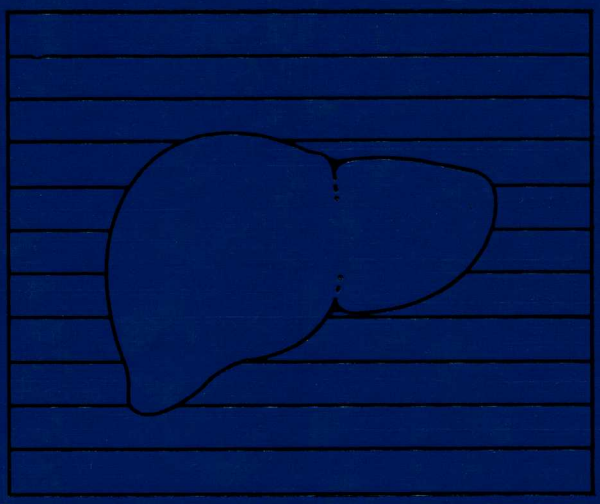
TEXTBOOK OF PEDIATRIC HEPATOLOGY

A. R. Colón



Second Edition

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You know, if Patricia Ann hadn't taken over most of the nuts and bolts of everyday living, I wouldn't have had the time to do the first edition, nevermind the second. For Pat, with love.

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PREFACE TO THE SECOND EDITION

New ideas as well as new understanding and refinement of past concepts have prompted a virtually complete rewriting of *Pediatric Hepatology*. This second edition includes new chapters on nutrition, hepatic imaging, and transplantation. The original chapter on hepatitis has been expanded to three—on viral, nonviral, and chronic hepatitis. A chapter on specific care protocols has been written with the many general gastroenterologists in mind who treat children and youth. There are seven new chapters in all, and all of the extant chapters have received extensive revision. The bibliography is current and comprehensive. The pathology mini-atlas of the first edition has been replaced by pertinent histopathologic figures interspersed throughout the text.

A pathophysiologic approach to liver disease invites a degree of overlap inasmuch as some diseases have variable mechanisms of action. Several entities therefore appear in more than one chapter. For example, total parenteral nutrition is examined with respect to both hyperbilirubinemia and cirrhosis. Similarly, ammonia metabolism is discussed in chapters that focus on steatosis and encephalopathy. The overlap is minimal, and should reinforce pathophysiologic concepts.

I have touched on tropical liver diseases in my desire to be all inclusive, and with hope that my comments will be of some use to those pediatricians and gastroenterologists who care for children globally, especially those friends and colleagues in Central and South America, Pacific Asia, and Africa.

The task of rewriting the text has reaffirmed the enjoyment and satisfaction I derive from work in my chosen field. My intentions and hope in writing and revising this book are to provide a service to my colleagues who have dedicated their professional lives to the care of sick children throughout the world. Given the opportunity, I will in the future continue this endeavor.

I would like to acknowledge the assistance of Gail Williams. I thank Pat Colón for her constructive suggestions and a patient reading of the text. As always, I acknowledge the children who have taught me compassion and a sense of humor.

A. R. Colón

PREFACE TO THE FIRST EDITION

This text is intended for students, pediatric residents, practicing pediatricians, and any busy physician wanting basic core information about childhood liver disease in a concise outline form. Full references are provided for more detail, or for those who learn better by traditional narrative form. But for those whose minds flow algorithmically, outlines, diagrams, tables, and algorithms form the core of the text. All microphotographs are gathered into an appendix as a mini-atlas of pathology. This atlas is intended to aid in the visualization and conceptualization of pathologic processes, not to identify specific diseases. In short, the text is designed to be practical and brief.

Acknowledgments are warmly given to: Gunnar Stickler, M.D., who put me onto pediatric gastroenterology; Douglas Sandberg, M.D., who, during my fellowship, encouraged me quietly but firmly; and Philip Calcagno, M.D., who put the original pediatric "bug" in my head. I am beholden to them and to my other good teachers, and to all of my students and residents who relentlessly probe, question, and teach. Many thanks.

Some of the histopathologic materials were kindly provided by Roma Chandra, M.D. The marvelous drawings are from the talented hands of Peter Stone. The typing, typing, and retyping was done ungrudgingly by Barbara Runner.

Finally, for all her pushing, intellectual prodding, and tireless scrutiny of this manuscript, I thank my friend, critic, and companion, P. A. Colón.

