MASTER’S PERSPECTIVE

Growth and Development of a New Subspecialty: Pediatric Hepatology

William F. Balistreri

Several major forces converged to catalyze the formal emergence of a body of knowledge and an organized focus on disorders of the liver in early life. Attendant to the development of a focused clinical subspecialty the pace of patient- and laboratory-based research in the field quickened in parallel to decipher the consequences of genetic or metabolic aberrations on immature liver structure and function. The key research observations that catalyzed the emergence and subsequent rapid growth of Pediatric Hepatology include: (1) an understanding of the dynamic events occurring during hepatobiliary development and the importance of these physiologic variables that occur during liver maturation; (2) the recognition of the unique nature of inherited and acquired liver diseases that affect infants and children—such as biliary atresia and Reye’s syndrome; and (3) redefinition of the once obscure inherited intrahepatic cholestatic diseases of the liver, which, in turn, provided insight into normal and abnormal hepatobiliary physiology. The clinical advances were highlighted by the development of specific approaches to the diagnosis and management of liver disease in infants and children, including both liver transplantation and nontransplant treatment options. These seminal events led to the expansion of the workforce, creating a critical mass consisting of individuals with focused, specialized skills and techniques. In-depth expertise allowed more accurate diagnosis and highly effective treatment strategies for advanced hepatobiliary disease in children. The demand for pediatric clinicians with experience in advanced hepatology allowed sub-sub-specialization to flourish. Continued maturation of the field led to definition of hepatology-focused curricular elements and educational content for Pediatric Gastroenterology training programs, and subsequently the development of program requirements for those who wished to acquire additional training in Pediatric Hepatology. A significant rite of passage was marked by the election of pediatric hepatologists to leadership positions in the American Association for the Study of Liver Diseases (AASLD). Further validation of the field occurred with approval of the petition for establishing a Certificate of Added Qualification in Transplant Hepatology by the American Board of Pediatrics. Here I relate my perspective on the history of the advances in our field and the contributions of many of the clinicians and scientists whose efforts led to the development of focused clinical, research, and training programs that improved the care of children with diseases of the liver. (HEPATOLOGY 2013;58:458-476)

The Challenge

Since there was not a single linear pathway it appeared at first to be a daunting task to reconstruct the history and sequence of events leading to the emergence and maturation of a field of subspecialization. Therefore, it was a bit overwhelming to be asked by the editors of Hepatology to “look back on my career” and not only “tell us about your life story” but also “illustrate specifically the development of Pediatric Hepatology.” However, I was deeply honored by the invitation and took the occasion to attempt to write not only a self-reflection but an impression of how careers in our...
specialty have evolved. Therefore, it is with great pleasure that I humbly represent my fellow “early adapters” of the subdiscipline of Pediatric Hepatology.

_Trees seem to be random, their arrival in fields and the top of hills unexplainable, their growth mysterious…. The growth of trees is not repetitive but additive, each year recorded in their flesh._

—Dust to Dust, Benjamin Busch

There was no “Grand Plan” for the study of liver disease in children to evolve as a focused clinical and research discipline. The tree analogy seems appropriate: the “arrival” of Pediatric Hepatology was additive—elements of the field have always been there but unnoticed until individuals ventured deeper into the forest. _De facto_, this branch sprung from the trunk of Pediatric Gastroenterology.

Often the clearest vision is through the “retrospectoscope”—indeed, upon looking back the critical elements that stimulated the growth of this field can be identified. With this sharper image in mind, I would like to offer my perspective on a series of fortunate events that allowed all of us interested in the care of infants, children, and adolescents with liver disease to have a “home” of our own and to find our individual and collective identity. Let me start by providing, as the Editors requested, my “life story.”

**Personal Growth and Development**

The clearest indication of the absence of a grand plan for my personal career development is the fact that I entered college as a journalism major. I was born and raised in Geneva, New York, and during high school my prime preoccupation was participating in interscholastic sports. I envisioned a career as a sports writer and thus, proudly, became the first in my family to attend college. After one exciting year of traveling with our university’s athletic teams, documenting their successes and failures, I realized that my passion was not to passively observe others addressing challenges, but to be actively involved in solving problems (a player, not an observer). I transferred schools, to a more challenging academic environment and changed my major to biology/biochemistry. This heavy science background combined with a dramatic exposure to the field of medicine led to the “rest of the story.” During my junior undergraduate year I developed mononucleosis and was confined to the university infirmary for what was, even then, an extreme period, almost 2 months. I felt well—but every time I asked my healthcare providers about their treatment strategy, my prognosis, or the rationale for my “continued observation,” my questions went largely unanswered. There was no subterfuge—they truly did not have evidence on which to base their decision. It is possible that their concern was related to the possibility that, if discharged, I might “spread the disease” around campus—after all, mono was considered to be the “kissing disease!” My frustration blended with extreme respect, fascination, and ultimately enlightenment. During one of those long nights in the infirmary, I reflected on the encounters of the day, and the gaps in basic understanding of a seemingly common disease process and its treatment. Thus, after my release I met with my guidance counselor and expressed my interest in applying to medical school. I was told, ironically, that it was unlikely that my application would be successful given the “set back” of the prolonged confinement! That “low chance of success” conversation has remained a clear stimulus to me over the years!

Two important life-changing events occurred during medical school. Of greatest importance, I met a nursing student, Becky McLeod, who became my wife and my major influence and support (Fig. 1). She has created and maintained stability in my life—allowing me to focus on the work at hand reassured by the fact that Becky has everything else in our lives “under control.” The second event was a summer spent working in the Pediatric Unit at Roswell Park Cancer Institute. This, at times, trying experience left me with a strong impression of the resiliency of a child in the presence of a serious illness. To see a child grow and thrive after surviving a devastating illness led to my decision to become a pediatrician.

**A Simple Decision Algorithm: “Do What Is Best for the Child”**

While an intern at Cincinnati Children’s Hospital (CCHMC) I admitted a patient with a puzzling
clinical picture of anicteric liver failure with hypoglycemia, suggesting underlying metabolic liver disease. My goal was to solve the problem. The attending, Dr. William K. Schubert (Fig. 2), Chief of Staff and Director of the Clinical Research Center, gave me free rein. Each morning he would look over my shoulder at my notes as I bumbled through a textbook-driven workup and reward me with an affirmative pat on the back. This experience stimulated my interest in metabolic pathways in the liver and experiments of nature that occur when pathways go awry. Therefore, at the end of my internship I conceived a career plan of study to focus on metabolic liver disease. I approached Dr. Schubert and asked if I could do a fellowship in Pediatric Gastroenterology. His response—“What’s that?” Nevertheless, he fully supported the concept and together we were able to take advantage of unique clinical and research opportunities that we encountered on this uncharted path (as detailed below). I relate that story to emphasize that there was no established discipline of Pediatric Gastroenterology and no obvious pathway to a focus on liver disease. This despite the fact that gastroenterology is arguably the oldest pediatric subspecialty. Historically, the traditional foundations of pediatric care were “GI-focused”—to ensure childhood health—as manifest by well-paced growth and adequate nutrition, and to prevent the major causes of infant mortality: infectious diarrhea and malnutrition.1 Pediatric Gastroenterology began to be “formally” recognized as a discipline separate from adult gastroenterology in the 1960s, when early practitioners, having been trained in Internal Medicine divisions of gastroenterology, were able to successfully adapt and extrapolate their skills, expertise, and techniques to the care of children with gastrointestinal (GI) diseases. In turn, internist gastroenterologists recognized the unique nature and complexity of conditions that specifically affected infants (“children are not little adults”) and were willing to defer to their pediatrician colleagues.

