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Problems in Liver Diseases

Edited by Ch. S. Davidson, M. D.

PROBLEMS IN LIVER DISEASES

Edited by
Charles S. Davidson, M.D., C.M.

William Bosworth Castle Professor of Medicine, Emeritus,
Harvard University, Boston, and
Senior Lecturer in Medicine
Massachusetts Institute of Technology

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Contributors

Elliot Alpert, M.D., Associate Professor of Medicine, Harvard Medical School; Assistant Physician, Gastrointestinal Unit, Massachusetts General Hospital, Boston, Mass.

Irwin M. Arias, M.D., Professor of Medicine, and Director, Liver Research Center, Albert Einstein College of Medicine, Bronx, N.Y.

Fathali Borhanmanesh, M.D., Professor of Medicine, Pahlavi University School of Medicine, Shiraz, Iran

Stanley E. Bradley, M.D., Samuel Bard Professor Emeritus of Medicine, Columbia University College of Physicians & Surgeons, New York, N.Y.

K. H. Brandt, M.D., Department of Medicine, Municipal Hospital, Arnhem, The Netherlands

F. B. Bronkhorst, M.D., Department of Histopathology and Morbid Anatomy, Municipal Hospital, Arnhem, The Netherlands

Sanjiv Chopra, M.D., Research Associate in Medicine, Veterans Administration Hospital, and Lecturer in Medicine, Boston University School of Medicine, Boston, Mass.

Harold O. Conn, M.D., Medical Service, Veterans Administration Hospital, West Haven, Conn., and Professor of Medicine, Yale University School of Medicine, New Haven, Conn.

Charles E. Cornelius, D.V.M., Ph.D., College of Veterinary Medicine, Division of Gastroenterology, Department of Medicine, University of Florida, Gainesville, Fla.

William A. Curby, M.S., Head, Biophysics Research Unit, Lahey Clinic Foundation, Boston, Mass.

Paul V. Desmond, M.B., B.S., Fellow in Gastroenterology, Vanderbilt University, School of Medicine, Nashville, Tenn.

Daniel Deykin, M.D., Chief, Medical Service, Boston Veterans Administration Hospital, and Professor of Medicine, Boston University and Tufts University Schools of Medicine, Boston, Mass.

Nicholas R. DiLuzio, Ph.D., Professor and Chairman, Department of Physiology, Tulane University School of Medicine, New Orleans, La.

Howard J. Eisen, M.D., Section on Physiological Control, Laboratory of Biomedical Sciences, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md.

Harold J. Fallon, M.D., William Branch Porter Professor and Chairman, Department of Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, Va.

Harry S. Greenberg, M.D., Senior Staff Investigator, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Md.

Charles H. Halsted, M.D., F.A.C.P., Associate Professor of Internal Medicine, University of California, Davis, Calif.

M. M. Howard, M.D., Clinical Associate Professor of Medicine, College of Medicine and Dentistry of New Jersey, New Jersey School of Medicine, Newark, N.J.

Anastacio M. Hoyumpa, Jr., M.D., Associate Professor of Medicine and Clinical Investigator, Vanderbilt University, School of Medicine, and Nashville Veterans Administration Hospital, Nashville, Tenn.

Don P. Jones, M.D., Professor of Medicine, Department of Medicine, Wayne State University School of Medicine, and Chief, Division of Gastroenterology, Hutzel Hospital Medical Unit, Detroit, Mich.

Marshall M. Kaplan, M.D., Professor of Medicine, Tufts University School of Medicine, and Chief, Gastroenterology Unit, Department of Medicine, New England Medical Center Hospital, Boston, Mass.

Barry J. Kemler, M.D., Research Fellow in Medicine, Harvard Medical School, and Clinical & Research Fellow in Medicine, Gastrointestinal Unit, Massachusetts General Hospital, Boston, Mass.

Raminder Kumar, M.D., Staff Physician, Boston Veterans Administration Hospital, and Instructor in Medicine, Boston University School of Medicine, Boston, Mass.

C. B. Leevy, student, New Jersey Medical School, Newark, N.J.

Carroll M. Leevy, M.D., Professor of Medicine, College of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, N.J.

Roger Lester, M.D., Professor and Chief, Division of Gastroenterology, Department of Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, Pa.

Frederick H. Lovejoy, M.D., Associate in Medicine, and Associate in Clinical Pharmacology, Children's Hospital Medical Center, Boston, Mass.

