

Pediatric Gastroenterology at The Mount Sinai Hospital

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Abstract

The history of pediatric gastroenterology at Mount Sinai begins in 1960. Early publications by Drs. Korelitz and Gribetz on the management of inflammatory bowel disease in children served as the preface to forty years of progress in this important area. The history of pediatric gastroenterology includes important work by many individuals, including Horace Hodes, Lotte Strauss and Frederick Kopel. Early observations on the nature of inflammatory bowel disease (IBD), and its course, preceded work on nutritional therapies for IBD, mechanisms of gene-nutrient interactions, regulation of gene transcription, and molecular processes involved in bile transport in the liver and small intestine. Over the last twenty years, the division has grown in size and reputation. Today there are fourteen full-time faculty — 9 M.D.'s and 5 Ph.D.'s — who work in three funded research laboratories. There are also five advanced practice nurses (including three nurse practitioners), two social workers and two nutritionists, as well as several administrators and assistants. In addition to being recognized as a premier center for the treatment of children with general pediatric gastroenterological problems, especially inflammatory bowel disease, the division is also known as one of the nation's largest pediatric liver and liver transplant centers, and it is rapidly becoming one of the largest pediatric short gut syndrome and small bowel transplant centers.

Key Words: Pediatric gastroenterology, inflammatory bowel disease, liver disease, short gut syndrome, liver transplant, small bowel transplant, Mount Sinai.

DR. FREDERICK KOPEL was probably the first "official" pediatric gastroenterologist at The Mount Sinai Hospital, specializing in cystic fibrosis. In the 1960s, Kopel was encouraged by Drs. Fenton Schaffner and Hans Popper to learn and adapt the techniques of liver biopsy to pediatrics. Dr. Lotte Strauss, together with Popper, studied neonatal hepatitis and attempted to correlate what was seen histologically through the microscope with what was seen clinically and biochemically. Kopel also joined Burton Korelitz and Donald Gribetz to publish a major report on granulomatous colitis (1). This work emphasized the importance of appropriate medical management for granulomatous disease, in contrast to the recommendations for surgery in ulcerative colitis.

Inflammatory Bowel Disease

Korelitz and Gribetz were struck by the devastation that resulted from inflammatory bowel disease (IBD) in children. They systematically examined the natural course of IBD in

the pre-steroid era and mentored one of their residents, Dr. Irwin Danziger, as he sought answers to important questions in pediatric gastroenterology. Korelitz, Gribetz and Danziger reviewed the records of children with IBD followed at that time by Korelitz and seen at Mount Sinai (2). They noted that, in the era before anti-inflammatory drugs, most children seen in the hospital became very ill, and many died. Anecdotal reports relate many animated discussions between Dr. Horace Hodes, the then-chief of pediatrics, who staunchly advocated medical management, and the well-known surgeon, Dr. John Garlock, chief of one of the surgical services. Drs. Garlock and Ginzburg usually favored surgical management. Danziger's review of the records suggested that if a child survived for two years after being hospitalized for severe colitis, not only was that child very fortunate, even remarkable, but that even after the two years the child might still become very ill. His review of patients with ulcerative colitis supported the surgical approach advocated by Garlock. Although this preemptive operative approach for these children was seriously criticized, Ehrenpreis concluded that a child with severe, acute colitis should be made as well as possible, and that the colon should be removed early in the course of the disease (3).

The work by Korelitz, Gribetz and Danziger reflects the highest level of pioneering work in