The Rise (and Fall) of Reye’s

During my “GI Fellowship” at CCHMC a major focus of our clinical attention was Reye’s syndrome—acute encephalopathy and fatty degeneration of the viscera.2-7 In the early 1970s there was a marked increase in the incidence of this enigmatic disease and the ability to recognize all stages of the illness. The challenges were enormous, since the disease represented an acute, and potentially devastating, interaction between the liver and the brain. The pathogenesis was poorly understood; the clinical, histologic, and biochemical picture suggested a generalized loss of mitochondrial function caused by an endogenously produced substrate or by an exogenous agent.8,9 The urinary metabolic profile was indicative of a pronounced catabolic state with excessive lipolysis, inefficient mitochondrial...
beta-oxidation of fatty acids, and increased excretion of carnitine. This resembled the biochemical picture seen in patients with known defects in hepatic fatty acid oxidation, such as the acyl-CoA dehydrogenase deficiencies. Studies done at CCHMC uncovered a link between Reye’s syndrome and aspirin administration, resulting in significant media attention. This led to warning labels on aspirin preparations and a dramatic decline in the incidence of Reye’s syndrome beginning in the late 1980s. Thus, a dramatic life-threatening disorder was virtually eliminated. In addition, insight into genetic defects in the synthesis of mitochondrial proteins and enzymes affecting multiple organ systems, including the brain and skeletal/cardiac muscle, had been elucidated. Therefore, this disease served as a model for mitochondrial disorders, as subsequently seen in fialuridine-induced mitochondrial inhibition. This “public health triumph,” likely the first major development in the field of Pediatric Hepatology, stimulated the unification of individuals interested in the care and investigation of children with liver diseases.

Why Bile Acids?

One of the early research challenges presented to me by Bill Schubert was to solve the problem of Donald—an infant with persistent, intractable diarrhea beginning on the second day of life, which caused failure to thrive. At 4 months of age he weighed 3.5 kg, well below his birth weight of 4.4 kg. Attempts at refeeding with a variety of elemental diets resulted in watery diarrhea, dehydration, acidosis, and shock; thus, he was total parenteral nutrition-dependent. Daily stool weight averaged >500 gm/day (normal <100) and fecal fat excretion was >50% of the daily intake. His serum cholesterol concentration was markedly depressed (<70 mg/dL). After several months of evaluation and fruitless investigations I came across an article by Alan Hofmann that described the clinical consequences of resection of the ileum, the main site of bile acid reabsorption. Donald manifested some of these clinical features; thus, my naïve thought was that he may well be malabsorbing bile acids. Indeed, a short-term trial of cholestyramine resulted in an initial improvement of his diarrhea, followed by a gradual exacerbation of his steatorrhea. This biphasic response supported the hypothesis that bile acid malabsorption might well be the cause of his prolonged diarrhea. We designed a study to prove that theory. Evaluation of bile acid kinetics in this patient with severe refractory diarrhea confirmed our hypothesis that bile acid transport in the terminal ileum was altered. Fecal excretion of labeled bile acid (14C-24-cholic acid) was increased, with the ratio of excretion of bile acid comparable to that of a nonabsorbable marker, consistent with primary bile acid malabsorption. The magnitude of loss of cholic acid was similar to that observed in infants who had undergone ileal resection. We found that the marked loss of bile acid in stool led to severely reduced levels of bile acid in bile, with low intraluminal bile acid concentrations, as well as the presence of a contracted bile acid pool size. We were able to specifically confirm the defect in ileal bile acid transport in subsequent studies with Jim Heubi, John Partin, and Joe Fondacaro. The mechanism of Donald’s diarrhea was thus explainable—bile acid malabsorption, as seen following ileal resection, led to elevated bile acid concentrations in the colonic lumen, inducing secretion of sodium and water. The effect of cholestyramine was paradoxical—initially binding bile acid and preventing diarrhea but ultimately severely depleting small intestinal intraluminal concentrations of micelle-forming bile acids causing fat maldigestion/malabsorption. Congenital defects in ileal bile acid transport are now a recognized cause of intractable diarrhea.

An Established Mentor

Throughout my investigation of Donald I had been in telephone contact with Alan Hofmann (Fig. 3),
who had developed a strong research program at the Mayo Clinic in Rochester, Minnesota, which focused on the chemistry and biology of bile acids in health and disease. In the spring of 1973 we began a series of discussions regarding the study of bile acid metabolism in children and reached a point where it became clear that we needed better methods to pursue this line of investigation. By that point in time two groups, John Watkins working with Roger Lester in Boston, and Harvey Sharp working with Jim Carey in Minneapolis, had begun to investigate bile acid metabolism in early life. Watkins had demonstrated “immaturity” of mechanisms that control bile acid metabolism leading to a “contracted” bile acid pool size. He reasoned that this was the factor responsible for insufficient fat absorption characteristic of normal newborn physiology.

Alan Hoffman invited me to work in his laboratory in Rochester. We agreed that a period of study at the Mayo Clinic would allow me to develop techniques to further investigate bile acid metabolism in children, including the use of nonradioactive-labeled bile acids in place of radioactive isotopes for measurement of bile acid kinetics. Thus, while learning the standard techniques of bile acid analysis, gas chromatography (GC) and thin layer chromatography (TLC), we validated the use of a stable isotope-labeled compound for the determination of bile acid kinetics by isotope dilution. By administering deuterated, as well as $^{14}$C-labeled bile acids we were able to show that estimates of the pool size and synthesis rate by both isotopes showed good correlation and similar precision. The availability of bile acids labeled with stable isotopes, $^2$H or $^{13}$C, allowed us to study bile acid metabolism by isotope dilution measurements in children without radiation hazard.

