PROGRESS IN

HEPATIC, BILIARY, AND PANCREATIC SURGERY

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UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
DEPARTMENT OF SURGERY
AND
CONTINUING MEDICAL EDUCATION

Progress in Hepatic, Biliary, and Pancreatic Surgery

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Year Book Medical Publishers, Inc.
Chicago • London • Boca Raton • Littleton, Mass.

1 2 3 4 5 6 7 8 9 0 CK 92 91 90

Library of Congress Cataloging-in-Publication Data

Progress in gastrointestinal surgery/[edited by] John S. Najarian, John P. Delaney.

Includes bibliographies and index.
1. Hepatic, biliary, pancreatic systems—Surgery. I. Najarian, John S., 1927– , II. Delaney, John P., 1930–
[DNLM: 1. Hepatic, biliary, pancreatic systems, surgery. WI 900 P964
RD540.P89 1989 617.4'3 89-9089
ISBN 0-8151-6304-5

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Preface

Since 1974, the proceedings of the surgery continuation course at the University of Minnesota have provided the basis for an annual book. Each course is designed to provide an update on a specific but fairly broad area of general surgery. We try to emphasize topics which are controversial or which represent recent advances. The course from which this book was generated dealt with the liver, biliary tract, and pancreas. Although the title implies that it presents advances in surgery, the fact is that a good many of the chapters deal with relevant disease processes, not necessarily from a surgical viewpoint. For example, the first three chapters are on inflammatory liver disease. The authors deal with various significant new areas of knowledge. Included among these are the use of intraoperative ultrasound for liver and pancreatic surgery and implantable hepatic artery pumps. At least two of the chapters include discussions of later-day anatomic insights which enhance liver resection or bile duct bypass. Percutaneous and endoscopic approaches to the liver, bile ducts, and pancreas have assumed a growing importance and are discussed extensively.

For physicians who attended the course, this book serves to provide a permanent record to document and reinforce what was presented. For others, the book provides a fairly succinct review of what is new in these areas. Our own resident staff has found the books to be quite helpful in preparing for qualifying examinations. A 5-year sequence of books provides an extensive survey of recent advances in general surgery. We make no claim that this volume is encyclopedic. There are others which admirably serve the role of an encyclopedia. Rather, it is selective, omitting much medical school level material and emphasizing more subtle aspects which are not generally dealt with in standard textbooks.

The book should be of value to surgeons in training or in practice who deal with the liver, biliary tract, and pancreas. It also can be of considerable interest to gastroenterologists and family medicine specialists whose patients include many with gastrointestinal disease.

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Contents

Acute Hepatitis: Classification, Diagnosis, and Natural History

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The classification, diagnosis, and course of acute hepatitis is a big subject. I have tried to summarize it in a way that will be of interest and will provide new data.

Acute hepatitis is a primary, diffuse, inflammatory necrosis of the liver. *Acute* usually implies that the duration of disease may be up to, but not exceeding, 6 months. Histologic features vary slightly in different disease states, but the general features of diffuse inflammation, acute necrosis, hepatocyte ballooning, and acidophilic necrosis of liver cells are characteristic of acute hepatitis. The etiologies of acute hepatitis range widely. They include both infectious and noninfectious processes. Under etiologies, I have simplified the list by including the primary viruses, the secondary viruses, which include Epstein-Barr virus and cytomegalovirus, and bacterial causes, which now include such diseases as Legionnaire's disease. The noninfectious etiologies include drugs, anoxia, and metabolic derangements.

I will concentrate on the primary hepatotrophic viruses. Most of the information to date has related to hepatitis A (HAV), hepatitis B (HBV), delta (HDV), and, most recently, hepatitis C virus (HCV). Serologic markers are utilized to predict the natural history, resolution, and disease prognosis. Most episodes of viral hepatitis are similar in clinical presentation. However, there are some distinctions. There is a wide range of clinical severity, from mild, anicteric hepatitis to fulminant and rapidly fatal disease. The latter now constitutes an indication for liver transplantation.

It is important to make a precise serologic diagnosis, since prognosis, preventive measures, and future effective therapy will depend on identifying the specific virus.

