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GASTROENTEROLOGY BOARD REVIEW MANUAL

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Jaundice and Cholestasis

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Preface

Board certification in gastroenterology and hepatology requires an understanding of all aspects of physiology, diagnosis, and therapy for gastrointestinal tract, liver, and pancreatic disorders. In addition to self-study of this discipline, candidates for board certification must have completed 2 years of fellowship, during which time the practical aspects of the diagnosis and treatment of gastroenterologic and hepatologic complications are learned through hands-on clinical investigation.

The *Hospital Physician Gastroenterology Board Review Manual* is a study guide intended to help candidates prepare for the written and oral components of this examination. The manual consists of quarterly publications that address the following areas:

- Acid peptic disease
- Acute appendicitis
- Aging and the gastrointestinal tract
- Basic biology
- Chronic cholestatic syndromes
- Cirrhosis and portal hypertension
- Diverticulosis coli
- Drug-induced and alcoholic liver disease
- Endoscopy of upper gastrointestinal hemorrhage
- Esophageal disorders
- Gallstones

- Gastrointestinal manifestations of AIDS
- Inflammatory bowel diseases and other diarrheal diseases
- Intestinal obstruction
- Irritable bowel syndromes
- Ischemic bowel disease
- Liver transplantation
- Malabsorption syndromes
- Nutritional support
- Pancreatic disease
- Small intestinal, colonic, and other tumors
- Viral and chronic hepatitis

Most of these topics are covered in the manual; however, some areas of interest are discussed in greater depth than others.

The manual presents clinical scenarios using a case-based format; questions and answers relating to the clinical presentation are provided. The editors believe that this question-and-answer format is an effective teaching tool and allows for adequate self-assessment. Each quarterly publication addresses only a few of the topics mentioned; board certification candidates should review the entire list of topics to be appropriately prepared for the examination. The *Hospital Physician Gastroenterology Board Review Manual* is prepared by the Series Editor and contributing authors and not in collaboration with the American Board of Internal Medicine, Gastroenterology/Hepatology.

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Jaundice and Cholestasis

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INTRODUCTION

One of the most important functions of the liver is bile formation. Disruptions in bile formation often become evident as cholestasis. Cholestasis is a condition in which there is impaired secretion of the numerous components of bile (which are normally removed from the portal circulation and transported into bile via hepatocytes, and secreted into the gut via the biliary system). Jaundice is a common presenting symptom of cholestasis. However, some conditions produce jaundice in the absence of cholestasis; jaundice is one of the most frequent (and typically the most obvious) presenting symptom of numerous diseases of the liver and biliary tract. Cholestasis can also be caused by numerous hepatobiliary diseases; it may be caused by diminished hepatic transport function (intrahepatic cholestasis) or by an anatomic obstruction to bile flow in the biliary system (extrahepatic cholestasis). This manual briefly describes mechanisms involved in the hepatocellular transport of substances into bile and uses case-based discussions to describe important steps in diagnosing the cause of jaundice and/or cholestasis in patients.

REVIEW OF HEPATOCELLULAR TRANSPORT

Jaundice, pruritus, and other symptoms and signs of cholestasis are caused by impaired elimination of numerous endogenous and pharmacologic substances, with a resultant increase in their serum levels. This impairment sometimes results from defects in the molecular mechanisms by which the liver transports these substances from the portal blood, across the hepatocyte, and into the biliary system. Over the past decade, many of these molecular mechanisms have been identified.^{1,2} Although a detailed discussion of these mechanisms is beyond the scope of this manual, a brief description of the uptake of these substances by the liver and their subsequent secretion into bile may be beneficial.

Figure 1 is a schematic representation of the general mechanisms involved in the hepatocellular uptake and secretion of the organic anions bilirubin (unconjugated)

and bile salts. Each of these substances has distinct liver sinusoidal and canalicular transport proteins, which transport the compounds from the blood (sinusoidal proteins) into bile (canalicular proteins). These transport proteins are representative of other hepatic transport systems for other substrates. A reduction in the physiologic function of hepatic transport systems results in intrahepatic cholestasis.

Moreover, the liver must also metabolize water-insoluble substances into water-soluble substances prior to their secretion into bile. Unconjugated bilirubin is the end product of heme degradation. Because unconjugated bilirubin is insoluble in water, it requires hepatic metabolism into a conjugated form (ie, bilirubin monoglucuronide or diglucuronide) by the endoplasmic reticulum enzyme, bilirubin uridine-diphosphate glucuronosyltransferase (UGT), before it can be secreted into bile. Conjugated bilirubin (a water-soluble substance) is secreted across the canalicular membrane. A disruption of either bilirubin metabolism (conjugation) or secretion can result in jaundice. Unconjugated (indirect) hyperbilirubinemia results from a disruption of bilirubin conjugation, whereas conjugated (direct) hyperbilirubinemia results from a disruption of bilirubin secretion.^{3,4}

Liver diseases frequently impair bilirubin secretion and result in clinical jaundice, the most easily “seen” manifestation of cholestasis. However, a clinician must remember that there may also be concomitant impairments of hepatic drug metabolism and secretion, as well as impairments regarding the excretion of endogenous toxins, which may be less easily “seen.”

EXTRAHEPATIC BILIARY OBSTRUCTION

CASE 1 PRESENTATION

Patient 1 is a 22-year-old woman with a 3-day history of acholic stools, dark urine, and painless jaundice. She had given birth 1 month ago to a boy who had neonatal jaundice; however, her son is now completely healthy. She had an uncomplicated pregnancy and delivery.

She denies experiencing any fevers, chills, pruritus, or abdominal pain. Physical examination findings are