**The Berry Plan and the “Philadelphia Story”**

Next in the series of fortuitous circumstances was the fact that I was able to delay entry into the military. Since this was during the midst of the conflict in Vietnam, and male physicians in training were subject to the draft, I was at risk for premature termination of my training. However, I was deferred, thanks to the Armed Forces Physicians’ Appointment and Residency Consideration Program (Berry Plan). Not only was I able to continue my training with Alan Hoffman, but with his connections and influence I was able to carry out my 2-year military obligation at the Philadelphia Navy Hospital, which had an outstanding gastroenterology research unit lead by Don Castell. This, in turn, allowed me to make strong connections with the University of Pennsylvania Liver Research Unit (Bruce Trotman, Roger Soloway, and Don Ostrow) and subsequently accepted a faculty position at Children’s Hospital of Philadelphia (CHOP) and the University of Pennsylvania. In collaboration with the Liver Research Unit we were able to establish methodology for techniques of liver perfusion and liver cell isolation and carry out clinical studies to assess the role of serum bile acid measurements in assessing liver disease. With this background we began to focus on neonatal cholestasis—since that was the greatest clinical challenge at that time.

**The Problem and the Challenge of Neonatal Cholestasis**

Clinicians had long been frustrated by the inability to effectively manage hepatobiliary disease in children. Contemporary therapeutic modalities were aimed primarily at management of the consequences of cholestasis—specifically, persistent and progressive disability, dominated by inadequate weight gain and intractable pruritus. Therapies directed at halting the progression to endstage liver disease were not available and liver transplantation was not an option in the 1970s.

The largest number of patients we saw at CHOP consisted of infants in whom a prompt differentiation of the cause of cholestasis was required. Specifically,
the task was to sort out those with “Neonatal Hepatitis” from infants with biliary atresia. The latter is an idiopathic, localized, complete obliteration or discontinuity of the hepatic or common bile ducts at any point from the porta hepatis to the duodenum. The rapidly progressive fibro-obliterative process represented a paradigm for other forms of hepatobiliary injury, perhaps reflecting a complex inter-relationship between genetic predisposition and environmental exposure.27-31 One of the earliest advances in Pediatric Hepatology was a refinement of the hepatoportoenterostomy operation (biliary-enteric anastomosis), which was devised in the late 1960s by Morio Kasai.32-34 Nevertheless, those of us who were caring for children with biliary atresia became increasingly disheartened, for although the Kasai hepatic portoenterostomy procedure was a reasonable initial approach, a significant proportion of children developed progressive biliary cirrhosis.29,31,35,36 For example, within a 2-year period 11 of my patients with biliary atresia died of endstage liver disease.

Equally frustrating was the group of infants with what was termed “idiopathic neonatal hepatitis,” since the exact nature of most cases remained enigmatic. This diagnosis, by default, accounted for >65% of the neonates presenting with cholestasis. Our initial efforts, therefore, were focused on cholestasis of infancy in hopes of simplifying the nosology, and expanding the diagnostic possibilities beyond biliary atresia and neonatal hepatitis. Our goal was to demystify and delineate the exact cause of their cholestasis. Specifically, patients labeled as having “Familial Neonatal Hepatitis” were viewed as candidates for undiscovered inborn errors in a fundamental physiologic process involved in generating bile flow. Specifically, the pattern of interfamilial recurrence suggested a genetic defect in bile acid transport, biosynthesis, or detoxification.27,28,31 It was reasoned that elucidation of the nature of the defect would allow a better understanding of liver physiology and lead to effective therapy.

**A Simple Theory.** A testable hypothesis was that exaggeration or persistence of the developmental deficits in hepatic bile acid synthesis or metabolism accounted for a subset of “idiopathic neonatal hepatitis.” 28,31,37 This seemed to be a reasonable concept. Bile acids are steroid compounds synthesized by the liver from cholesterol through a complex series of reactions involving multiple specific enzymatic steps. Thus, deficiency in activity of any of the constitutive enzymes would theoretically result in diminished production of the “normal” primary bile acids that are essential for promoting bile flow. Contributing to the cholestasis would be the concomitant overproduction and accumulation of hepatotoxic atypical bile acids synthesized as intermediates in the pathway proximal to the inactive enzyme. The analogy that came to mind was that of the syndromes of congenital adrenal hyperplasia (CAH), which result from a defect in enzymes involved in the synthesis of another class of cholesterol derivatives—the steroid hormones. The clinical manifestations in patients with CAH are due to the absence of a critical metabolite and accumulation of compounds that exert adverse effects. Recognition allows replacement therapy. By analogy, the spectrum of presentation of inborn errors of bile acid biosynthesis should reflect metabolite accumulation and endproduct deficiency, with the potential for causing liver injury.27 The problem was how to accurately detect affected patients. We made crude attempts to analyze the bile acid composition of infants with cholestasis using GC and TLC—however, it became clear that a more sophisticated analysis would be required.

**A Prototype**

In parallel to our research efforts, we began to develop a clinical program. My early role model was Alex Mowat (Fig. 4), who had established a prototype for Pediatric Liver Care Units at King’s College Hospital (KCH) in London. Alex had developed an interest in bilirubin metabolism in newborns and infants. He served as a postdoctoral fellow at the Albert Einstein College of Medicine under the guidance of Win Arias. The Einstein model was influential,
as Alex returned to KCH in 1970 with an appointment as “Consultant Pediatrician and Pediatric Hepatologist.” At the time of his appointment there had been no sustained academic interest in liver disorders in children in the United Kingdom. Under Alex’s influence, hard work, dedication, and organizational ability the KCH became a first-class clinical service for children with liver disease combined with a productive research unit. His vision also led to the recruitment of parents of children on the Liver Service to develop what has become the Children’s Liver Disease Foundation. Alex Mowat developed a close partnership with Professor Ted Howard, a pediatric surgeon, thereby integrating medical and surgical care of children with liver disease into this unique unit. Giorgina Mieli-Vergani joined as the unit grew to become a supraregional center in the UK for the treatment of hepatobiliary disease in children. Alex Mowat’s experience at KCH was compiled into his textbook Liver Disorders in Childhood, first published in 1979, which carefully cataloged and characterized the myriad patients cared for by his “team” at KCH from 1970 to 1976.38 In his preface, Alex stated that his aim was to “summarize recent developments and indicate some of the outstanding clinical problems in areas in which research is urgently needed.” His plea motivated me and others to take up the challenge, stimulating focused investigation in this discipline. This may have been the first time that we had the distinct sense that a new area of subspecialization was developing. Mowat’s vision therefore predated the flurry of activity in Pediatric Hepatology attendant to the development of centers of excellence in Pediatric Hepatology around the world.

