The Fifty-Fifth Hahnemann Symposium

New Diagnostic Techniques

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We dedicate this book to our wives, Mauree, Carol, and Hannah, whose love, inspiration, and encouragement made our efforts all the more satisfying.

H.M.
S.T.
L.G.

Preface

In the past few years, many new diagnostic techniques have been developed that have markedly altered both the ordering of medical tests and the approaches taken in diagnosing and treating many diseases. Non-invasive techniques can now correctly identify certain diseases, and needle biopsy techniques have helped to eliminate certain diagnostic surgical procedures. With cooperation between the radiologist, the internist, the pathologist, and the surgeon, diagnostic acumen can be sharpened, patient trauma minimized, and cost reduced.

The symposium from which this volume evolved was triggered by the advent of computerized tomography, nuclear imaging, ultrasonography, and other new diagnostic procedures. The objectives of the symposium were to elucidate new methods of diagnosis, help establish proper sequencing of medical tests, and identify the yield and complications of the new procedures.

This symposium was directed toward the primary care physician. Medical students and paramedics, in particular, should benefit from the material covered in this volume. The techniques that are discussed are up-to-date and practical. It is hoped that this information will help provide a firm foundation of knowledge, for as these techniques continue to be used, new applications will be found and old ones discarded.

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PART I

Pancreaticobiliary Disease

Martin Black

1

Clinical Approaches to Pancreaticobiliary Disease

Patients with pancreaticobiliary disease commonly present with jaundice or are found to have abnormal liver function tests. Their evaluation and the formulation of an appropriate diagnostic plan requires that the physician have a good understanding of the significance of liver function abnormalities.

Serum tests of so-called liver function typically include alkaline phosphatase, 5′nucleotidase, glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), and protein electrophoresis. It should be noted that the serum 5′nucleotidase, SGPT, and serum protein electrophoresis are not routinely included in the automated battery of serum tests available in many hospital and commercial laboratories. They are, nevertheless, extremely valuable in the complete evaluation of patients with liver disease, and internists should request them as supplementary studies where necessary.

The results of the liver profile enable the internist to classify the type of liver disease present into "necroinflammatory" or "cholestatic," as outlined in Table 1. Results that do not fall easily into one category or the other should be regarded as "mixed" or "nonspecific" depending on the degree of abnormality present. Thus, if the alkaline phosphatase, 5′nucleotidase, SGOT, and SGPT are all substantially increased, it would be reasonable to consider the laboratory abnormality as indicating a "mixed" disorder. The majority of these will result from primary hepatic parenchymal disorders, and their workup follows the plan for necroinflammatory liver disease unless other information suggests otherwise. On the other hand, more modest increases of these tests could result from either category of disease and are appropriately defined as *nonspecific*. Careful consideration of the clinical setting is necessary to determine whether nonspecific liver function test abnormalities need any further workup as well as what direction such a workup ought to take.

A necroinflammatory liver profile almost always results from primary inflammatory disorders of the liver cells. Thus, the eventual diagnosis in such patients will be some form of hepatitis. Exploratory surgery (to exclude extrahepatic causes of jaundice) in patients with necroinflammatory diseases of the liver is not only clearly inappropriate but dangerous, being associated with a greatly increased morbidity and mortality. The appropriate additional workup involves identification of causative agents (e.g., accurate drug history, blood tests for hepatitis B surface antigen [HBsAg], antibody to hepatitis A

Table 1
Classifications of Liver Disease*

Serum Test	Necroinflammatory	Cholestatic
Serum bilirubin	N or I (direct reacting)	N or I (direct reacting)
Alkakaline phosphatase	N or Sl I	MI
5′ nucleotidase	N or Sl I	MI
SGOT	MI (e.g., > 1000 IU)	Sl I (e.g., < 300 IU)
SGPT	MI (e.g., > 1000 IU)	Sl I (e.g., < 300 IU)

*Key: N = normal, I = increased, Sl = slightly, M = markedly.

virus [anti-HAV], etc.) and assessment of chronicity and prognosis (which commonly requires evaluation of liver biopsy material). Therapy is generally reserved for the more chronic forms of hepatitis and if indicated, will comprise administration of drugs such as prednisone and azathioprine.