Craig J. McClain, M.D., Department of Medicine, Minneapolis Veterans Hospital, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minn.

Thomas C. Merigan, M.D., Professor of Medicine, Infectious Disease Division, Stanford University, Stanford, Calif.

Anatol G. Morell, M.S., Professor of Medicine, Albert Einstein College of Medicine, Bronx, N.Y.

A. G. F. dePagter, M.D., General Practitioner, Ijsselmuiden, The Netherlands

John W. Popp, Jr., M.D., Research Fellow in Medicine, Harvard Medical School, and Clinical & Research Fellow in Medicine, Massachusetts General Hospital, Boston, Mass.

Hans Popper, M.D., Ph.D., Gustave L. Levy Distinguished Service Professor, The Mount Sinai School of Medicine, City University of New York, New York, N.Y.

Ananda S. Prasad, M.D., Ph.D., Professor of Medicine, and Director, Division of Hematology, Wayne State University, School of Medicine, Detroit, Mich.

Roderick K. Roberts, M.B., B.S., Fellow in Gastroenterology, Vanderbilt University, School of Medicine, Nashville, Tenn.

William S. Robinson, M.D., Professor of Medicine, Infectious Disease Division, Stanford University, Stanford, Calif.

Victor M. Rosenoer, M.B., Ph.D., F.R.C.P., Head, Gastroenterological Research, Lahey Clinic Foundation, Harvard Medical School, Boston, Mass.

I. Herbert Scheinberg, M.D., Professor of Medicine, and Head, Division of Genetic Medicine, Albert Einstein College of Medicine, Bronx, N.Y.

Steven Schenker, M.D., Professor of Medicine and Biochemistry, and Head of Gastroenterology, Vanderbilt University School of Medicine, and Nashville Veterans Administration Hospital, Nashville, Tenn.

Elihu M. Schimmel, M.D., Chief, Gastroenterology Unit, Veterans Administration Hospital, and Associate Professor of Medicine, Boston University School of Medicine, Boston, Mass.

Sheila Sherlock, D.B.E., M.D., Professor of Medicine, University of London, and Chairman, Department of Medicine, Royal Free Hospital, London, England

Walton W. Shreeve, M.D., Ph.D., Chief, Nuclear Service (115), Veterans Administration Center, Northport, N.Y., and Professor of Medicine (Nuclear Medicine), State University of New York at Stony Brook, Stony Brook, N.Y.

Arnold L. Smith, M.D., Professor of Pediatrics, Department of Pediatrics, University of Washington, School of Medicine, Seattle, Wash.

Richard J. Stockert, Ph.D., Assistant Professor of Medicine, Albert Einstein College of Medicine, Bronx, N. Y.

Gregory J. Taggart, M.D., Medical Service, Veterans Administration Hospital, West Haven, Conn., and Department of Internal Medicine, Yale University, School of Medicine, New Haven, Conn.

Tsunenobu Tamura, M.D., Assistant Research Nutritionist, University of California, Davis, Calif.

G. P. van Berge-Henegouven, M.D., Division of Gastroenterology, Department of Medicine, Saint Radboud Hospital, University of Nijmeger, The Netherlands

David H. Van Thiel, M.D., Assistant Professor, Division of Gastroenterology, Department of Medicine, University of Pittsburgh, School of Medicine, Pittsburgh Pa.

Elliot S. Vesell, M.D., Professor and Chairman, Department of Pharmacology, Pennsylvania State University, College of Medicine, Hershey, Pa.

J. M. Walshe, Sc.D., F.R.C.P., University of Cambridge Clinical School, Department of Medicine, Addenbrooke's Hospital, Cambridge, England

Jack R. Wands, M.D., Assistant Professor of Medicine, Harvard Medical School, and Assistant in Medicine, Massachusetts General Hospital, Boston, Mass.

Patrick Y. Wong, M.D., Associate Professor of Medicine, Department of Medicine, Albany Medical College, Albany, N.Y.

Leslie Zieve, M.D., Department of Medicine, Minneapolis Veterans Hospital, Hennepin County Medical Center, University of Minnesota, Minneapolis, Minn.