The Inflection (and Reflection) Point on the Growth Curve

A major seminal event in the maturation of the discipline, and in my personal development, was a meeting held in 1977 that focused on the codification and delimitation of the field of interest of Pediatric Hepatology. An international workshop, sponsored by the National Institutes of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), was convened by Norm Javitt.39 This conference gathered together individuals such as Morio Kasai, Alex Mowat, Daniel Alagille, Birgitta Strandvik, and Andrew Sass-Kortsak, among others. As stated by G. Donald Whedon (NIAMDD) “…one of the goals of this conference is to develop a uniform nomenclature with specific criteria for diagnosis. With the convergence of expertise from virologists, microbiologists, epidemiologists, embryologists, immunologists, neonatologists, hepatologists, pediatric gastroenterologists, pathologists, and surgeons, we are going to either make great strides forward or build a new tower of Babel … as a spinoff of this conference, there may be a continuing effort to plan cooperative clinical trials or to set up a registry of cases and a repository of sera or tissues. In this way, perhaps the limited number of cases seen in any one medical center or in any one country when combined with several others can contribute to a meaningful data base.” This conference clearly was a step forward towards clarifying the nosology of pediatric hepatobiliary diseases and determining directions in research.

“An Offer I Couldn’t Refuse”

In 1978 I received an offer from Bill Schubert to return to Cincinnati. We were clearly ready to investigate the immature liver and its diseases, specifically neonatal cholestasis. Schubert offered an environment to carry out these studies and the resources, including a dedicated mass spectrometer facility. CCHMC had established programs for specialized care of complex patients such as neonates and patients with cardiac disease. In addition, CCHMC had a long history of successful experience as a center for renal and bone marrow transplantation. In light of the growing number of children with chronic liver disease in the primary and secondary service areas of CCHMC and the national reputation of the institution in patient care and research, our plan was to establish a formalized Pediatric Liver Care Center (PLCC). The goal of the PLCC was to focus on the evaluation and comprehensive care of patients with liver disease, including medical, surgical, social service, and institutional support, including transplantation where required. This would be combined with basic and clinical research into the physiologic, biochemical, and immunologic aspects of disease. We hoped to create a network/support group of parents of children with liver disease and we envisioned a training program for clinical and research fellows. The concept of the center, the first of its kind in the United States, was unique because it integrated novel and existing aspects of liver patient care and treatment with intensive ongoing research and education regarding pediatric liver disease.

Assembling the Tools

A significant force driving the nascent field of Pediatric Hepatology was the utilization of clinical and research procedures and techniques to investigate the
child with presumed liver disease. An important step was the development of a safe and reliable method to “sample” tissue for examination and analysis; this greatly aided the deciphering of the many potential causes of neonatal liver injury. The percutaneous liver biopsy technique had been developed by Bill Schubert, who with Dick Hong showed the technique to be safe in infants and children. They clearly demonstrated that a diagnosis could be established by assessment of tissue biopsy specimens by light and electron microscopy. In addition, liver tissue samples of adequate size could be obtained to allow biochemical dissection and enzyme analysis, which led to investigation into aspects of disordered hepatic physiology and to a better understanding of metabolic liver disease. “Unique” pediatric liver diseases were therefore uncovered, such as alpha-1-antitrypsin deficiency as a cause of “familial neonatal hepatitis.” This was first reported by Harvey Sharp, who used histologic techniques to document that the low serum levels of alpha-1-AT resulted from its reten-

Immaturity of Hepatic Metabolic and Excretory Function: “Physiologic Cholestasis”

It became clear that if we were to study diseases such as neonatal cholestasis we needed to understand the normal physiologic events occurring at this stage of liver development. A series of adaptations must occur during transition of the infant to extrauterine life; specifically, the liver of a newborn must conform to the unique metabolic demands that result from discontinuation of the bidirectional exchange of nutrients through the placenta and the biotransformation mechanisms shared with the mother. These maturational changes as the transition is made from an intrauterine existence to independent life occur predominantly through enzyme induction triggered by substrate and hormonal input. The efficiency with which these anatomic and physiologic adaptations are established determines the ability of the newborn to cope with a new environment. Historically, there are dramatic examples of inefficiency of hepatic metabolic and excretory function in early life, most notably “physiologic jaundice” (unconjugated hyperbilirubinemia characteristic of the newborn). We therefore were not surprised to discover an analogous phase, which we termed “physiologic cholestasis.” We documented that in newborns there is a cholestatic phase of liver development, manifest by delayed hepatic clearance of endogenous and exogenous compounds. The morphological and functional differences that characterize the neonatal versus the mature liver are responsible not only for a decrease in bile flow but also the production of abnormal bile acids. This renders the developing liver uniquely vulnerable to exogenous insults such as E. coli sepsis with endotoxemia, the intravenous administration of amino acids during total parenteral nutritional support, and hypoxia/hypoperfusion.

Good fortune once again intervened—my first fellow in Pediatric Gastroenterology at CCHMC was Fred Suchy, who enthusiastically joined me for studies further delineating normal and abnormal hepatobiliary function in neonates. We were able to document that multiple steps in the enterohepatic circulation were reduced in early life, evidenced by elevated serum bile acid levels, reduced intraluminal bile acid concentrations, and reduced hepatocellular transport (uptake and excretion) of bile acids. Another striking feature of “physiologic cholestasis” was the presence of a large proportion of “atypical” bile acids (yet typical for the developmental phase) that are not found in adult human bile. Of note, the bile acid composition of biological fluids in early life resembled that of adults with severe cholestasis, suggesting that in the presence of liver disease/cholestasis there is a reversion to “primitive pathways.” A subsequent series of studies further documented the inefficiency of hepatic excretory mechanisms, which correlated with a decrease in hepatic bile acid excretion and decreased bile flow. Fred Suchy, who very soon became an accomplished independent investigator, then documented delayed expression of bile acid transport proteins in the immature liver. Next, Ron Sokol joined us as a fellow in 1980 and became interested in studying complications of cholestasis. He focused on vitamin E deficiency and developed a protocol for detection and correction of this and other fat soluble vitamin deficiencies in children with chronic cholestasis. Sokol later became a major leader for multi-center collaborative studies that have greatly advanced our understanding of pediatric hepatobiliary disease.
thereafter, Jorge Bezerra joined us as a fellow and rapidly established a highly productive research program devoted to studies of the pathogenesis of biliary atresia. The training program continued to flourish, with the recruitment of a large number of trainees focusing on Pediatric Hepatology—including Hassan A-Kader, Nada Yazigi, Looi Ee, Jeff Schwimmer, Vicky Ng, Mike Leonis, Kathy Campbell, Alex Miethke, Bernadette Vitola, Kyle Jensen, Samar Ibrahim, and Frank DiPaola—who have gone on to successful careers in our field.

A MASS-ive Recruitment

In the UK, Ken Setchell was applying mass spectrometry (MS) methods to correlate clinical disease with biochemical profiles, specifically related to steroid hormones. As a scientist in the Division of Clinical Chemistry at the Medical Research Council Clinical Research Centre he began to focus on cholesterol and bile acid metabolism. 

