in cases of suspected ductal obstruction, allergic reactions to contrast may occur, and the patient is exposed to the infrequent but definite risks of upper gastrointestinal endoscopy as well as the occasional risk of inducing cholangitis or clinical chemical pancreatitis. The choice between PTC and ERCP is usually made according to the skill and experience of the operator.

Mesenteric arteriography has been supplanted in the investigation of jaundice by other procedures that can more accurately assess the liver and pancreas for neoplasm or inflammation. Nevertheless, arteriography is still valuable to determine the operability of and surgical approach to a neoplasm or inflammatory mass by visualizing its vascular supply and adjacent vessels. Magnetic resonance imaging (MRI) is at least as sensitive as CT in detecting hepatic metastases and is much more sensitive than CT for this purpose when iodinated contrast cannot be used. MRI is also highly reliable in distinguishing benign from malignant hepatic masses. MRI is presently inferior to CT in pancreatic imaging. At this time MRI has no place in imaging of the biliary tract (Council on Scientific Affairs, 1989).

Liver Biopsy

Percutaneous needle liver biopsy is a safe procedure in experienced hands provided that the patient's coagulation mechanism is normal (Menghini, 1970). Even if the clotting process is abnormal, a needle biopsy may be performed by correcting individual factor deficiencies (i.e., transfusion of fresh-frozen plasma or platelets) provided that the potential diagnosis obtained from the specimen warrants the risk. The safety and diagnostic yield of the biopsy may also be increased by its performance via laparoscopy which allows for direct visualization of the liver and tamponade of a bleeding biopsy site (Friedman and Wolff, 1977). In the vast majority of instances, however, liver biopsy is an elective procedure that can wait until conditions are optimal. With the advent of imaging procedures that can reliably identify extrahepatic obstruction in almost 100% of instances and with the ease of diagnosing many acute and chronic he-

patocellular diseases by clinical, biochemical, and serologic means, needle liver biopsy is primarily useful in the jaundiced patient today to: (1) follow chronic liver disease to determine progression of the natural process or the effects of therapy; (2) determine the cause of hepatomegaly; (3) distinguish between intrahepatic and extrahepatic obstruction (patients with drug-induced jaundice, primary biliary cirrhosis, and intrahepatic neoplasm may present with jaundice and defy diagnosis until liver tissue is obtained); and (4) provide liver tissue for special investigations such as culture, enzyme assay (i.e., glycogen storage disease), chemical analysis (i.e., hemochromatosis, Wilson's disease) or immunologic studies (i.e., hepatitis B virus, delta agent). A normal or nondiagnostic percutaneous needle liver biopsy in a jaundiced patient who has already had negative imaging procedures for extrahepatic obstruction is an indication for laparoscopy and liver biopsy by direct visualization.

Basic Science

Bilirubin Production and Metabolism

Bilirubin is a breakdown product of heme metabolism (Bissell, 1975; Billing, 1978). Heme is an iron-containing porphyrin found in hemoglobin, myoglobin, and several enzymes of which the hepatic cytochromes are the most important representatives. Approximately 80% of daily bilirubin production derives from senescent red blood cells. These are broken down in the reticuloendothelial systems of spleen, liver, and marrow where iron is removed from the heme molecule and the remaining porphyrin ring is oxidized and cleaved at a single site to form the tetrapyrrole chain structure of biliverdin. Further reduction of biliverdin results in the formation of bilirubin. Up to 20% of normal bililrubin production may derive from degradation of nonhemoglobin heme-containing hepatic enzymes or from erythrocytes that never reached the circulation but were destroyed in situ (ineffective erythropoiesis). This fraction is called early labeled bilirubin (ELB) because injection of isotopically labeled glycine appears as this bilirubin fraction within 2 hours, while bilirubin produced from circulating old erythrocytes appears 90 to 150 days after injection (Robinson et al, 1967).

The ELB fraction enlarges with marked ineffective erythropoiesis that occurs in pernicious anemia, thalassemia, and sideroblastic anemia and in primary shunt hyperbilirubinemia, a rare condition in which erythroid hyperplasia, reticulocytosis, splenomegaly, and normal peripheral red blood cell survival coexist.

Unconjugated bilirubin has limited aqueous solubility and is therefore transported from the reticuloendothelial system cells to the liver reversibly bound to albumin. Bilirubin may be displaced from albumin by conditions predisposing to acidosis and hypoxia and by certain drugs, most notably salicylates and sulfonamides. High plasma levels of free fatty acids may also displace bilirubin from its protein binding sites. Circulating unconjugated bilirubin is chemically identified as the "indirect" fraction in the Van den Bergh reaction.