Foreword

The ever increasing amount of scientific literature, and especially biomedical literature, creates an unresolvable problem for medical students, house officers, practitioners (both family physicians and specialists) as well as for clinical and basic scientists, probably in increasing order of severity. The frustration which results from the inability of one person to select, read and digest the many reports published in general and specialty journals is aggravated by the creation of many new journals every year. Clichés such as "information explosion" and "paper pollution" are being applied to this difficulty which necessitates the search for defense mechanisms. These mechanisms vary according to the prejudice and life style of the individual reader.

The probelm is particularly acute as it applies to literature on the liver and its diseases, as is indicated by the existence of about fifty journals devoted to gastroenterology which deal with liver disease to a great degree. As a large, seemingly homogenous organ, the liver has served as the model for the study of many basic biologic processes. For example, much of our knowledge of the principles of metabolic processes is based to a great extent on the study of the liver. Also, much of our knowledge of mammalian molecular biology has been derived from the study of this organ. As a result, observations related to the biology of the liver are being published in books and journals of many disciplines.

Although liver disease and particularly its symptoms have elicited fascination in Latin countries for centuries, it is only since World War II that symptomatology and mechanisms of liver disease have aroused wider interest in Anglo-Saxon countries where, before, the investigations centered on the study of the biology of the liver. Three developments may have played a role in this shift of emphasis. One was the recognition of the social impact of liver disease, which is more common in the disadvantaged segment of the population, where inadequate nutrition and unsavory hygiene increase the risk of acquiring liver diseases and favor a more chronic course. The second development is the recognition that in the less developed countries, liver disease—particularly in its parasitic and carcinomatous forms—is a major threat to the public health, resulting in the death of many young persons. Improved communication throughout the world has raised interest in these diseases within the developing countries themselves, at the same time it has increased the sense of responsibility among developed nations for the study and possible relief of those diseases which are rampant in less developed areas. Thus far, major success has been accomplished or is on the horizon, at least in the control of parasitic disease. The third reason for increased interest in hepatic diseases is the realization of the role of the liver in human reactions to the environment, especially in disorders created by an undesirable life style, with alcoholism and drug abuse the most glaring examples.

Paradoxically, the metabolism of exogenous agents in the liver represents a threat to our health by creating ultimate carcinogens, at the same time as it serves as the main site of human defense against environmental hazards. The editor of this book has contributed greatly to all three of these developments which raised interest in liver diseases and thus contributed to the creation of hepatology as a new discipline.

Various defense mechanisms against the avalanche of information exist. The future may bring computerized storage and analysis of information which could be readily available to anyone having access to a computer terminal linked to a national or even international central storage and answering installation. The "reader" could ask questions appropriate to his or her level of sophistication and specific purpose. The answers, whether simple or highly complex, would have been previously evaluated and agreed on by experts and thus would be the most valid data available at the time. In the "Brave New World," which may be rapidly approaching, the classical Gutenberg culture, based on the printed word, would give way to a new electronic system.

Reliable and effective as this system might be, it would not provide the pleasure, stimulation and charm of reading a book which, if it is skillfully written, pleases and excites the imagination. Gone would be the discovery of some pearl of wisdom or of understanding which unpredictably fascinates and which sometimes initiates a new pathway of thinking, a new direction for research, or an especially astute clinical diagnosis. Serendipity, providing a hunch or a gut reaction, which influences diagnosis or research, as well as career choices, is the potential benefit of a well written book. The benefit of reading an informative, interesting book compares to contact with a teacher in the laboratory or at the bedside, or even to a stimulating lecture. Therefore, even in the computerized world of the future, some other defenses against the information explosion will be desirable. One mechanism is reviews covering and analyzing the original publications appearing in the abundant number of journals.

Franz Ingelfinger* has aptly spoken of a "secondary literature," consisting of textbooks, review articles in journals, abstract collections and serial volumes, generally designated as "progress," "advances," or "annual review." In pointing out that some hundreds of such biomedical serial publications now exist, Ingelfinger has emphasized the fact that this secondary literature is approaching the primary literature in volume.

Contributions to a "progress" series are characterized by the comprehensive coverage of a specific subject, supported by an extensive literature. Such series, usually rapidly published, bridge primary and other secondary literature and try to cover all recent developments as much as possible.