At a Bile Acid Symposium in 1983 in Cortina, during an informal discussion, I asked Ken for recommendations as to whom we could recruit to develop our nascent MS facility in Cincinnati to focus on bile acid metabolism. The number one name on the list was his! Thus, Ken Setchell joined us a member of the faculty of the Department of Pediatrics in 1984 to become Director of our Clinical Mass Spectrometry facility at CCHMC. He rapidly established the techniques of fast atom bombardment-mass spectrometry (FAB-MS) and gas chromatography-mass spectrometry (GC-MS) to delineate disorders of bile acid synthesis. This facility was ultimately to become an international center for the diagnosis and treatment of liver disease caused by genetic defects in cholesterol and bile acid synthesis.

Inborn Errors of Bile Acid Biosynthesis

Mass spectrometric techniques, “biochemical fingerprinting,” provide the most accurate means of characterizing defects in bile acid synthesis. The presumed defect can be pursued using the screening modality of FAB-MS analysis of a urine sample. If an abnormal pattern is detected, the FAB-MS analysis can be complemented by detailed GC-MS analysis to confirm the presumed inborn error. These steps are necessary since signature metabolites will not be detected by routine methods for bile acid measurement. With Setchell’s methodology established, we were ready to screen infants with cholestasis.

**Δ^4-3-Oxosteroid 5β-Reductase Deficiency: An Experiment With an “n” of One (Actually Two).** In 1988 male twins who presented with cholestasis and coagulopathy in the first days of life were referred to us for further evaluation. A similarly affected sibling had died at 4 months of age 3 years previously with what was called “idiopathic neonatal hepatitis / giant cell hepatitis.” Our initial evaluation of the twins strongly suggested a defect in bile acid biosynthesis. Setchell’s lab was able to document that their rate of primary bile acid synthesis was reduced, that cholic acid was absent from blood, and that gallbladder bile contained only trace amounts of bile acids. Urine served as the main route of excretion, with the excreted compounds in the form of Δ^4-3-oxo bile acids. This biochemical picture suggested a defect in bile acid synthesis—specifically, a lack of conversion of Δ^4-3-oxo intermediates to 3α-hydroxy-5β products, a reaction catalyzed by cytosolic Δ^4-3-oxosteroid 5β-reductase (Fig. 5). The presumed pathophysiology of the hepatocellular and bile ductular injury was directly attributed to inadequate synthesis of primary bile acids (cholic) needed to generate bile acid-dependent bile flow, and accumulation of hepatotoxic Δ^4-3-oxo bile acids. These precursors were shown to act as cholestatic agents by inhibiting canalicular adenine triphosphate (ATP)-dependent bile acid transport, the rate-limiting step in the overall process of bile acid transport across the hepatocyte.

Of interest, electron microscopy of the twins liver biopsies revealed abnormal collapsed bile canaliculi, suggesting that maturation of the canalicular membrane and transport system for bile acid excretion requires a threshold concentration of primary bile acids in early development. This was consistent with studies of fetal rat liver, in which poorly formed bile canaliculi can be demonstrated by histology and immunocytochemistry. Bile canalicular morphologic maturation in the immediate postnatal period correlates with transition and acceleration of bile acid synthesis. This demonstrates the relationship between the pattern and pace of bile acid synthesis in fetal and neonatal rat liver and bile canalicular development.

In the analogy to CAH syndromes, we chose to use cholic acid (3α,7α,12α-trihydroxy-5β-cholanoic acid) as replacement therapy to treat these twins with Δ^4-3-oxosteroid 5β-reductase deficiency. The rationale was that cholic acid would restore physiological feedback inhibition of bile acid synthesis at the level of the rate-limiting enzyme, cholesterol 7α-hydroxylase (the role of farnesoid X receptor [FXR] and small heterodimer partner [SHP]-dependent mechanisms were not known at that time). The goal was to prevent further accumulation of potentially hepatotoxic Δ^4-3-oxo bile acids. Cholic acid was administered orally in an empiric dose (10-15 mg/kg/day) and titrated...
against the desired biochemical response of a reduction or disappearance of atypical metabolites in urine measured by FAB-MS. Indeed, cholic acid therapy was found to down-regulate endogenous bile acid synthesis by way of feedback inhibition of cholesterol 7α-hydroxylase and Δ4-3-oxo bile acids disappeared. The twins recovered, thrived, and grew and developed normally.

**Translational Medicine: Bed to Bench to Bed.** At present there are nine known primary defects in bile acid biosynthesis; each is specifically reflected by precursor accumulation and excretion of unusual metabolites. For most of the defects molecular confirmation has been accomplished by gene sequencing. In affected patients oral bile acid replacement therapy is lifesaving and is effective in reversing liver injury, as in the initial twins. Inborn errors in bile acid synthesis account for at least 2% of the cases of liver disease in infants, children, and adolescents, making this an important and specific category of metabolic liver disease. 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency (3β-HSD), the most common inborn error of bile acid biosynthesis, is usually manifest in early childhood; however, it has recently been described in adults. Molho-Pessach et al. reported a 24-year-old woman with cirrhosis of unknown etiology whose sister and cousin died of cirrhosis at ages 19 and 6 years. The diagnosis of 3β-HSD deficiency was confirmed and the affected family members were found to be homozygous for a mutant allele inherited identical-by-descent. These cases illustrate the wide variation in
expressivity of 3β-HSD deficiency and underscore the need to consider a bile acid synthetic defect as a possible cause of liver disease in patients of all ages.

**Progressive Familial Intrahepatic Cholestasis (PFIC)**

A unifying stimulus leading to the development of the field of Pediatric Hepatology was the shared goal of defining the nature of the syndromes of intrahepatic cholestasis, a heterogeneous subset of neonatal cholestatic diseases, each representing a series of specific syndromes with different prognostic implications.

*The beginning of wisdom is to call things by the right names.*

—Chinese Proverb

In the past 20 years the discovery of defects and genes involved in hereditary forms of intrahepatic cholestasis has advanced our understanding of molecular mechanisms of bile secretion and further clarified the nature of many forms of “idiopathic neonatal hepatitis.” The understanding of the importance of defective bile acid synthesis and transport in the pathophysiology of intrahepatic cholestasis allowed further deciphering of the spectrum of disorders traditionally known as “PFIC.” The clinical and pathologic features, as well as the natural progression of this family of disorders, were highly variable. Therefore, the term was *de facto* imprecise. In an individual patient, especially a firstborn, it was unclear whether the liver disease was indeed progressive or familial.

A series of studies that directly addressed the molecular mechanisms that control liver development and hepatic excretory function served as the biologic basis for enhanced understanding of the molecular basis of hepatobiliary dysfunction manifest as intrahepatic cholestasis. The heterogeneity reflected inherited defects in mechanisms involved in the generation of bile flow, specifically canalicular transport proteins resulting in substrate retention manifest as cholestasis. Patients with the most common types of PFIC were shown to harbor mutations in genes encoding proteins involved in bile acid transport: (1) *ATP8B1* gene, encoding FIC1 (patients with PFIC Type 1); (2) *ABCB11* gene, encoding the bile salt export pump (BSEP, patients with PFIC Type 2); and (3) *ABCB4* gene, encoding the multidrug resistance protein-3 (MDR3, patients with PFIC Type 3). In addition, the complex phenotype, molecular genetics, and inheritance pattern of Alagille syndrome were defined, with linkage to mutations in human Jagged1 (*JAG1*), which encodes a ligand for the Notch receptor. The Notch gene family encodes evolutionarily conserved transmembrane receptors involved in cell fate specification during embryonic development. This locus controls the ability of cells that are nonterminally differentiated to respond to differentiation and proliferation signals. In Alagille syndrome, mutations in *JAG1* disrupt the gene product, altering cell-to-cell signaling during development. These investigations allowed classification of these disorders into distinct subsets (Table 1).