In patients with biochemical evidence of cholestatic liver disease, the next step in the diagnostic plan is to determine whether the causative disorder is intrahepatic or extrahepatic. Subsequent workup and management are determined accordingly. The advent of ultrasound examination of the abdomen has had a significant impact on the diagnostic sequence to be employed, and in many centers it now represents the starting point. The radiologist attempts to evaluate the caliber of the common bile duct and also the intrahepatic bile ducts. Dilatation of these structures is suggestive of the presence of anatomic obstruction within the biliary tree and points toward an extrahepatic cause for cholestasis. Additionally, identification of biliary calculi in a dilated common bile duct has very obvious diagnostic implications in jaundiced patients, whereas calculi in the gallbladder with a normal caliber common bile duct need to be considered more cautiously. Mass lesions in the head of the pancreas may also provide important diagnostic information when accompanying a dilated biliary tree.

Demonstration of a dilated biliary tree by ultrasound examination is strong evidence for the presence of an extrahepatic cause for the jaundice in which a surgical approach may prove to be necessary for histopathologic diagnosis and relief of biliary obstruction. Nevertheless, additional diagnostic workup is indicated before exploratory laparotomy is proceeded with. Visualization of the biliary tree by intravenous cholangiography is rarely successful in the jaundiced patient, and the value of the recently introduced technetium-labeled biliary scanning agents in the differential diagnosis of cholestasis has yet to be established. The next diagnostic procedure, therefore, is either (skinny-needle) transhepatic cholangiography or endoscopic retrograde cholangiopancreatography (ERCP).

In the great majority of patients with a cholestatic liver profile and nondilated bile ducts on ultrasound examination, the causative disorder will be some form of intrahepatic cholestasis. A careful history and examination will commonly point to the particular disorder, but histopathologic examination of hepatic tissue is usually required to establish the diagnosis. Percutaneous biopsy of the liver may be performed either by the blind percutaneous approach or during laparoscopy. The latter technique is most valuable for focal disorders of the liver (e.g., metastatic carcinoma, lymphoma, etc.), particularly where the left lobe is the predominant site of involvement. Laparoscope-directed biopsy of the area of abnormality ensures that the material aspirated will facilitate accurate and complete diagnosis. In view of this, the author utilizes the technetium liver scan to identify focal disease (in addition to providing any other information) before deciding whether to proceed to blind liver biopsy or laparoscopy.

Despite the fact that percutaneous liver biopsy has been widely utilized as a diagnostic tool in the United States for more than 20 years, there remains a reservoir of apprehension and misunderstanding regarding its use which is difficult to comprehend. With a skilled biopsyist and a normal coagulation state, the procedure has as low a morbidity and mortality rate (nowadays about 1 in 5000 to 10,000) as it is feasible to expect for any invasive procedure. Furthermore, it can be expected to yield significant new information at a much higher rate than most other hospital studies. Nevertheless, physicians continue to express fear regarding liver biopsy in cholestatic liver disease, apparently because of the possibility of extrahepatic biliary obstruction being present. The inference is that morbidity and mortality of the procedure are considerably increased by that circumstance, whereas actual evaluation of the risk does not justify such a belief. In any case, as the approach presented here indicates, percutaneous liver biopsy is not normally utilized in patients with probable extrahepatic biliary obstruction; therefore, this particular situation should occur infrequently.

To maximize the information to be derived from histopathologic examination of liver obtained by percutaneous biopsy, the internist needs to have a degree of familiarity with (and interest in) what happens to the specimen after it is delivered to the pathology department. Table 2 lists factors that may play a role in the final interpretation of the biopsy. For the most part they are commonsense issues and merit little additional comment. However, in examining large numbers of biopsies and pathologic reports from outside hospitals, I have been impressed by such regular occurrences as too small a specimen, poor sectioning and staining technique, absence of special stains (hematoxylin and eosin, trichrome, reticulin, and iron stains should be routine for all liver sections), and incorrect diagnosis. My own view is that the local internist has a personal responsibility to ensure that the biopsy specimen submitted to the laboratory is appropriately processed and diagnosed.

Histopathologic examination of the liver biopsy specimen will establish the particular cause of cholestatic liver disease in the majority of patients. In others it will suggest a disorder that may be confirmed by additional laboratory studies (e.g., antimitochondrial antibody in primary biliary cirrhosis). Occasionally it will be nondiagnostic, and in still others it will be suggestive of extrahepatic biliary tract obstruction. These patients will normally have undergone a negative ultrasound examination, and the biliary tree will be of normal caliber, so its visualization is best secured by ERCP.

