GASTROENTEROLOGY and NUTRITION

Neonatology Questions and Controversies

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Series Foreword

"Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning."

Albert Einstein

"The art and science of asking questions is the source of all knowledge."

Thomas Berger

In the mid-1960s W.B. Saunders began publishing a series of books focused on the care of newborn infants. The series was entitled *Major Problems in Clinical Pediatrics*. The original series (1964–1979) consisted of ten titles dealing with problems of the newborn infant (*The Lung and its Disorders in the Newborn Infant* edited by Mary Ellen Avery, *Disorders of Carbohydrate Metabolism in Infancy* edited by Marvin Cornblath and Robert Schwartz, *Hematologic Problems in the Newborn* edited by Frank A. Oski and J. Lawrence Naiman, *The Neonate with Congenital Heart Disease* edited by Richard D. Rowe and Ali Mehrizi, *Recognizable Patterns of Human Malformation* edited by David W. Smith, *Neonatal Dermatology* edited by Lawrence M. Solomon and Nancy B. Esterly, *Amino Acid Metabolism and its Disorders* edited by Charles L. Scriver and Leon E. Rosenberg, *The High Risk Infant* edited by Lula O. Lubchenco, *Gastrointestinal Problems in the Infant* edited by Joyce Gryboski and *Viral Diseases of the Fetus and Newborn* edited by James B. Hanshaw and John A. Dudgeon. Dr. Alexander J. Schaffer was asked to be the consulting editor for the entire series. Dr. Schaffer coined the term "neonatology" and edited the first clinical textbook of neonatology entitled *Diseases of the Newborn*. For those of us training in the 1970s, this series and Dr. Schaffer's textbook of neonatology provided exciting, up-to-date information that attracted many of us into the subspecialty. Dr. Schaffer's role as "consulting editor" allowed him to select leading scientists and practitioners to serve as editors for each individual volume. As the "consulting editor" *for Neonatology Questions and Controversies*, I had the challenge of identifying the topics and editors for each volume in this series. The six volumes encompass the major issues encountered in the neonatal intensive care unit (newborn lung, fluid and electrolytes, neonatal cardiology and hemodynamics, hematology, immunology and infectious disease, gastroenterology, and neurology). The editors for each volume were challenged to combine discussions of fetal and neonatal physiology with disease pathophysiology and selected controversial topics in clinical care. It is my hope that this series (like *Major Problems in Clinical Pediatrics*) will excite a new generation of trainees to question existing dogma (from my own generation) and seek new information through scientific investigation. I wish to congratulate and thank each of the volume editors (Drs. Bancalari, Oh, Guignard, Baumgart Kleinman, Seri, Ohls, Yoder, Neu and Perlman) for their extraordinary effort and finished products. I also wish to acknowledge Judy Fletcher at Elsevier who conceived the idea for the series and who has been my "editor and friend" throughout my academic career.

Richard A. Polin, MD

Preface

In the past 4 decades, neonatology – collaborating with fetal maternal medicine, pediatric surgery and other pediatric subspecialties – has been remarkably successful in improving the survival of critically ill newborns. Unfortunately, the genetic potential for both optimal physical health and neurodevelopment of too many of these survivors remains unmet, partially due to the long-term effects of preventable stresses occurring in early neonatal life.

Despite burgeoning knowledge that nutritional optimization is a modulator of many of these stresses, nutritional management during the most stressful periods has continued to be overshadowed by other "more critical" aspects of care in the neonate. The major "hot topics" in neonatology continue to focus on lung development, respiratory support measures, neuroprotection of asphyxiated infants, pharmacologic management strategies for infections, and bilirubin metabolism. However, small but important steps are beginning to be made in early initiation of parenteral and enteral feedings in these infants. Nevertheless, we have a long way to go in understanding the actual metabolic capabilities of the critically ill neonate, as well as the digestive absorptive and other physiologic potential of the neonatal gastrointestinal tract.

The recognition that the gastrointestinal tract is much more than an organ of digestion and absorption – also a major conduit of immunologic and endocrine signals that can become "hard wired" into adult life and even into next generations – requires considerable further elucidation. The recent discovery of a "new organ" – the intestinal microflora (or "microbiome"), which is an integral part of the ecosystem that the largest part of the human surface area interacts with – has major implications for optimal nutrition, development and immunologic defenses as well as tolerance.

This unique book incorporates clinical neonatal gastroenterology and nutrition with up-to-date research. It provides the reader with a better understanding of the developmental biology of the gastrointestinal tract, nutritional needs of the premature infant, and methods for supporting these needs. It discusses pathophysiology and treatment of diseases such as necrotizing enterocolitis, cholestatic liver disease, and short bowel syndrome. It also provides a primer for exciting research directions, including the intestinal microbiome, the relationship of intestinal inflammation and barrier dysfunction to intestinal and more generalized disease, tissue engineering, and epigenetic mechanisms of developmental origins of adult health and disease.