To translate this knowledge into practical applications in the clinic, Jorge Bezerra and co-workers developed the “Jaundice Chip,” which uses a “resequencing” platform that enables the detection of mutations of these genes. Studies also addressed the importance of heterozygosity for these genes in creating genetic susceptibility to injury initiated by other agents such as drugs, toxins, or viruses. In addition, detailed understanding of the underlying pathophysiology of altered bile acid transport allowed for the development of specific targeted therapy. Based on initial studies, ursodeoxycholic acid became popular as a therapeutic agent in patients with intrahepatic cholestasis; this is now an accepted form of therapy worldwide.

**Other Significant Advances**

The body of knowledge related to hepatobiliary disease in children expanded in other needed areas. Enigmatic disorders presenting as acute liver failure, chronic hepatitis, or hepatocellular carcinoma yielded

<table>
<thead>
<tr>
<th>Table 1. Proposed Subtypes of Intrahepatic Cholestasis²⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Disorders of bile acid synthesis:</td>
</tr>
<tr>
<td>1. 3β-hydroxy-C27-steroid dehydrogenase deficiency</td>
</tr>
<tr>
<td>2. Δ⁴—3-oxosteroid 5β-reductase deficiency</td>
</tr>
<tr>
<td>3. Oxysterol 7α-hydroxylase deficiency</td>
</tr>
<tr>
<td>4. 27-hydroxylase deficiency</td>
</tr>
<tr>
<td>5. 2-methylacyl CoA racemase deficiency</td>
</tr>
<tr>
<td>6. Peroxisomal defects (single-enzyme defects)</td>
</tr>
<tr>
<td>7. Amidation defects</td>
</tr>
<tr>
<td>II. Disorders of membrane transport:</td>
</tr>
<tr>
<td>1. PFIC, BRIC Type I = FIC1 deficiency (PFIC1) ATP8B1</td>
</tr>
<tr>
<td>2. PFIC, BRIC Type II = BSEP deficiency (PFIC2) ABCB11</td>
</tr>
<tr>
<td>3. PFIC, BRIC Type III = MDR3 deficiency (PFIC3) ABCB4</td>
</tr>
<tr>
<td>III. Disorders of embryogenesis</td>
</tr>
<tr>
<td>1. Alagille syndrome</td>
</tr>
<tr>
<td>2. ARC Syndrome (Arthrogryposis, Renal disease, Cholestasis)</td>
</tr>
<tr>
<td>IV. Acquired forms</td>
</tr>
<tr>
<td>1. Sepsis-related</td>
</tr>
<tr>
<td>2. Drug-induced Cholestasis</td>
</tr>
<tr>
<td>3. Intrahepatic Cholestasis of Pregnancy</td>
</tr>
<tr>
<td>V. Unclassified</td>
</tr>
</tbody>
</table>
to biochemical analysis and molecular dissection and were proven to be caused by inborn errors of lipid, amino acid, or carbohydrate metabolism. The recognition of the metabolic basis for liver disease allowed for targeted nontransplant strategies for the management of affected patients.82,83 In addition, early practitioners of Pediatric Hepatology in Taiwan were largely responsible for the initial steps towards reducing the global burden of hepatitis B.84-88 The obvious solution to this problem was to interrupt perinatal transmission by way of hepatitis B virus (HBV) vaccination combined with the administration of hepatitis B immune globulin at birth.85-87 This strategy has been nearly universally applied, leading to a worldwide decrease in the prevalence of hepatitis B surface antigen (HBsAg) positivity and a decrease in the incidence of HBV-related liver disease, including hepatocellular carcinoma.88

**Pediatric Liver Transplantation**

Despite these obvious successful advances, there were many children who reached endstage liver disease. Thus, there was a need for alternative strategies—namely, the establishment of pediatric liver transplant programs. Actually, the first recorded orthotopic liver transplantation was performed in a child with biliary atresia.89 Continued advances were made since that landmark case with innovations in surgical techniques, methods of organ preservation, postoperative care, and immunosuppression strategies. In the early 1980s the only center performing liver transplantation in children was that led by Tom Starzl in Pittsburgh; in that program the medical care was proved by a gifted group of pediatric generalists (Basil Zitelli, Carl Gartner, Jeff Malatack, and others) working directly with the transplant surgeons.90-92 In 1983, the National Institutes of Health Consensus Development meeting concluded that “liver transplantation was no longer an experimental procedure” and that it “deserved broader application.”93 Technological advances allowed rapid expansion of this option to children. Liver transplantation thus emerged as the standard of care for children with irreversible acute and chronic liver failure and certain metabolic disorders. As a result, the need for skilled, qualified “pediatric hepatologists” to manage patients before and after liver transplantation significantly increased.

**Pediatric Liver Transplantation: The Team Approach.** One of the lessons derived from my adolescent interest in sports was the value of learning to play on a team that has great diversity in background, knowledge, and specific skills. As part of our PLCC strategy we established a liver transplant program—in addition to Fred Suchy and I—the CCHMC “team” (Fig. 6) consisting of pediatric surgeons—Fred Ryckman and John Noseworthy, along with nurse coordinators—Sue Pedersen and Joanne Mitchell. Working side-by-side as clinical team, with shared responsibilities and perseverance, liver transplantation became a realistic, effective, and life-saving therapy for infants and children with endstage liver disease.30,94,95 However, a factor that limited more widespread application of liver transplantation was a lack of size-matched donors—a disparity compounded by the fact that the most common indication for liver transplantation in the pediatric population was biliary atresia. In this disease, liver replacement is often required at a young age and small size because of the rapid progression. This epidemiologic disparity between donor size and recipient needs led to the use of reduction hepatectomies/segment liver transplantation and the development of other innovative transplant surgical techniques based on reduced size grafts, including split liver transplantation and the use of organs from living donors.96-99 These advances allowed more widespread application of liver transplantation for children. During 2011-2012, 64 centers performed at least one liver transplant in a patient <18 years of age; 23 programs performed 20 or more transplants in this population during that time frame.100 Pediatric pretransplant mortality has steadily decreased, most dramatically for candidates less than 1 year of age. The number of new pediatric candidates added to the liver transplant waiting list was 704 in 2011.100,101 In 2011, there were 477 deceased donor pediatric liver transplants and 59 living donor transplants. Graft survival has continued to improve for pediatric recipients. Despite this high success rate, challenges remain, including the need for
targeted preoperative management to address the problems of malnutrition, and improved methods to prevent graft loss while avoiding the consequences of immunosuppression, such as posttransplant lymphoproliferative disease (PTLD) and renal injury.99