Within the liver, bilirubin dissociates from albumin at the hepatocyte membrane and is transported into the hepatocyte. Although the hepatic uptake potential of bilirubin is rarely utilized to capacity and is therefore not a rate-limiting step in its elimination, reduced hepatic sinusoidal flow can limit the removal of bilirubin from the circulation and contribute to clinical jaundice. Patients with Gilbert's syndrome (see below) may also have a component of impaired bilirubin uptake. The pathway of hepatic bilirubin uptake is shared by bromsulphthalein (BSP) and indocyanine green (ICG) but not by bile acids.

Within the cytosol, bilirubin binds to the Y (ligand) and Z proteins and is then transported to the endoplasmic reticulum where bilirubin conjugation occurs. Unconjugated bilirubin is loosely bound to the Y and Z proteins; under normal circumstances, up to 40% of bilirubin attached to these proteins may reflux back into the plasma. There are no well-defined circumstances in which impaired hepatic intracellular binding of bilirubin contributes to jaundice.

Excretion of bilirubin into bile requires its conversion into a more hydrophilic molecule. This is accomplished by the microsomal enzyme bilirubin uridine diphosphate glucuronyl transferase (UDPGT) which, in its monomeric form, conjugates bilirubin with a single molecule of glucuronic acid to produce bilirubin monoglucuronide (BMG). However, in its tetramer state, UDPGT catalyzes production of bilirubin diglucuronide (BDG) (Peters and Jansen, 1986), which accounts for 80% of bilirubin in bile. All forms of conjugated bilirubin are identified as the "direct" fraction in the Van den Bergh reaction. The conjugation process is impaired in Gilbert's and Crigler–Najjar syndromes and in neonatal processes such as breast milk jaundice, the Lucey–Driscoll syndrome, congenital hypothyroidism, and high intestinal obstruction (Andres et al., 1977). In the last instance, the cause of decreased bilirubin conjugation is unknown but it is relieved following surgical correction of the obstruction. Conjugating ability is usually preserved even in severe hepatic inflammatory disease but is decreased during fulminant hepatic failure.

Following conjugation, bilirubin is transported to the bile canaliculus by an unknown carrier-mediated mechanism that it shares with other organic anions including BSP, ICG, and cholecystographic dyes, but not with bile acids. However, taurocholate can increase biliary excretion of bilirubin, possibly by incorporating the pigment into mixed micelles. Under normal circumstances, canalicular excretion of bilirubin is the rate-limiting step of bilirubin elimination. Thus, diseases that affect the liver and cause jaundice usually produce a disproportionate rise of the conjugated fraction. Impaired canalicular transport results in regurgitation of conjugated bilirubin into plasma where it circulates attached to albumin. The small unbound fraction of conjugated bilirubin is available for renal excretion which, under normal conditions, is a quantitatively insignificant mode of pigment removal. As the plasma content of conjugated bilirubin rises, whether due to hepatocellular or obstructive disease, an increasingly large percentage of available bilirubin becomes strongly (covalently) bound to albumin (Weiss et al., 1983). As the patient's liver recovers or the obstructive process is relieved, the fraction of conjugated bilirubin that is either loosely bound or unbound to albumin is rapidly cleared from the blood. However, the protein-bound molecule is cleared slowly in accordance with the 2-week half-life of the albumin molecule. This accounts for the slow fall in bilirubin levels as inflammation or obstruction subsides and also accounts for the absence of urinary bilirubin in the presence of abnormal plasma levels because the protein-bound pigment is not filtered by the glomerulus. Canalicular excretion of bilirubin is impaired in patients with drug-induced cholestasis, decreased hepatic oxygenation, acute infection (i.e., bacterial sepsis, viral hepatitis, toxoplasmosis, syphilis), metabolic diseases (i.e., galactosemia, hereditary fructose intolerance, ty-

rosinemia) or genetic diseases of unknown etiology (i.e., benign recurrent intrahepatic cholestasis, Byler's disease, Dubin–Johnson and Rotor's syndromes). Ductular flow may be decreased by portal inflammatory processes such as primary biliary cirrhosis, sarcoidosis or primary sclerosing cholangitis or by other processes such as paucity of the intrahepatic bile ducts. Ductal excretion is impaired by carcinoma, gallstones or non-neoplastic stricture (induced by surgery, chronic pancreatitis or primary sclerosing cholangitis) but also by conditions favoring stasis such as choledochal cyst or Caroli's disease.

Effects of Abnormal Bilirubin

The complexities of bilirubin metabolism and the varied influences impinging on each step of bilirubin excretion often combine to produce multiple causes of jaundice for any given disease process. For example, cirrhosis may produce excess unconjugated hyperbilirubinemia by favoring erythrocyte destruction (via hypersplenism) and by reducing hepatic uptake of pigment (via rearrangement of vascular channels) but may also increase the conjugated fraction by decreasing canalicular excretion or ductular flow or by favoring gallstone production (25% of patients with cirrhosis have gallstones) and possible choledocholithiasis. Massive blood loss into soft tissues or the retroperitoneal space may favor excess bilirubin production, decreased bilirubin extraction (through diminished hepatic blood flow), and decreased canalicular excretion (by causing hepatic ischemia).

