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Nikhil Thapar
Carlo Di Lorenzo
Editors

Pediatric Neurogastroenterology

Gastrointestinal Motility and Functional Disorders in Children

Second Edition

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To my parents with love.

Christophe Faure

To my parents for their unconditioned support and love.

Carlo Di Lorenzo

To my beloved father Baldev Sahai Thapar—blessed by your and mum's unending love, forever my guiding light and inspiration.

Nikhil Thapar

To our patients and all the children afflicted by motility and sensory digestive disorders.

Christophe Faure
Carlo Di Lorenzo
Nikhil Thapar

Foreword

Neurogastroenterology is certainly not an arcane or secretive branch of medicine. Still, if one were to judge from the proportion of physicians who are knowledgeable about the subject, especially in its pediatric version, one might come away with the idea that the tenets of neurogastroenterology are imparted only to initiates who are sworn to secrecy in midnight rituals over pots filled with boiling entrails. In fact, Nikhil Thapar, Carlo Di Lorenzo, and Christophe Faure have succeeded masterfully in dispelling this aura of mystery in their wonderful textbook *Pediatric Neurogastroenterology*, which is now entering its second edition. There is no longer an excuse for medical ignorance. Pediatric neurogastroenterology is laid out clearly, logically, and encyclopedically for anyone who has mastered and enjoys the art of reading. The chapters are chosen to make the field approachable and significantly, in an age where clinical understanding has to compete with insurance companies for doctors' attention, clinically relevant. The authors of individual chapters are authorities, which is to be expected, but many are more than that. They are truly the leaders to whom other authorities direct their questions, and they are so because they are the actual discoverers of many of the answers.

It has always seemed to me to be to be axiomatic that there is too much known about any field of medicine to be able to encompass all of it as a single compendium of facts. Indeed, those textbooks that try to do this tend to read like dictionaries, to become dated almost before they appear in print, and to be, in a word, useless. Valuable textbooks, like this one, deal with concepts and understanding. They present logical frameworks in which normal anatomy and physiology make the pathophysiology of a kaleidoscopic variety of disorders comprehensible and therefore easily learnable. If the structural/functional flaws that give rise to disease can be understood, then diagnosis, prognosis, and treatment become logical and easily learned. Pithy sentences, rhymes, and words put to music are much more readily committed to memory than a series of unrelated words or phrases. This textbook of pediatric neurogastroenterology uses the basic science of neurogastroenterology as the music that makes the medicine, not just a good read but a retainable one as well.

The editors, of course, are distinguished scientists and clinicians. They have recruited an admirable list of cowriters to do individual chapters. It is impossible to mention all of them, but it would be hard to find a better person than Alan J. Burns to write about the development of the enteric neuromuscular system. Alan traces his training back to Nicole Le Douarin who, with Alan at her side, brought on the modern understanding of the development of the enteric nervous system from the neural crest. One person who might have done as well is the author of the chapter about Hirschsprung's disease, Robert Heuckeroth, who probably understands that condition and knows more about it than Hirschsprung, who lacked the background knowledge that Alan J. Burns has provided in his earlier chapter. These chapters all fit well with that of Cheryl Gariepy on the genetics of motility disorders and Nikhil Thapar on the future with cell-based therapies. All told, this is a great textbook that should bring all of pediatrics up to speed with its neurogastroenterological branch and all of adult neurogastroenterology up to speed with its pediatric branch.

New York, NY, USA

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Preface to the First Edition

In the past 20 years, major advances have been achieved in the care of children with pediatric gastrointestinal motility and sensitivity disorders. This is a reflection of the progress that has been made understanding such conditions at the developmental and molecular level as well as the development of novel tools to investigate and treat them. These progresses have led to the birth of a new "science," namely, *neurogastroenterology*, which is devoted to "study the interface of all aspects of the digestive system with the different branches of the nervous system" and which has now established itself as a major area of clinical practice and research. In the past two decades, there has been an almost exponential increase in publications of scientific papers in the field, a plethora of international fora for the discussion of such conditions and creation of dedicated journals with respectable citation indices. Pediatric neurogastroenterology and motility has not lagged behind and arguably is fast becoming a major and popular subspecialty in its own right.