There are arbitrarily three clinical stages of viral hepatitis. The first is incubation, the second, acute hepatitis, and the third, convalescence. The stages are recognized utilizing viral serologic markers. The incubation stage is essentially asymptomatic. The acute stage includes a preicteric interval, during which the patient develops nonspecific symptoms of anorexia, nausea, fatigue, and malaise, followed by an icteric phase, which is usually accompanied by resolution of symptoms. Viral markers signal that the disease is resolving. Combining clin-

ical, biochemical, and histologic features with viral markers, we can now confidently predict disease resolution.

Hepatitis A is the most familiar. The virus is a small, 27-nm RNA virus (an enterovirus) that is resistant to gastric digestion as well as intestinal enzyme digestion. There is no envelope. It has single-antigen specificity on its surface and only one serotype. The incubation period is short, with a mean of approximately 4 weeks.

Hepatitis A commonly has respiratory and gastrointestinal symptoms, more frequently than HDV or non-B. About 75% of the patients are anicteric. Hepatitis A may be difficult to recognize unless your index of suspicion is high. It has a higher incidence in children than adults, probably because of the fecal-oral route of inoculation. There is no carrier state or chronic hepatitis. Rarely is HAV hepatitis fulminant. However, with the new generation of patients who are severely immunosuppressed, i.e., those with acquired immunodeficiency syndrome, cases of HAV hepatitis leading to fulminant hepatic failure are being reported.

From a surgical standpoint, remember that the virus is shed into the bile and feces and is highly infective at that stage. The peak shedding of the virus occurs before one can detect abnormalities in liver chemistry tests, i.e., before hypertransaminasemia or hyperbilirubinemia. The virus often disappears 1 or 2 weeks after the onset of jaundice. There is a period of brief viremia, but because of its brevity, HAV hepatitis is rarely transmitted by transfusion.

The virus begins to shed early in the incubation period and antedates the development of symptoms as well as transaminase and bilirubin elevation. Before clinical recognition, the virus is being shed and the patient is infective, which is a strong incentive for precaution, hand washing, and good hygiene.

The key serologic marker for diagnosis is the acute antibody (IgM anti-HAV). For detection, we use IgM anti-HAV, which is present early and also present during the convalescent period. The IgG form of anti-HAV is also present in the early convalescent form and probably persists in most patients throughout life, thus rendering lifelong immunity.

Hepatitis B is a 42-nm DNA virus. It contains, unlike HAV, a coat and core. During infection, there is excess coat synthesized, i.e., hepatitis B surface antigen (HBsAg); HBsAg circulates in the blood and is not infectious. The virus core, HBcAg, replicates in the hepatocyte nucleus, then acquires the coat of HBsAg in the cytoplasm before the virus is shed. The Dane particle contains the coat of HBsAg, the inner core antigen, DNA polymerase, and viral DNA. The latter two are markers of infectivity and in special research laboratories can be measured. When present, they indicate a high degree of infectivity. On electron microscopy, we commonly see the smaller particle of HBsAg and the tubular form.

In contrast to HAV, HBV hepatitis has a longer incubation period, ranging from 6 weeks to 6 months. The symptoms often include rash, joint pain, arthritis, and arthralgia. Sixty percent of the acute fulminant hepatic failure in the United States is due to HBV either alone or in combination with HDV.

Most laboratories have a 5% to 10% margin of error in failing to detect low levels of HBsAg. The marker of acute hepatitis is the acute antibody, IgM against core. We recognize that there is some core antigen in the blood, but it

is usually in very low titer and, therefore, essentially undetectable. Anti-HBV of the IgM class appears early and is an important marker of acute disease.

Remember that the hepatitis B e antigen (HBeAg), which is associated with the highly infective state, is a component of the core. The HBeAg appears early, then elicits its own antibody. Anti-HBe signifies convalescence.

These markers in the blood correlate with the infectious stage, resolving hepatitis, and convalescence.

A typical case of acute type B hepatitis has an incubation period followed by the development of HBsAg followed by the HBeAg. DNA polymerase, and HBV-DNA titers, if prolonged for more than 4 to 5 weeks, may predict that the patient will have chronic disease. Notice that the markers—for example, the IgM anti-HBC—occur early and then in convalescence completely disappear. The markers of recovery and further immunity are the presence of the anti-HBsAg and the IgG anti-HBC. We have now observed the sequence of markers of acute infectivity, recovery, and, in some instances, lifelong immunity.