There are several chronic hyperbilirubinemic conditions (Crigler–Najjar syndrome types I and II, Gilbert's syndrome, Dubin–Johnson syndrome, Rotor's syndrome) that have in common genetic transmission, normality of standard liver function tests other than serum bilirubin, normal liver architecture, and, in most cases, absence of associated morbidity and mortality (Bissell, 1975; Berthelot and Dhumeaux, 1978). These conditions are genetically heterogeneous; families have been described in which Gilbert's syndrome predominates but Dubin–Johnson patients appear too, or in which Crigler–Najjar type II predominates but Gilbert's syndrome also occurs. Moreover, these entities may not necessarily be pathophysiologically distinct. Although patient's with Gilbert's syndrome have an isolated bilirubin conjugation/uptake defect, some may also be unable to eliminate ICG or ICG and BSP as well.

Gilbert's syndrome may actually represent several entities whose cause may range from decreased bilirubin uptake to decreased bilirubin glucuronidation. However, it is manifest by a total serum bilirubin up to but no greater than 6 mg/dl, more than 90% of which is in the unconjugated form. Serum bilirubin in these patients is increased by fasting for up to 24 hours, but the mechanism for this phenomenon is not clear. Liver morphology is typically normal. Gilbert's syndrome does not produce symptoms or adverse effects and is associated with a normal life span. Indeed, up to 5% of an unselected population may have a decreased ability to dispose of injected radioactive bilirubin. Treatment of Gilbert's syndrome is unnecessary, although phenobarbital can lower serum bilirubin in many patients, presumably because of its ability to induce microsomal enzymes (UDPGT). Gilbert's syndrome is probably transmitted as an autosomal dominant gene with incomplete penetrance.

The rare *Crigler–Najjar syndrome* is due to either partial or total deficiency of UDPGT. Type I, representing total enzymatic deficiency and probably transmitted by an autosomal recessive gene, is fatal in early life due to development of kernicterus. Bilirubin levels are typically greater than 20 mg/dl and are totally unconjugated; the patient's bile is colorless. Phenobarbital and other microsomal enzyme inducers are ineffective. Type II, a partial enzymatic deficiency, typically produces serum bilirubin levels between 6 and 20 mg/dl. It is probably transmitted by an autosomal dominant gene with incomplete penetrance and is compatible with a normal life span. Phenobarbital can decrease serum bilirubin by enzymatic induction of UDPGT.

Dubin–Johnson syndrome, a disorder characterized by increased conjugated and unconjugated serum bilirubin and transmitted by an autosomal recessive gene, is due to inability of the hepatocyte to excrete conjugated bilirubin into the canaliculus. These patients are also unable to excrete BSP, ICG or cholecystographic dyes, although their serum bile acids are normal. Their hepatic architecture is normal but there is an accumulation of hepatic pigment compatible with melanin. Serum bilirubin levels are usually no greater than 5 mg/dl, although levels higher than 20 mg/dl have been reported. Dubin–Johnson syndrome is sometimes unmasked during pregnancy or by use of estrogens, which impairs canalicular excretion of bilirubin. The healthy patient with long-standing conjugated hyperbilirubinemia, other normal liver function tests, and a nonvisualized gallbladder should be suspect for Dubin–Johnson syndrome, and the gallbladder should be analyzed sonographically before considering surgery. BSP 5 mg/kg injected intravenously produces a characteristic finding in which a blood sample drawn 90 to 120 minutes after injection has a higher BSP concentration than a sample taken 45 minutes after injection whether the BSP concentration in the latter is normal or elevated. The condition is asymptomatic and compatible with a normal life span.

Rotor's syndrome is a harmless chronic hyperbilirubinemia transmitted by an autosomal recessive gene in which the serum bilirubin is usually less than 10 mg/dl and equally split between conjugated and unconjugated fractions. Other liver function tests are normal. Like Dubin–Johnson syndrome, the Rotor's syndrome patient has an impairment of BSP and ICG elimination. However, in Rotor's syndrome the storage capacity of the hepatocyte for bilirubin is markedly decreased, while in Dubin–Johnson syndrome the excretory defect is primarily due to decreased transport of bilirubin into the canaliculus. In Rotor's syndrome the gallbladder opacifies normally with cholecystographic dye and the liver is not pigmented. Rotor's and Dubin–Johnson syndrome can be further distinguished because urinary coproporphyrin studies in the former show elevated total coproporphyrin excretion due to an increase in both the coproporphyrin I and III isomers, while studies in the latter show normal total coproporphyrin excretion with a large relative increase of the coproporphyrin I isomer (Wolkoff et al., 1976).