However, there exists another, far less frequent type of secondary literature, which is exemplified by this volume. Such publications consist of a group of essays, each dealing with one facet of a broader biomedical subject,

* Ingelfinger F: Foreword. *In* Popper H, Schaffner F (Eds): Progress in Liver Diseases, Volume V. New York, Grune & Stratton, 1976, pp viii–ix.

a facet of particular interest to the author at the time. Such a facet is appropriately designated as a "problem" since it may cover topics about which the reader may be quite uncertain. Comprehensive coverage of the general area is not attempted, and the literature quoted is selected to support a particular point, either speculative or substantial. These essays are not intended as reference sources, although their function as such may be an incidental benefit.

In writing an essay for this kind of book, the primary purpose of the author is not to present an all embracing review based on intense study of literature, but rather to enjoy the pleasure of writing on an intriguing subject. The benefit to the reader thus derives from the enthusiasm of the writer as well as from his scholarly coverage of the chosen field. Similarly, the function of the editor of such a book is to identify these writers who have something to say in an essay and who want to say it. However, the end result, as in this volume, still gives a panorama of the advancing field, in this instance of hepatology, by looking at the peaks rather than the valleys. These peaks may include discovery of physiologic or pathologic phenomena, certain aspects of disease entities, diagnostic modalities, design of new clinical or laboratory procedures, and finally, developments in therapy. Such an essay collection differs from a progress series in conception, scope, execution and particularly in the length of individual contributions.

Thus, collections of essays such as this one undoubtedly provide serendipity, stimulation, and particularly pleasure. They contrast especially with the electronic literature of the future, however comprehensive it may be. I know the editor of this volume enjoyed putting this book together and that he approached his task with enthusiasm. I assume that the same holds true for the authors, all experts in their fields, and I hope that the reader will share these feelings. I myself look forward to the pleasure of reading the articles in quiet moments.

Hans Popper, M.D., Ph.D.

Preface

My more than 35 years largely spent working with and worrying about patients with severe liver disease have highlighted many unsolved problems. My colleagues and I have worked together on some of these problems at the Thorndike, occasionally with fruitful results, while other problems remain partially or completely unsolved but are being studied in centers throughout the world.

The purpose of this book, then, is to provide the reader with short essays, each expressing a scholar's views of the present knowledge concerning some of these problems. The authors who have been chosen are among the recognized authorities in each field. I suggested to each that a "review" was not expected, but rather a terse statement of modern knowledge with a few references for more in-depth study by an interested reader. Some followed this suggestion, while others chose a longer and more penetrating style with an extensive literature backup. After first submission, some bibliographies were shortened, but by and large I have not attempted to require uniformity of length or of style.

I have made a few changes in order to conform to certain editorial prejudices of my own, and on occasion have made changes in the manuscripts for what I believe is greater clarity or succinctness. I apologize to authors and readers alike if or when I have failed in these attempts.

Most of the responsibility for what has been written, however, rests with the authors, and I thank them from the bottom of my heart for the general excellence of their essays and the promptness of their submissions. The publisher has been extraordinarily helpful throughout and has hastened publication. The book is, in a fair measure, up-to-date because of this excellent cooperation of authors and publisher. The order of presentation, as shown in the Table of Contents, is arbitrary.

Finally, my thanks to my long-time friend and colleague, Hans Popper, who suggested that I get this book together. I have learned much from him over the years.

Charles S. Davidson, M.D.
Cambridge, Massachusetts
December 1978

Contents

CHAPTER 1

Explanations of Jaundice in Hepatocellular Diseases

IRWIN M. ARIAS, M.D.

Knowledge of the pathogenesis of jaundice in hepatobiliary disease is directly related to advances in the understanding of bilirubin formation, transport, metabolism and excretion. Prior to 1952, the van den Bergh reaction of serum bilirubin was the major method for differentiation of hemolytic, hepatocellular and obstructive jaundice. The discovery that bilirubin is excreted in bile as a glucuronic acid conjugate resulted in differentiation of hepatic uptake, conjugation and excretion as discrete physiological processes in the transfer of bilirubin from blood to bile. In the past 10 years, these processes have been studied at cellular and molecular levels. The following are highlights of these advances:

1. Uptake is a non-energy-dependent process which is influenced by the binding of bilirubin to albumin in serum and to ligandin in the liver cell. Transmembrane transfer appears to involve nonionic diffusion, has kinetic characteristics of carrier-mediated transport, and, according to recent discoveries, may involve a specific membrane receptor.