A New Subspecialty Truly Emerges: The Field of Pediatric Hepatology

All elements were in place for expansion and validation of Pediatric Hepatology. In the mid-1990s centers that focused on Pediatric Hepatology became a component of many divisions of Pediatric Gastroenterology. Research flourished with the application of state-of-the-art cellular and molecular biology techniques and the emergence of molecular genetics, which enhanced our understanding and recognition of the pathophysiological and genetic basis of an increasing number of disorders of the liver in children.102 With clinical and research efforts converging, the field rapidly gained momentum. The next key ingredient to establishing the formal field was to create and sustain a critical mass and validate the concept of Pediatric Hepatology as an academic subspecialty. In a decision that reflected validation and maturity, “Hepatology” was added to the name of the major Pediatric Gastroenterology society—which became the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). This is symmetrical with the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). In 1993, perhaps as a measure of the growth of the field (or the verbosity of the author) the chapter on Liver Disease in Infancy and Childhood in the 7th Edition of Diseases of the Liver (Leon and Eugene Schiff; editors) was 104 pages long!103

Networking: Face-To-Face—Not Facebook

A community of colleagues interested in Pediatric Hepatology was being built. The increasing number of “practitioners” and the robust research enterprise created a demand for greater opportunities to meet and share science, thus a gathering place was needed. Extensive discussions about research on liver diseases in children among hepatologists, surgeons, pathologists, and basic scientists occurred at meetings and scientific fora. The annual meetings of the American Association for the Study of Liver Diseases (AASLD) and Digestive Disease Week (DDW) were excellent venues for enrichment and engagement. With the increasing number of high-quality abstract submissions and research addressing liver diseases in children, these meetings embraced pediatric input. Communication with colleagues facing similar “liver-related” issues in other countries was catalyzed by international conferences, such as the Falk Symposia. The excellent scientific basis and collegiality of these conferences stimulated collaboration and promoted clinical and basic research, which directly led to advances in Pediatric Hepatology.

Following my appointment to the National Digestive Diseases Advisory Board (NDDAB) in 1985, I was the chair of a conference addressing the issues of “Mechanisms and Management of Pediatric Hepatitis.” This conference was organized and sponsored by the NDDAB, the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), and the American Liver Foundation.104 The sessions addressed potential areas of research, such as morphology and functional differentiation of the liver, development of hepatic excretory function, and therapeutic strategies directed to the spectrum of liver disease in children. These discussions brought to the attention of the research community some of the perceived needs and served to encourage research in pediatric hepatobiliary disease, specifically as collaborative studies in certain clinical areas.

In September 1994, another important symposium that focused on pediatric liver disease, “Biliary Atresia, Current Status and Research Directions,” was organized by Jay Hoofnagle and sponsored by the NDDAB.29 The goal of the symposium was to address the pathogenesis and the clinical challenges presented by biliary atresia, including the need for rapid and precise diagnosis and improved management. The ultimate objective was to stimulate basic and translational investigation regarding this enigmatic disease.29 Because a small number of patients were being seen in individual centers and patients were not managed in a uniform manner between centers, a collaborative, multicenter study of biliary atresia was viewed as imperative.105,106 In 2002 the NIDDK of the NIH initiated funding of a consortium; the overall goal was to gather clinical and biochemical data along with serum, tissue, and DNA samples in a prospective manner in order to facilitate research. The consortium members generated and tested hypotheses regarding the pathogenesis and optimal diagnostic and treatment modalities for biliary atresia and related disorders.28,105 What ultimately emerged is the encompassing Childhood Liver Disease Research and Education Network (ChiLDREN), a collaborative team of doctors, nurses, research coordinators, medical facilities and patient support.
organizations. The ChiLDREN Network supports the discovery of new diagnostics, etiologies and treatment options for children with liver disease, and those who undergo liver transplantation. The network also supports training for the next generation of investigators of pediatric liver diseases.107

Subspecialty Certification in Pediatric Transplant Hepatology

During a Strategic Planning Meeting held in 2000 the AASLD Governing Board set out to codify a body of knowledge that would establish criteria to develop hepatology as a focused, distinct discipline within the medical subspecialty of gastroenterology and to identify the special training that individuals involved in “advanced” hepatology and liver transplantation required. The goal was to ensure recognition of individuals who had acquired the training, expertise, and skills to be considered a “hepatologist.”108 Up to that time the discipline of hepatology was largely viewed as a focused research activity. However, the clinical profile was rapidly expanding, driven by the growth of liver transplantation programs, the discovery of the hepatitis C virus, and the nascent epidemic of obesity-related liver disease.

As a member of the AASLD Governing Board at that time (Fig. 7), I was excited about the concept and the opportunity for the development of Advanced/Transplant Hepatology as a subspecialty of gastroenterology. Equally exciting, as the first pediatrician to be elected president of the AASLD, I had a unique perspective and thus envisioned the impact on those of us who were predominantly involved in the care of children and adolescents with liver disease.

Around that time the leadership of NASPGHAN separately addressed the question as to whether special certification or qualifications in Pediatric Hepatology were necessary within the field of Pediatric Gastroenterology.109 Data generated from a NASPGHAN workforce survey estimated that there were approximately 300 practitioners of Pediatric Hepatology. The United Network for Organ Sharing (UNOS) had specific qualifications for the designation of pediatric liver transplant physicians, which included fellowship training in Pediatric Gastroenterology with a minimum exposure of clinical care of 10 pediatric patients undergoing liver transplant. Furthermore, it was required that the trainee provide ongoing care for at least 20 children who have undergone liver transplantation, under the guidance of a qualified liver transplant physician and surgeon. The problem, therefore, for individuals interested in training in the field or pursuing careers focusing on Pediatric Hepatology was the need to find appropriate mentors and training programs. The NASPGHAN leadership recognized the demand for validated practitioners and the need for increased recognition for individuals who achieved a specified level of competence in the field. It was also supportive of codification of a knowledge base of information related to liver diseases in children.