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pediatric gastroenterology. Their studies of the prognosis of ulcerative colitis with onset in childhood in the pre-steroid era are historic. To quote from their discussion (2), “the relentless morbidity menacing the child with ulcerative colitis is given somber testimony by this study of the history of the disease in the pre-steroid era.” Korelitz, Gribetz and Danziger (2) also reported that 43% of the children who developed ulcerative colitis in the pre-antimicrobial era died as a result of their disease, the mean age of death occurring at 22 years. After the development of antibiotics, that mortality was cut in half, but was still 22%, with a mean age at death of 17 years. The article, which detailed the complications and long-term follow-up, is a landmark in the study of pediatric inflammatory bowel disease. The companion paper by Korelitz and Gribetz on the prognosis of ulcerative colitis with onset in childhood, in the steroid era (4), was also important. They reported that with the use of adrenocorticotrophic hormone (ACTH) and adrenal steroids, the number of complications from ulcerative colitis (inflammatory bowel disease) has “not been obviously reduced.” The number of patients with ulcerative colitis treated by surgery increased during the early years of this period, and surgery seems to have been performed when the patients were less ill. This reduction in urgent surgery seems to have been accompanied by fewer operative stages and fewer operative complications in morbidity and mortality. After six years of disease, 30% of the patients had ileostomies, but almost 90% were alive and 40% were well without definitive surgery. The authors concluded that the response to steroids helped determine which children with inflammatory bowel disease would benefit from colectomy. They concluded that surgery should be performed early enough to avoid irreversible complications of the disease and to minimize surgical mortality.

The Mid-1970s

Events occurring in the mid-1970s (1973–1974), while Horace Hodes was Chairman of Pediatrics, confirmed the significance of some of his earlier findings from the 1940s. Hodes, while studying diarrhea in calves, had found a filterable (viral) agent that could not be identified with the existing technology; stool samples were frozen for future investigation. Years later, with the use of electron microscopy, it was discovered that the viruses he had isolated, but not identified, be-

longed to the same family of viruses that was found to cause infantile winter diarrheas, i.e., rotavirus (personal communication).

In 1975, Gribetz and Korelitz worked with another Mount Sinai pediatric resident, Dr. Michael Berger, to report their findings of growth retardation in children with ulcerative colitis, and the effects of medical and surgical therapy (5).

After Kopel’s untimely death, in 1971, Dr. Richard Bonforte helped fill the void. He worked with the then-chief resident, Dr. Neal LeLeiko, to re-establish the sweat test as the procedure for diagnosis of cystic fibrosis. Bonforte established the Cystic Fibrosis Center and the Pediatric Pulmonary Center. LeLeiko went on to the Massachusetts Institute of Technology, where he earned his Ph.D. in nutritional biochemistry and metabolism in the laboratory of Dr. Hamish Munro. He then went to the Boston Children’s Hospital to train in pediatric gastroenterology, following which he was recruited (in 1979) by Dr. Kurt Hirschorn, Chairman of Pediatrics, at Mount Sinai, to establish a major division of pediatric gastroenterology.

LeLeiko’s expertise was in nutritional metabolism and the use of parenteral nutrition and special feeding regimens to treat children with a variety of diseases, especially inflammatory bowel disease and short gut syndrome. He rapidly established Mount Sinai as a major referral center for children with both ulcerative colitis and Crohn’s disease, and his interest in nutritional metabolism led to published papers on energy expenditure in patients with Gaucher’s disease (6), inflammatory bowel disease (7), and also in elderly Alzheimer patients (8). LeLeiko, along with Dr. Martin Walsh, studied the use and effects of 6-mercaptopurine on intestinal metabolism and found that often the effects of 6-mercaptopurine could be biochemically mimicked by the use of an elemental diet (9). LeLeiko trained many pediatric gastroenterologists, some of whom have remained at Mount Sinai. Dr. Keith Benkov, for example, became a recognized clinical consultant of the division’s clinical practice in caring for children with inflammatory bowel disease. Benkov was invited to discuss the case of a child with inflammatory bowel disease for the case records of the Massachusetts General Hospital (10).

LeLeiko’s interest in short gut syndrome and nutrition has continued to develop, and 1999 saw the successful inauguration of the region’s first small bowel transplant program.

Patients whom LeLeiko had been following, and who in past years had been sent to other centers, could now receive all of their care at Mount Sinai.

Of the 26 fellows trained in the division, 8 are now division chiefs and directors elsewhere, 8 are full-time academic pediatric gastroenterologists, 2 full-time laboratory researchers and 8 pediatric gastroenterologists in private practice. The members of the division, under LeLeiko's leadership, continue to see children with inflammatory bowel disease and attract a large number of children with nutritional problems, especially children with short gut syndrome and liver disease.