2. Conjugation with glucuronic acid provides the major polar substrate for subsequent excretion. UDP glucuronyl transferase, a lipoprotein enzyme localized in the endoplasmic reticulum, catalyzes formation of bilirubin monoglucuronide (BMG). A second enzyme, BMG glucuronosyl glucuronoside transferase, is concentrated in plasma membrance fractions and converts 2 moles of BMG to 1 mole of bilirubin diglucuronide and 1 mole of bilirubin. UDP glucuronyl transferase activity is increased after administration of various drugs, such as phenobarbital, whereas the second enzyme is unaffected.

3. Excretion appears to be the site at which energy is coupled to transport. It constitutes the rate-limiting step in over-all transfer of bilirubin from blood to bile. Bilirubin and its conjugates interact with bile acids, micelles and proteins; however, the physiologic importance of these interactions is uncertain.

Other significant advances involve the conversion of heme to bilirubin, binding of bilirubin to albumin and ligandin, multiple sources of bilirubin formation, and the unique structure of bilirubin IXα.

Albert Einstein College of Medicine, Bronx, N.Y.

Inheritable defects in these processes in man and animals result in hyperbilirubinemia and jaundice, which is a readily detectable phenotypic abnormality. Many inheritable disorders have been described and provide exciting opportunities for study.

The processes involved in transport, metabolism and excretion of bilirubin are not unique for bile pigment and apply to other organic anions of greater biologic importance, such as certain drugs, metabolites, hormones, etc.

Bilirubin is a waste-product of heme catabolism, has no known useful function and, with the exception of a few neonates in whom bilirubin encephalopathy (kernicterus) occurs, does not appear to be harmful. In internal medicine, the major application of bilirubin chemistry and biology is in the differential diagnosis of jaundice. Major controversies of the past, such as the role of the van den Bergh reaction in differentiating hepatocellular from obstructive jaundice or in differentiating cholestatic from biliary obstructive jaundice, have been resolved by better technics for visualization of the biliary tract. These technics include ERCP, transhepatic cholangiography and ultrasonography. Nevertheless, the pathogenesis of jaundice in hepatobiliary diseases remains challenging and is summarized in this article.

TABLE 1. Pathophysiologic Classification of Jaundice

I. Predominantly unconjugated hyperbilirubinemia
  A. Overproduction
    1. Hemolysis (intra- and extravascular)
    2. Ineffective erythropoiesis (intramedulary hemolysis)
  B. Impaired hepatic uptake
    1. Gilbert's syndrome
    2. Drugs, flavaspidic acid, cholecystographic agents.
  C. Impaired bilirubin conjugation (decreased glucuronyl transferase activity)
    1. Gilbert's syndrome
    2. Hereditary absence or deficiency of UDP glucuronyl transferase (Crigler-Najjar syndrome, Types I and II).
    3. "Immaturity" of UDP glucuronyl transferase ("physiologic" juandice of neonates and prematures)
    4. Neonatal jaundice with inhibition of UDP glucuronyl transferase
      a) Transient familial neonatal hyperbilirubinemia
      b) Breast milk jaundice
II. Predominantly conjugated hyperbilirubinemia
  A. Impaired hepatic excretion (intrahepatic defects)
    1. Familial or inheritable disorders
      a) Dubin-Johnson and Rotor syndromes
      b) Recurrent (benign) intrahepatic cholestasis
      c) Cholestatic jaundice of pregnancy
      d) Familial neonatal cholestatic syndromes of viral, drug, chemical or immunologic etiology
    2. Acquired disorders
      a) Hepatocellular necrosis
      b) Intrahepatic cholestasis
  B. Extrahepatic biliary obstruction (complete and partial)

Jaundice may be pathophysiologically classified on the basis of the predominant nature of the plasma bile pigment. This classification is presented in Table 1.

I. UNCONJUGATED HYPERBILIRUBINEMIA

Predominantly unconjugated hyperbilirubinemia results from increased production, diminished hepatic removal or decreased conjugation of bilirubin. Bilirubin absorption from the intestinal tract in neonates provides another mechanism, but does not occur after the neonatal period because intestinal bacteria reduce bilirubin to colorless urobilinogens.

A. Increased Bilirubin Production

Increased bilirubin production results from intravascular or extravascular hemolysis or from sources other than mature circulating erythrocytes (i.e., ineffective erythropoiesis). Hemolytic disorders are manifested by anemia, reticulocytosis, saturation of serum haptoglobin, erythroblastic proliferation, and changes in peripheral blood morphology. In compensated hemolytic states, anemia is absent but survival of the patient's labeled erythrocytes is reduced.