An AASLD task force led by Joe Bloomer was created and a “game plan” for the development of a process for certification in the subspecialty identified as Transplant Hepatology was rolled out. The proposal stated that qualified candidates upon successful completion of the process, including an examination, would receive a Certificate of Added Qualification.
(CAQ) in Transplant Hepatology—equivalent to board certification in this new subdiscipline. As the name implies, this CAQ would denote knowledge of hepatology over and above that expected of a board-certified gastroenterologist. A needs assessment and workforce analysis gathered information as to the volume and type of patients referred to transplantation centers and the special skills required to care for complex patients, before and after liver transplantation. This analysis documented that advanced/transplant hepatology was considered by gastroenterologists to be a distinct discipline outside the purview of the typical practicing gastroenterologist, regardless of the amount of hepatology training possessed by that individual. The task force concluded that a benefit to patient care would be derived if the discipline were codified with the certification in this new subdiscipline. As the name implies, this CAQ would denote knowledge of hepatology over and above that expected of a board-certified gastroenterologist. A needs assessment and workforce analysis gathered information as to the volume and type of patients referred to transplantation centers and the special skills required to care for complex patients, before and after liver transplantation. This analysis documented that advanced/transplant hepatology was considered by gastroenterologists to be a distinct discipline outside the purview of the typical practicing gastroenterologist, regardless of the amount of hepatology training possessed by that individual. The task force concluded that a benefit to patient care would be derived if the discipline were codified with the certification process. Therefore, a CAQ proposal was submitted to the American Board of Internal Medicine (ABIM) and to the American Board of Pediatrics (ABP), which cited the growing interest in adult and Pediatric Hepatology, including the rapid expansion of knowledge in the field. It emphasized the projected profound impact of certification on the quality of existing practice of advanced hepatology, by dictating standards to ensure competence and by providing a framework for monitoring continued competence. The proposal was reviewed and endorsed by the ABIM and ABP gastroenterology subspecialty boards, and approved by the respective boards of directors. The formal application was then approved by American Board of Medical Specialties (ABMS) in 2003.

A conjoined examination process for the CAQ was developed by a Test and Policy Committee on Transplant Hepatology which consisted of 10 members, two of whom were pediatricians (John Bucuvalas and Phil Rosenthal). The group defined requirements for certification, including training and practice admission requirements, and developed a detailed content outline as a “blueprint” for the initial certifying examination. This served to delineate the intellectual boundaries and knowledge that a certified subspecialist in Transplant Hepatology must acquire beyond that learned during their GI Fellowship. The core examination included two separate modules—one for pediatrician applicants and one for internal medicine applicants. In November 2006, the first certifying examination in transplant hepatology was administered to 47 ABP board-certified pediatric gastroenterologists and 83% passed. The Pediatric Transplant Hepatology certifying examination is now offered biannually. Since the certification of the initial “class” of board-certified Pediatric Transplant Hepatologists, 89 certificates have been awarded in our subspecialty as of December, 2012.

The Accreditation Council for Graduate Medical Education (ACGME) was then responsible for establishing the criteria for accreditation of training programs in transplant hepatology. This ensured that a variety of educational objectives were in place, along with a curriculum, to allow individuals to become adequately trained and monitored. There are currently five ACGME-certified programs in Pediatric Transplant Hepatology in the US.

**Quo Vadis?**

In my opinion the goals and expectations of the AASLD task force, which had the vision of certification of liver disease specialists, have been met. The end result is a thriving clinical and academic subspecialty that continues to attract the “best and the brightest,” carry out high-quality basic and translational research, and use innovative strategies to improve patient care. The certification process ensures that those caring for patients of any age with advanced liver disease possess the necessary knowledge and training. The latter is governed by the high standards set by the ACGME. Buoyed by the success, the trend of “subspecialization” within the broad field of gastroenterology is viewed as likely to continue.

**What Do We Want Subspecialty Training to Look Like in the Future?** It is still a bit unclear as to the optimal process for training the next generation of transplant hepatologists. It has been suggested that the current model of a dedicated year of training in Transplant Hepatology after a 3-year fellowship in gastroenterology may be “unworkable and unsustainable.”

This additional year of postgraduate training may not be a popular option, a concern predominantly related to the perceived financial disincentives. One proposal emanating from gastroenterology subspecialty groups suggests that subspecialty training such as Transplant Hepatology be incorporated within the 3-year gastroenterology core fellowship. The endpoints for training and the criteria for credentialing might then focus not on process measurement but on the measurement of actual accomplishments or outcomes—the acquisition of competencies within the field. In fact, pilot programs in Internal Medicine are being established that incorporate specialty specific milestones that trainees must attain as they progress. Of course, the ultimate desired outcome is the quality of care provided to our patients.
Reflection: The Past Informs the Future of Pediatric Hepatology

The lessons for me are enduring—focus, persevere, commit. While times may be different, I recall that Bill Schubert fostered independence and that Alan Hofmann was kind enough to take the time to listen to an unknown young fellow. These traits remain key ingredients to successful mentoring/career development of trainees. I also emphasize to trainees the value of dedicating time to work within a community of like-minded individuals. It is also clear to me that detailed study of a single patient can lead to a new scientific and medical horizon.

A single “organ of interest”, the liver, has rapidly reached a status in which an entire field of study is committed to its long-term health and longevity. Pediatric hepatologists are major components of clinical practices, education and training programs, and investigative initiatives to advance human health and to improve clinical care and outcomes. Research programs are providing insight into the combined role of genetic predisposition and environmental factors in the expression of a variety of liver diseases. This offers the opportunity to prevent or modify phenotypic expression of diseases by addressing a potential chronic liver disease during early life. For example, a major current research goal is to define the pathogenesis of biliary atresia and to develop effective preventative strategies. In the interim it is important to emphasize strategies for early recognition to allow for optimal intervention.

Despite the progress, our field is still quite undeveloped. The cited advances and interventions have clearly improved outcomes for children with liver disease. Along the way we learned a great deal about hepatobiliary physiology, developmental biology, and the role of genetic variants in determining the risk of liver disease and in predicting the response to therapy. Much more needs to be done. We must focus on ensuring the continued development of our field by training the workforce of the future. In addition, definitive, cost-effective treatment strategies must be developed such that liver transplantation may not be needed in the treatment of certain diseases, such as metabolic liver disease. In this regard, it will be important for funding agencies and foundations to continue to support research and to foster innovation and collaboration in Pediatric Hepatology. The success of the well-established multicenter ChildDREN Network serves to emphasize that point. Societies such as the AASLD and NASPGHAN must also continue to recognize the important role that pediatric hepatologists play in their mission and foster career development in the field.

The emerging number of pediatric patients with nonalcoholic fatty liver disease suggests that a focus on prevention and recognition of obesity is clearly needed. This combined with efforts to prevent liver disease in early life, thoughtful medical management, precise decision-making, and conscientious, creative, and courageous use of nontransplant options can both save lives and save lives.

Acknowledgment: I express my gratitude, admiration, and appreciation to all those who have made our field viable and vibrant. I especially want to recognize the commitment and collaboration of the many parents and patients who have dedicated their time to clinical studies which have clearly advanced our field. I also want to thank Mitchell Cohen and Frank DiPaola for their critical review of this article. We have tried to cover the relevant elements in the development of Pediatric Hepatology, but could not include all names and details in this brief overview. Please accept my apology if something or someone that individual readers deem important was excluded.

References