With this book, we aimed to draw upon an extensive international expertise to provide a contemporary state-of-the-art reference textbook for pediatric neurogastroenterology and motility that both specialists and generalists alike will find helpful.

Overview of the Book

The first chapters are dedicated to some of the success stories of the field. Utilizing a range of animal models and studies in the human itself, we now have a remarkable understanding of the mechanisms involved in the formation of a functional enteric neuromusculature. It is clear that development is a complex spatiotemporal process involving the coordinated interplay of a number of genes regulating cellular properties and organogenesis. This complexity is reflected in one of the most commonly recognized gut motility disorders, Hirschsprung's disease, a condition caused by a failure of development of the enteric nervous system. The ontogeny of motility patterns within the GI tract is now understood in great detail. Utilizing new technologies, animal models, and some studies in humans, researchers have been able to show that GI motility is regulated by a number of mechanisms that vary in relation to stage of development, maturity, and region within the GI tract. It is very likely that the coming years will see an increasing recognition of the developmental and related functional pathogenic mechanisms underlying a range of disorders involving enteric nerves, muscles, and interstitial cells of Cajal. The rich sensory innervation that not only underlies the normal functioning of the GI tract but has increasingly been implicated in a range of functional GI disorders is thoroughly described. This sensory innervation and its processing appear to be plastic and influenced by a number of disease mechanisms and clinical states including infection, inflammation, and psychological stress. How visceral sensation is modulated by the interplay among the CNS, neurogastrointestinal system, inflammation, and gut microbial ecosystem especially in relation to irritable bowel syndrome is addressed in a subsequent chapter. This theme is further developed with the discussion of the biopsychosocial influences on enteric neuromuscular function and how the social and cultural settings of patients act to modify physiologic responses.

The belly of the book summarizes the practical investigations that are available in the pediatric neurogastroenterologist's armamentarium. In many respects, this is where much of the recent strides of the field have taken place, moving it into the realms of a high-tech futuristic specialty. Major highlights have been the advent of impedance and high-resolution manometry technologies, which did not exist when the first textbook on pediatric gastrointestinal motility was published but are now well accepted and standardized diagnostic techniques. The role of sensitivity tests, namely, barostat and satiety drinking tests, in recognizing altered gut sensation as a key pathophysiologic component of functional gastrointestinal disorders is discussed. The application to clinical investigation of radionucleotide scintigraphy tests, which have seen in recent years a wider application given their improved tolerability, cost, and safety profile, is described in detail. Older and newer technologies ranging from electrogastrography and transit studies to 3D ultrasonography and the wireless motility capsule are presented. Finally, there is a discussion of autonomic function testing as indirect measure of gastrointestinal function. The subsequent chapters deal with the practical approach to and description of the pathology of disorders of enteric neuromusculature and the genetic underpinning of motility disorders.

The next section of the book focuses on a journey through the GI tract, detailing motility disorders that occur in each region. Feeding and swallowing disorders in a range of GI and systemic diseases are discussed. Pediatric esophageal and gastric motor disorders are summarized, and intestinal pseudo-obstruction syndrome and Hirschsprung's diseases, the most severe forms of GI dysmotility, are discussed in great detail. The book then focuses on secondary (malformative) and postsurgical motor disorders.

The book then transitions from more classic motility disorders to functional GI disorders, arguably one of the most common and challenging group of conditions encountered by primary care providers and subspecialists. The role of the Rome criteria in developing the field of pediatric functional disorders is highlighted. Infant regurgitation and gastroesophageal reflux disease, infantile colic, functional dyspepsia, irritable bowel syndrome, cyclic vomiting syndrome, aerophagia, adolescent rumination syndrome, and functional constipation are discussed.

The final section of the book is dedicated to therapy, including pharmacotherapy, cognitive behavioral therapy, gastric electrical stimulation, intestinal transplantation, and the potential use of stem cells.

Montreal, QC, Canada — Christophe Faure
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Preface

We are thrilled to be able to present the second edition of our textbook. In 2012 when we launched the first edition, we remarked on the rapid emergence of clinical pediatric neurogastroenterology and motility as a major focus within pediatrics and as a specialty in its own right. Only 4 years later did we come to realize that this transformation was occurring at an unprecedented rate (somewhat at odds with the normal rate of flow in the world of motility disorders!) and we needed to respond with a state-of-the-art revision of the textbook. This was followed by the recognition of the tremendous expertise that now exists within the field and how attractive it had become among an up and coming genre of young clinicians and researchers. The plethora of experts that we are able to garner has of course made our task easier, and we are hugely grateful to all those who have kindly agreed to devote their valuable time to have their brain power harnessed and crammed it into this second edition of the textbook.