In patients with normal liver function, hemolysis is rarely associated with serum bilirubin concentrations in excess of 3–4 mg%, virtually all of the serum bilirubin is unconjugated, and there is no bilirubinuria. The mechanism responsible for the relatively constant unconjugated hyperbilirubinemia in hemolytic disease is unknown. Results of kinetic studies using bilirubin-C^{14} suggest that hepatic uptake and conjugation are normal, and that jaundice results from reduced fractional disappearance of bilirubin from the plasma.

Superimposition of hemolysis on liver injury of any type produces predominantly conjugated hyperbilirubinemia and a bile pigment pattern similar to that seen in patients with parenchymal liver cell injury or biliary obstruction.

Increased "early-labeled" bilirubin results from enhanced bilirubin production in bone marrow or liver. Increased production of bilirubin from nonerythroid sources has not been shown to contribute to jaundice in man. Unconjugated hyperbilirubinemia with serum bilirubin concentrations of 1.5–3 mg% occurs in hematologic disorders associated with increased intramedullary erythrocyte destruction including pernicious anemia, lead poisoning, and other entities usually diagnosed by hematologic tests. There are rare individuals in whom peripheral blood morphology and survival of mature circulating erythrocytes are normal; however, the bone marrow is erythroblastic, serum haptoglobin is saturated and fecal urobilinogen is increased often to four times normal. This disorder is called Hereditary Erythroblastic Megalocytosis with "Positive" Acid Test (HEMPAS) and is manifested by scleral icterus. Patients often develop bilirubin cholelithiasis

during adolescence. The etiology is believed to be an abnormality in red blood cell membrane structure which renders erythrocytes susceptible to intramedullary destruction.

B. Decreased Bilirubin Removal

Impaired transfer to bilirubin from plasma to the site of bilirubin conjugation in the hepatocyte accounts for jaundice observed after administration of flavaspidic acid and various cholecystographic agents, as well as possibly in Gilbert's syndrome. Flavaspidic acid is present in oleoresin aspidium, which is used to treat fish tapeworm infestation. Individuals receiving oleoresin aspidium manifest unconjugated hyperbilirubinemia with serum bilirubin concentrations of 2–4 mg% and moderate retention of BSP and other dyes. Flavaspidic acid displaces bilirubin and BSP from intracellular hepatic binding sites on ligandin and Z protein. Cholecystographic agents also compete with bilirubin and BSP for binding to ligandin and Z protein, and produce transient elevations in serum unconjugated bilirubin concentrations and modest dye retention. These abnormalities occur within 24 hours after oral cholecystography and are rapidly reversible.

1. Gilbert's Syndrome

Gilbert's syndrome is common in all population groups. Despite considerable investigative effort, its pathophysiology remains uncertain. Reduced hepatic UDP glucuronyl transferase has been demonstrated in some patients using bilirubin as a substrate. Most of the bilirubin in bile is BMG rather then BDG. Other investigations suggest that the defect results from impaired hepatic uptake of bilirubin. Hepatic ligandin concentrations were normal in the small number of patients with Gilbert's syndrome who have been studied. In Gilbert's syndrome, serum bilirubin concentrations range from normal to 5 mg%. Conventional BSP tests give normal results, although abnormal kinetics have been described in some patients. Other liver function tests and histologic examinations are normal. Regardless of etiology, Gilbert's syndrome is benign, nonprogressive and not associated with chronic active liver disease or cirrhosis. The syndrome results from multiple etiologies, including compensated hemolytic disease, post-portalcaval shunt, thyrotoxicosis, high altitude and congestive heart failure, and may be initially recognized as a sequel to viral or drug-related hepatitis. Gilbert's syndrome is frequently discovered by serendipidity as, for example, following routine analysis of serum by autoanalyzers or in association with systemic diseases which bring the patient to medical attention. The latter circumstance is probably responsible for the frequent association of Gilbert's syndrome with cardiac disease, fatty liver, alcoholism, biliary tract disease, cirrhosis, malignant tumors, and bacterial or viral infections. Physicians often unwittingly contribute to patients' anxieties by incorrectly associating Gilbert's syndrome with chronic active liver disease.

Gilbert's syndrome also occurs as an inherited autosomal dominant characteristic, and patients appear to be heterozygous for a single mutant