A. R. Colón, M.D.

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Chapter 1

Pediatric Hepatology—A Historic Overview

Prior to and throughout the 1st and early 2nd millenia, the medical literature made no reference whatsoever to diseases of the liver in children[1] (Table 1–1). Jaundice in the adult, to be sure, was noted even in ancient writings, and several terms were used to describe the condition, including *icterus, aurigo, morbus regius,* and *morbus arquatus.*[2] It was not, however, until the 15th century that even passing mention was made of this most obvious reflection of liver dysfunction in children. In 1473, Bartholomaeus Metlinger wrote in *Ein Regiment der Jungen Kinder* (Fig 1–1) that:

> Jaundice comes of coarse thick milk of the nursing woman through which the passages of the liver and bile become stopped up. The nursing woman should avoid pastry, fish, and cheese. . . .[3]

No clinical significance was attributed to the condition. Two centuries later, Michael Ettmuller (1644–1683) wrote about jaundice in the newborn in *De Infantum Morbis* and suggested that it be treated with saffron.[4] In 1742, John Burton published *A Full View of All the Disease Incident to Children.* His observations of benign, physiologic jaundice astutely noted the response to mobilized enterohepatic metabolism through the universal "physik"[5]:

> . . . at birth or soon after, Children are often observed to have the Jaundice . . . [which] generally yields to any gentle Purgative, and very often is carried away by any medicine that increases the Contraction of the Gut. . . .

The first reference to a congenital and malignant form of jaundice appeared in 1784 in Michael Underwood's *Treatise on Diseases of Children.* He described a mother of 11 children, ten of whom had died after jaundice appeared days to weeks after their births. Underwood conducted an autopsy on that last child and found "a livid liver with permeable ducts."[6]

The distinction between benign and malignant jaundice, however, was not made until William Dewees published his *Treatise on the Physical and Medical Treatment of Children* in 1825. Dewees thoroughly described physi-

TABLE 1–1.
Chronology of Adult Hepatology: To 1900

To the Early 19th Century	
Hippocrates (?460–377? BC)	Recognized infectious hepatitis, hydatid cysts; refined palpation
Erasistratos (300–250 BC)	Tapped ascites; coined term parenchyma
Galius Galen (130–200)	Distinguished hemolytic from obstructive jaundice
Leonardo DaVinci (1452–1519)	Described cirrhosis
Andreas Versalius (1514–1564)	Defined hepatic anatomy
Thomas Bartholin (1616–1680)	Ascribed the liver as the "body's master cook and engineer"
Francois Glisson (1597–1677)	Described liver capsule and blood supply
Marc. Malphighi (1628–1694)	Ascribed glandular bile production to the liver
Johann Wepfer (1620–1695)	Defined the lobule
Thomas Sydenham (1624–1689)	Conducted studies of epidemic hepatitis
John Browne (1642–1700?)	Gave first good description of cirrhosis
Fred. Ruysch (1638–1731)	Described hydatid liver
Alb. von Haller (1708–1777)	Described liver anatomy in detail
Giov. Morgagni (1682–1771)	Described hepatic necrosis and cirrhosis
William Heberden (1710–1801)	Emphasized alcoholic cirrhosis
Thomas Coe (1704–1761)	Wrote a text on gallstones
Gaspare Bayle (1774–1816)	Described fatty liver
Sam. Soemmerring (1755–1830)	Detailed study of gallstones
Francis Kiernan (1800–1874)	Described lobule microscopy
Michael Chevreul (1786–1889)	Studied bile composition
Rene Laennec (1781–1826)	Defined macroscopic cirrhosis
Thomas Williams (1819–1865)	Studied microscopy of acute necrosis
Carl Rokitansky (1804–1878)	Coined "acute yellow atrophy"
Richard Bright (1789–1858)	Discussed hepatic coma
George Budd (1808–1882)	Discussed liver coma and congestion
William Bowman (1816–1892)	Performed microscopy of fatty liver
To the Late 19th Century	
Hans Chiari (1851–1916)	Endarteritis and thrombosis of the liver
Luigi Lucatello (1863–1926)	Puncture biopsy of the liver
Claude Bernard (1813–1878)	Opened the door to biochemical study of the liver with *De la Presence du Sucre dans le Foie*
Theodor Frerichs (1819–1885)	Wrote *A Clinical Treatise on Diseases of the Liver* (1860)
von Libermeister (1833–1901)	Separated portal from biliary cirrhosis
Victor Hanot (1844–1896)	Refined the description of biliary cirrhosis
vonRecklinghausen (1833–1910)	Described liver hemochromatosis
Paul Ehrlichs (1854–1915)	Performed blind liver biopsy
Carl Langerbuch (1846–1901)	Performed the first cholecystectomy
Louis Courvoisier (1843–1918)	Popularized cholecystectomy
Friedel Pick (1867–1926)	Described pseudocirrhosis of pericarditis

TABLE 1–1 (cont.).
Chronology of Adult Hepatology: To 1900

Karl Wilhelm von Kupffer (1829–1902)	Described the stellate cells of the liver
Bernhard Riedel (1846–1916)	Described the lobe of the liver

ologic jaundice, and, while admitting ignorance of its cause, emphasized its benign nature:

> The skins of newly born children are frequently of a yellow colour; but this does not constitute the disease in question. The yellowness here spoken of is not of a deep tone though very generally diffused. This appearance may continue for several days, and then disappear without the aid of remedy, or without leaving any evil behind. It is difficult to say, to what this yellow tinge may be owing; certain it is, it cannot be attributed to the presence of bile, since, neither the urine, nor the whites of the eyes, assume the yellow hue.[7]

Understanding the significance of the color of stools in the jaundiced child, Dewees went further:

> So long as the stools are dark green, or yellow, we need not give ourselves any anxiety about it. But if on the contrary, the above marks are attended by deficiency of colour in the stools . . . jaundice, in its most formidable form, is present . . . the common duct obstructed as in the jaundice of adults.