What happens in a case of acute type B hepatitis? Of 100 patients with acute HBV infection, about 65% are going to have transient subclinical infections, often without jaundice. The great majority of those patients recover. Twenty-five of an initial 100 patients will have an acute, clinically recognizable form of hepatitis. About 1% of that group will go to fulminant hepatic failure. The remainder will recover. Approximately 10 of the initial 100 patients will develop a *chronic* form of type B hepatitis. Some patients will go on to persistent or chronic active hepatitis.

A subdivision of chronic HBsAG hepatitis is the so-called healthy HBsAg carrier state. This subgroup of patients have had acute HBV hepatitis and now continue to be positive for HBsAg but have normal hepatic histologic findings, are asymptomatic, and have normal hepatic enzymes.

There are "windows" during which time "markers" may be absent. There are periods during the course of the disease when serologic markers may be absent or their detection delayed. For example, there is an early incubation period when we do not see the HBsAg and the HBeAg, yet the patient has been inoculated and infected. There is also a period where the HBV antigen has been cleared early, as well as the HBeAg, but there is delay in the formation of the anti-HBsAg. Therefore, there are periods during which the resolution or development of the disease may be difficult to identify.

Hepatitis delta virus represents a defective RNA virus. The HDV causes hepatitis only in the presence of HBV. It requires HBsAg for its infectivity. It has an outer core HBsAg, donated by the HBV. The inner viron of HDV is in the center and the viral DNA in the center.

Characteristics of the HDV are the following. Fulminant hepatitis is approximately ten times more common than in any other viral disease. The delta virus is highly infective and frequently is associated with fulminant hepatitis. It has been shown to be endemic in the Mediterranean, Middle East, Africa, and South America. In the United States, we diagnose it primarily in drug addicts and the hemophiliac population. There are two types of HDV infection. The first is designated "simultaneous or coinfection." That is, the patient is inoculated with both HBV and HDV simultaneously. Alternatively, HDV may cause a superinfection, that is, HDV is inoculated at some interval after the patient

has been exposed to HBV. There are significant differences between these two types of infection. A patient may be simultaneously inoculated with HBsAg, HBeAg, and HDV. When this happens, the patient usually has an acute hepatitis course, most often self-limiting, with evidence of recovery and resolution indicated by the specific viral markers of recovery. Coinfection is usually a self-limiting disease. In contrast, the patient who has been an HBsAg carrier and is now inoculated with the HDV demonstrates a further rise in the transaminase and bilirubin levels. Many of these patients go on to chronic liver disease, cirrhosis, and, in some instances, hepatocellular cancer. The detection of HDV includes the detection in the blood of IgM or IgG anti-HDV and by microscopic identification of HDV antigen in the liver.

There is much current interest in non-A, non-B hepatitis. For surgeons, this is probably one of the most important viral infections. There are probably two, if not more, non-A, non-B viruses involved.

The diagnosis of non-A, non-B hepatitis has, until recently, been a process of exclusion. The diagnosis was made only after we had excluded other viruses that cause liver disease and other causes of acute hepatic injury, such as toxins, drugs, or congestive heart failure, that may produce an inflammatory necrosis of the liver. There are two epidemiologically distinct types of non-A, non-B viruses.

The first virus, now referred to as HCV, is the virus most commonly associated with acute hepatitis following blood transfusions. The HCV has also been recognized in sporadic cases in developed countries, including the United States. A second virus, which has a fecal-oral route of entry, is similar to HAV in terms of route of inoculation and clinical features.

With regard to posttransfusion hepatitis, we now recognize that patients, despite being anicteric, have a high incidence of chronic liver disease, 40% to 50%. There is also a higher mortality in pregnant women who develop posttransfusion hepatitis. The serum alanine aminotransferase levels, although only modestly elevated, are protracted and fluctuate. Bone marrow suppression is more common in HCV than in HAV, HBV, or HDV hepatitis.

Fulminant hepatitis is rare with HCV. The anti-HCV is the Chiron antibody. This is the dominant antibody in acute and chronic HCV hepatitis. As currently measured, the antibody to HCV may be present in only 50% of the patients. Not every patient suspected of having HCV hepatitis will have measurable antibody at the time, because seroconversion is often delayed 6 to 12 months after the initial episode of hepatitis. To detect antibody to HCV, we must obtain multiple blood samples at varying intervals after recognition of hepatitis. The commercial assay (Chiron) antibody will be available at the end of 1989. Characteristically, levels of transaminase and bilirubin fluctuate.