Clinical Significance

The most important question to answer in the evaluation of any jaundiced patient is, "Will this patient require surgery to relieve biliary obstruction?" In most patients, the answer is reasonably straightforward, but in some, this problem may tax the diagnostic skills of the finest clinician. Surgical relief of jaundice will be indicated almost exclusively for

obstructive problems situated at or distal to the porta hepatis and only occasionally for patients with intrahepatic abscesses or other nonmalignant intrahepatic space-occupying lesions. Some extrahepatic obstructive conditions, such as primary sclerosing cholangitis, may not be amenable to surgical correction.

The icteric patient with extrahepatic obstruction due to gallstones or postsurgical biliary stricture has usually had acute symptoms for less than 2 weeks, while those with pancreatic or biliary ductal carcinoma, chronic pancreatitis, or primary sclerosing cholangitis have had symptoms of longer duration. A prominent history of recent weight loss suggests malignancy, while fever and chills suggest cholangitis. Intermittent right upper quadrant pain radiating to the back or right shoulder favors gallstones, while constant epigastric or right upper quadrant pain radiating to the back suggests malignancy. Past biliary tract surgery, especially within 2 years of the patient's presentation, should alert the physician to possible biliary stricture. On physical examination, the obstructed patient appears icteric but not acutely ill unless septic. Liver size is either normal or slightly enlarged, while the spleen is usually not palpable. Ascites may be present if a malignancy obstructing the biliary tree has also invaded the liver or parietal peritoneum. On laboratory examination, the patient with extrahepatic obstruction and jaundice has a bilirubin equal to or less than 30 mg/dl; if the bilirubin is higher than 30 mg/dl, the jaundice also has a hepatocellular component. At least 50% of the serum bilirubin of obstructed patients is in the conjugated form. The serum alkaline phosphatase level is often three times the upper limit of normal or higher while transaminases are either normal or only mildly elevated. The prothrombin time may be prolonged but corrects easily to normal with parenteral vitamin K. Globulins are usually normal although serum albumin may be decreased if the patient has suffered recent weight loss.

Patients with jaundice due to intrahepatic problems may have had symptoms for less than 2 weeks (i.e., acute hepatitis of any cause) or more than 2 weeks (i.e., cirrhosis, chronic hepatitis, familial liver conditions). Abdominal pain often plays a minor role in the patient's history, while the major complaints are usually malaise, fatigue, and other constitutional symptoms. The history may reveal exposure to hepatotoxins (especially alcohol or other drugs), recent contact with other similarly ill patients or sources of viral exposure (i.e., needles, transfusions, sexual contacts, unsanitary environment), decreased hepatic blood flow or hypoxemia, or familial liver disease. On physical examination, the icteric patient with hepatocellular disease often appears acutely or chronically ill, sometimes both. However, patients with hereditary chronic hyperbilirubinemias (Gilbert's, Crigler–Najjar, Dubin–Johnson or Rotor's syndromes) appear completely well. The icteric patient with hepatocellular disease often has an enlarged liver, which, in the case of viral or bacterial infection, is frequently tender. Splenomegaly is often present, whether secondary to portal hypertension, reaction to infection or occasionally to primary hematologic malignancy. Spider telangiectases are common in patients with chronic liver disease of any cause. Ascites is frequently associated with hepatic malignancy or chronic liver disease, especially cirrhosis. Laboratory examination of patients with hepatocellular disease is highly variable. Serum bilirubin may range from slightly greater than normal to more than 60 mg/dl and may be composed almost exclusively of the unconjugated or predominently of the conjugated form. Serum alkaline phosphatase is often less than twice the upper limit of normal but may be particularly elevated in primary biliary cirrhosis, granulomatous hepatitis, intrahepatic cholestasis, acute alcoholic liver disease or infiltrative or space-occupying lesions. Transaminase elevations greater than 1000 are typical of hepatocellular disease. An elevated prothrombin time that does not correct to normal with parenteral vitamin K indicates hepatocellular disease. The jaundiced patient with elevated globulins often has chronic hepatitis or cirrhosis.

From a diagnostic standpoint, sonography of the liver, biliary tree, and pancreas should be the first specific imaging screening test. If biliary dilation is present, the patient should have either PTC or ERCP. If sonography is equivocal or if the sonogram is interpreted as normal but there is a strong clinical suspicion of biliary obstruction, CT or HBS should be performed. PTC or ERCP may provide more definitive anatomic diagnosis of the site and nature of an obstructive process than is available by the noninvasive imaging procedures. If there is no imaging evidence of obstruction and hepatocellular disease is suspected, a needle liver biopsy is indicated. If the needle liver biopsy is normal or equivocal, laparoscopy with liver biopsy under direct visual guidance may prove diagnostic.

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