Surely this was the first reference in the medical literature to what is now known as biliary atresia "with a shrunken, shriveled duct." He laments the inability to treat the condition:

> When a genuine jaundice attacks a newborn child, it is but too often fatal, with whatever propriety or energy we may attempt to relieve it.

The distinction between a benign and malignant form of jaundice in the child marked the beginnings of pediatric hepatology as a distinct field of study and treatment. It was not, however, until 50 years later—about 1880—that authorities on the subject of childhood liver disease emerged.

Writing in John Keating's *Cyclopedia of Diseases of Children*[8] (1890), H. Dwight Chapin elaborated on *grave icterus neonatorum*, or choledochal cyst and/or biliary atresia, as distinguished from *grave icterus familiorum*, or erythroblastosis fetalis. Chapin also gave a vivid description of biliary obstruction secondary to ascariasis.

J. H. Muser combed the existing literature and compiled all the then known causes of hepatomegaly in children. He wrote:

> The growth of population and the increase of special hospitals for children have made it more

FIG 1–1.
Frontispiece from Metlinger's *Ein Regiment der Jungen Kinder*, ed 4, appearing in 1497.

practicable for single observations to be made. The accumulated results of the more careful observations scattered through the literature of medicine form sufficient data for intelligent writing on any disease of the liver incident to—or, rather occurring in—childhood.[8]

In the same tome, Marcus Hatfield described the various causes of contractions (cirrhosis) of the liver and offered the supportive and expectant treatment modalities of the time.

Thereafter, a cascade of anatomic descriptions and clinical reports followed,[9, 10] culminating in the 20th century with the recognition and formalization of pediatric hepatology as a specialized field of endeavor.

I have elected to list chronologically the major contributions to pediatric hepatology (Table 1–2) in order to provide, at a glance, a capsulization of the rapid advancements and understanding in the last 100 years as compared with the antecedent millenia (Tables 1–1 and 1–3). The list is not carved in stone, and surely, with time, the import of current thought and research will amend the contents.

TABLE 1–2.
Chronology of Pediatric Hepatology

1892	Thompson	Published reports of 50 necropsies of biliary malformations
1894	Swaine	Corrected first biliary cyst
1900	Gilbert	First example of metabolic liver dysfunction
1913	Ylppo	Concept of immaturity of biliary metabolism
1927	Ladd	First surgical cure of biliary atresia
1935	Gross	Described inspissated bile
1949	McMahon, Taunhauser	Described intrahepatic biliary atresia
1952	Illingworth, Cori, Cori	Series of papers describing glycogen storage disease
1952	Crigler, Najjar	Metabolic familiar jaundice
1953	Cole, Lattle	Glucuronyl transferase immaturity
1954	Hsia	Micromethod for bilirubin
1954	Jelliffe	Veno-occlusive disease
1956	Isselbacher	Congenital galactosemia
1959	Kasai	Biliary atresia surgery
1963	Reye	Visceral steatosis and encephalopathy
1963	Starzl	Transplantation
1967	Scriver, Larochelle	Hereditary tyrosinemia
1968	Sharp	Alpha-1-antitrypsin liver disease
1971	Peden	Total parenteral nutrition cholestasis
1973	Alagille-Watson	Arteriohepatic dysplasia syndrome
1973	Goldfischer	Peroxisome/mitochondrial defect
1983	Balistreri, Huebi, Suchy	Physiologic cholestasis concept

TABLE 1–3.
Adult Hepatology in the 20th Century

1916	vandenBergh	Diazotized sulfanilic acid determination
1930	Rosenthal	Bromsulphalein dye excretion test
1933	Kalk	Conjoined laparoscopy and biopsy
1937	Eppinger	Wrote *Die Leberkrankheiten*
1938	Liverson, Roholm, Silverman	Developed needle biopsy techniques
1955	Karmen	Transaminase determination
1955	Sherlock	*Diseases of the Liver and Biliary System* (first edition)
1956	Schmid	Direct hyperbilirubinemia
1956	Schiff	*Diseases of the Liver* (first edition)
1958	Menghini	Further refined needle biopsy
1958	Popper, Schaffner	Extensive survey of liver literature
1965	Blumberg	Australia antigen

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