In 1990, the existence of the division's significant liver program was instrumental in New York State authorizing the liver transplant program at Mount Sinai. The pediatric portion of the liver transplant program has developed into one of the major pediatric liver transplant programs in the country. Two of LeLeiko's fellows, Drs. Audrey Birnbaum and Joel Rosh, developed a particular interest in liver diseases and liver transplant, and they helped guide the program through its nascent years. In 1997, Dr. Birnbaum reported, with the rest of the group, on the recurrence of autoimmune hepatitis after liver transplantation (11), thus revising the then accepted view that the disease did not recur. In 1996, Dr. Frederick Suchy, a world-renowned pediatric hepatologist, was recruited as Chairman of Pediatrics. Dr. Benjamin Shneider was recruited from Yale to be director of the division's section for liver diseases.

Current Research

The division has had an active research program. The focus of the work by Walsh and LeLeiko has been on mechanisms of gene transcription in epithelial cells. Research has also focused on the study of gene regulation in the developing and differentiated epithelium and the special effects of nutrition on intestinal epithelium. The current goal of the laboratory is to understand the mechanisms of transcriptional control in epithelial cells. The division's studies have identified transcription factors and co-factors involved in the regulation of the cystic fibrosis transmembrane conductance regulator (CFTR) and N-myc genes. The studies have provided evidence for the function of transcription factors, mediated by protein kinase A and cyclic adenosine monophosphate (AMP), in the modification of chromatin structure and gene

transcription. Discovery of a unique member, epithelial cell DNA binding factor- α (ECDF α), of the paired-homeobox class of transcriptional regulatory proteins encoding guanosine triphosphatase (GTPase) activity, has helped our understanding of the importance of these proteins in directing transcription through a GTPase-activated pathway. Analysis of these factors has also helped clarify the role of specific transcription factors in determining the fate of differentiating epithelial cells during development and oncogenesis. Many original research publications in prestigious scientific journals have resulted from this work (12–18). The group has also made significant contributions in this area, in the form of chapters in standard texts and reviews in specialty journals (19–22).

Suchy, working with Drs. M. Ananthanarayanan and An-Qiang Sun, focused on the ontogeny and regulation of bile formation, using the rat as an animal model. Since arriving at Mount Sinai they have focused on Na⁺ taurocholate co-transporting polypeptide (ntcp) (NTCP in humans) gene, whose product is involved in the Na⁺-dependent uptake of conjugated bile acids from sinusoidal blood into the hepatocyte across the basolateral membrane. They have successfully mapped and localized the chromosome in rat and mouse, and are working on mapping the human gene. In addition, they are in the process of generating transgenic mice that carry promoter regions for ntcp with a reporter gene whose activity can be assayed as an index of promoter activity. Effects of hormones, cytokines, or other agents on the activity of ntcp promoter are of great interest. Studies are in progress using the latest molecular techniques to create "knockout mice" in which the ntcp genes have been deleted. The laboratory also investigates a gene called "sister to p-glycoprotein (spgp) gene," which has been shown to be an adenosine triphosphate (ATP)-dependent bile acid transporter on the canalicular membrane of the hepatocyte, its human homolog has been found to be mutated in PFIC-2 (Progressive Familial Intrahepatic Cholestasis Type 2). The work at Mount Sinai has already resulted in several important contributions to the literature (25–29).

The primary focus of Shneider's research has been to elucidate the regulatory mechanism(s) associated with the ileal sodium-dependent bile acid transporter, including molecular events involved at the developmental and transcriptional levels. Descriptive studies of the response of this system to changes in

bile acid homeostasis are also being undertaken in a variety of animal species, including rat, rabbit, and mouse. Other activities include analysis of bile acid transport proteins in acquired human liver disease and in previously poorly understood inherited pediatric liver diseases (28–32).

In 1998, more than 43 students and residents came from 10 medical centers and 6 medical schools to spend time at Mount Sinai. The Division of Pediatric Gastroenterology, with three funded laboratories, consists of 14 faculty (9 M.D.'s and 5 Ph.D.'s), three nurse practitioners, two social workers, three nurses, two medical assistants, and two nutritionists. Each year, approximately 4,000 patient visits are made to the doctors of the division.

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