Josef Neu, MD

Chapter 1

Gastrointestinal Development: Morphogenesis and Molecular Mechanisms

Robert K. Montgomery, PhD

Survival of the newborn human infant depends on a successful transition from the intrauterine to the extrauterine environment. A major factor is the maturation of sufficient gastrointestinal function to provide for adequate nutrition. At birth the gastrointestinal tract is uniquely adapted to the absorption of breast milk and its nutrient components, exclusion of foreign antigens, pathogens, and some xenobiotics, adaptation to the intestinal microflora, and, with the kidney, maintenance of water balance. In the full-term infant, these processes are integrated and support normal growth and development.

Many essential mechanisms are mature at birth, but some, such as bilirubin conjugation and excretion, and hepatic drug metabolism, are only completed in the early post-natal period. The interaction between the initially sterile gastrointestinal tract and the microbiota that colonize it after birth is increasingly being recognized as a crucial component of postnatal development (1, 2). Other mechanisms develop later in the post-natal period, such as esophageal sphincter function and motility, gastric acid and intrinsic factor secretion, gastric motility, intestinal glucose absorption, vitamin B12 and bile salt absorption, synthesis of bile acids and the expansion of the bile acid pool, and the secretory response to bacterial toxins. Pancreatic exocrine function is completed after approximately 6 months of age and endocrine function characterized by insulin release after feeding is also delayed, but for not quite as long.

Detailed descriptions of the morphogenesis of the human gastrointestinal tract are available in standard texts. More extensive discussion of gastrointestinal tract development is provided in several reviews (3–8). This chapter will provide an overview of morphogenesis and focus on the current understanding of the molecular mechanisms of gastrointestinal development. Selected milestones in the anatomic and morphological development of the human gastrointestinal tract are summarized in Table 1-1.

Table 1-1 Developmental Milestones

Event	Time of first expression
Gastrulation	week 3
Gut tube largely closed; liver and pancreas buds	week 4
Growth of intestines into cord	week 7
Intestinal villus formation	week 8
Retraction of intestines into abdominal cavity	week 10
Organ formation complete	week 12
Parietal cells detectable, pancreatic islets appear, bile secretion intestinal enzymes detectable	week 12
Swallowing detectable	week 16–17
Mature motility	week 36

MORPHOGENESIS

Proliferation of cells from the fertilized egg gives rise to the blastocyst. The embryo proper will develop from a compact mass of cells on one side of the blastocyst, called the inner cell mass. It splits into two layers, the epiblast and hypoblast, which form a bilaminar germ disc from which the embryo develops. At the beginning of the third week of gestation, the primitive streak appears as a midline depression in the epiblast near the caudal end of the disc. During gastrulation, epiblast cells detach along the primitive streak and migrate down into the space between the two germ layers.

The process of gastrulation generates the endoderm cells which will form the epithelia lining the gastrointestinal tract. Some of the cells migrating inward through the primitive streak displace the lower germ layer (hypoblast) and form the definitive endoderm. Gastrulation establishes the bilateral symmetry and the dorsal/ventral and craniocaudal axes of the embryo. Formation of the three germ layers brings into proximity groups of cells, which then give rise to the organs of the embryo through inductive interactions. As described below, the molecular mechanisms of many of these processes are now being elucidated.

The gut tube is formed by growth and folding of the embryo. The tissue layers formed during the third week differentiate to form primordia of the major organ systems. A complex process of folding, driven by differential growth of different parts of the embryo, converts the flat germ disc into a three-dimensional structure. As a result, the cephalic, lateral, and caudal edges of the germ disc are brought together along the ventral midline, where the endoderm, mesoderm, and ectoderm layers fuse to the corresponding layer on the opposite side, converting the layers into the gut tube.

Folding of the embryo first forms a closed gut tube at both the cranial and caudal ends. The anterior and posterior ends of the developing gut tube where the infolding occurs are designated the anterior and posterior (or caudal) intestinal portals. Initially, the gut consists of blind-ending cranial and caudal tubes, the foregut and hindgut, separated by the future midgut, which remains open to the yolk sac. As the lateral edges continue to fuse along the ventral midline, the midgut is progressively converted into a tube, while the yolk sac neck is reduced to the vitelline duct. Remnants of this duct occasionally fail to regress and form Meckel's diverticulum.

Three pairs of major arteries develop caudal to the diaphragm to supply regions of the developing abdominal gut. The regions of vascularization from these three arteries provide the anatomical basis for dividing the abdominal gastrointestinal tract into foregut, midgut, and hindgut. The celiac artery is the most superior of the three. It develops branches that vascularize the foregut from the