Table 2
Factors Influencing Liver Biopsy Interpretation

- *Relating to patient*
  1. Confidence in biopsyist (if necessary, sedate)
  2. Obesity
  3. Ascites (not a contraindication)
  4. Small liver
  5. Markedly fibrotic liver
- *Relating to biopsyist*
  1. Size of specimen
  2. Number of aspirations
  3. Fragmentation of specimen
  4. Selection of investigation
  5. Type of fixative
- *Relating to laboratory*
  1. Level embedding
  2. Sectioning, mounting
  3. Quality of stains
  4. Number of stains utilized
  5. Additional levels
- *Relating to pathologist*
  1. Training/experience
  2. Awareness of clinicopathologic correlates
  3. Willingness to share specimens with other liver pathologists

SUGGESTED READINGS

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Vicente P. Dinoso, Jr.

2

Diagnostic Tests of Pancreatic and Biliary Tract Function

Functional evaluation of the gallbladder, biliary tree, and pancreas are useful adjuncts to radiologic visualization of the biliary and pancreatic ductal systems. Regarding the pancreas, they provide documentation of pancreatic exocrine function if maldigestion secondary to pancreatic exocrine deficiency is suspected clinically.

Most tests measure water, bicarbonate, total protein, or specific enzymes such as amylase, trypsin, and lipase. These constituents of pancreatic juice are measured after direct stimulation by intestinal hormones such as secretin and cholecystokinin or by test meals (Lundh test meal) and food products (amino acids). Their main drawback is the requirement of gastroduodenal intubation. A trained technician with a well-equipped gastrointestinal laboratory is essential for the proper performance of these tests. Furthermore, the pure synthetic or natural hormones are relatively expensive and are not readily available to most routine clinical laboratories. If these requirements are available, however, these tests are useful adjuncts to current radiologic methods of assessing pancreatic diseases.

Tests for functional evaluation of the gallbladder and biliary tree are not as numerous or as readily available as pancreatic exocrine function tests. Determinations of bile acid pool and enterohepatic circulation of bile, for instance, require complex analysis of radiolabeled bile acids in blood, intestinal lumen, and feces—procedures that do not lend themselves to routine clinical use. A test that held some promise initially as a clinical tool for assessing the motor function of the biliary tree, the morphine–prostigmine test, recently has been shown to be nonspecific and unreliable. In some medical centers, exogenous cholecystokinin is used in conjunction with the oral cholecystogram to provide information on the motor function of the gallbladder, cystic duct, common bile duct, and sphincter of Oddi. Endoscopic measurement of pressures of the sphincter of Oddi and common bile duct is being performed investigationally in some centers, but whether it will prove to be clinically reliable and useful awaits further experience.

Common and certain uncommon tests employed for the evaluation of pancreatic and biliary tract function are listed in Tables 1 and 2. Only the tests of practical use to clinicians will be described. Further analyses of blood and urine for amylase and lipase,

Table 1
Diagnostic Tests of Pancreatic Function

- *Pancreatic electrolytes and enzymes in duodenal fluid*
  - Direct hormonal stimulation
    - Secretin*
    - Cholecystokinin*
    - Secretin–cholecystokinin
    - Caerulin
    - Caerulin–secretin
    - Bombesin
  - Indirect tests
    - Lundh test meal*
    - Intraduodenal infusion of amino acids
    - Synthetic pepetide *para*-aminobenzoic acid (Bz-Ty-PABA) test
- *Examination of food products and pancreatic enzymes in stools*
  - Fat globules and meat fibers in stools*
  - 72-h fecal fat (van de Kamer method)*
  - Fecal chymotrypsin
  - Fecal nitrogen
- *Pancreatic enzymes in blood and urine*
  - Serum amylase and lipase†
  - Urinary amylase†
  - Amylase–creatinine clearance test†
  - Amylase in pleura and ascitic fluid†

*Available in well-equipped GI laboratories.
†Available in routine laboratories.

including amylase clearance in the urine, are described in most laboratory manuals and will not be discussed here.

GENERAL METHOD OF GASTRODUODENAL INTUBATION AND ASPIRATION

The patient is fasted overnight and is intubated by a double lumen tube (Dreiling) or a triple lumen polyvinyl tubing with a mercury balloon at its end. The proximal openings are for aspiration of gastric juice, the middle opening for infusion of a marker

Table 2
Functional Evaluation of the Biliary Tree and Gallbladder

- *Motor function*
  Cholecystokinin cholecystography; morphine-prostigmine test (Nardi's test); direct measurement of choledochal and sphincter of Oddi pressure during endoscopic retrograde cannulation (ERCP)
- *Examination of the blood*
  Total, direct, and indirect bilirubin, alkaline phosphatase (AP), gamma glutamyl transferase (GGT), transaminases (SGOT and SGPT), antimitochondrial antibody (AMA)
- *Microscopic examination of bile*
  Cholesterol and bilirubin crystals