We have tried to make the book more practical and clinically applicable yet provide the reader with an up-to-date insight into the basic science that underlies the spectrum of motility disorders.

The overall layout of the book has remained the same but we have made key changes and additions. All chapters have been updated along with an emphasis on clinical application. Chapters on investigations contain color images and have been restructured to provide a uniform overview of techniques and their practical use. New chapters have been commissioned including, among others, the introductory section on the functional interconnectivity of the enteric nervous system, the microbiome, an update on the Rome criteria, chronic intestinal pseudo-obstruction, infantile colic, imperforate anus, rumination syndrome, constipation, electrical stimulation/pacing, and drugs affecting the brain.

We are pleased that this book has become the reference textbook for pediatric neurogastroenterology and motility and trust that both specialists and generalists will continue to find this invaluable. Happy reading!

Montreal, QC, Canada — Christophe Faure
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Part I

Physiology and Development of Enteric Neuromuscular System and Gastrointestinal Motility

Introduction to Gut Motility and Sensitivity

1

Christophe Faure, Nikhil Thapar, and Carlo Di Lorenzo

Evolution, the Gastrointestinal Tract, and the "First Brain"?

Whether or not one believes in the theory of evolution, it is apparent that some of the first multicellular organisms to have inhabited the earth, including the presumptive earliest ancestors of humans, were elongated structures with a core gut tube [1, 2]. In the absence of an obvious heart, brain, or liver, this core system helped sustain life by performing fundamental processes including respiration, the assimilation of nutrition, and metabolism. On this basis it is perhaps not surprising that the gastrointestinal (GI) tract has evolved to become one of the most complex and diverse organs of the human body, with an incredible repertoire of activities from digestion, absorption, and excretion to homeostatic, endocrine, and immune functions. Many of these processes are dependent on highly coordinated sensory and effector mechanisms, which monitor the GI lumen and wall and respond to specific cues. In conjunction with a drive to maintain homeostasis within the body, the effector mechanisms regulate blood flow, adjust the balance between absorption and secretion, and coordinate mixing and propulsion of luminal contents along the length of the bowel. This latter "motility" activity is executed by region-specific peristaltic contractions and emptying mechanisms, which are dependent on highly coordinated interactions among the components of the gut neuromusculature. These components comprise the intrinsic nervous system of the gut (enteric nervous system—ENS), the smooth muscle coats, and the interstitial cells of Cajal (Fig. 1.1).

It is the mere presence and complex characteristics of the ENS that also lends itself to the notion of the gastrointestinal tract as a pioneer organ, with the potential emergence of the ENS prior to that of a recognizable brain. Therefore, perhaps, the ENS should be referred to as the "first brain," with the argument that the central nervous system (CNS) evolved subsequently, as organisms acquired locomotion and more complex interactions with the environment. Either way, perhaps reflective of a common development, the ENS shares many similarities with the CNS, including an overall inherent complexity in structure, organization, and function. It contains as many neurons as the spinal cord and a diversity of neuronal subtypes and properties of enteric glial cells akin to that seen in the CNS [3, 4]. Perhaps even more importantly, the brain and ENS appear to be functionally hardwired reflected in an almost complete interrelation between stress or psychological factors and gut function. Many of the functional gastrointestinal disorders discussed within this book appear to have a clear basis in complex interactions between biological, psychological, and social factors. Equally, nonfunctional or organic conditions have significant impacts on psychosocial well-being. This interplay has made neurogastroenterology and motility one of the most interesting but challenging fields requiring a multidisciplinary approach.

The Enteric Nervous System

The enteric nervous system (ENS) represents the intrinsic nervous system of the GI tract and is present along its entire length. The ENS is one of the largest and more complex components of the peripheral nervous system and organized as plexuses of interconnected ganglia that enmesh the GI tract. In the small and large intestine, these plexuses are present in two distinct layers, the outer myenteric plexus that sits between the inner circular and outer longitudinal muscle layers and the inner sub-

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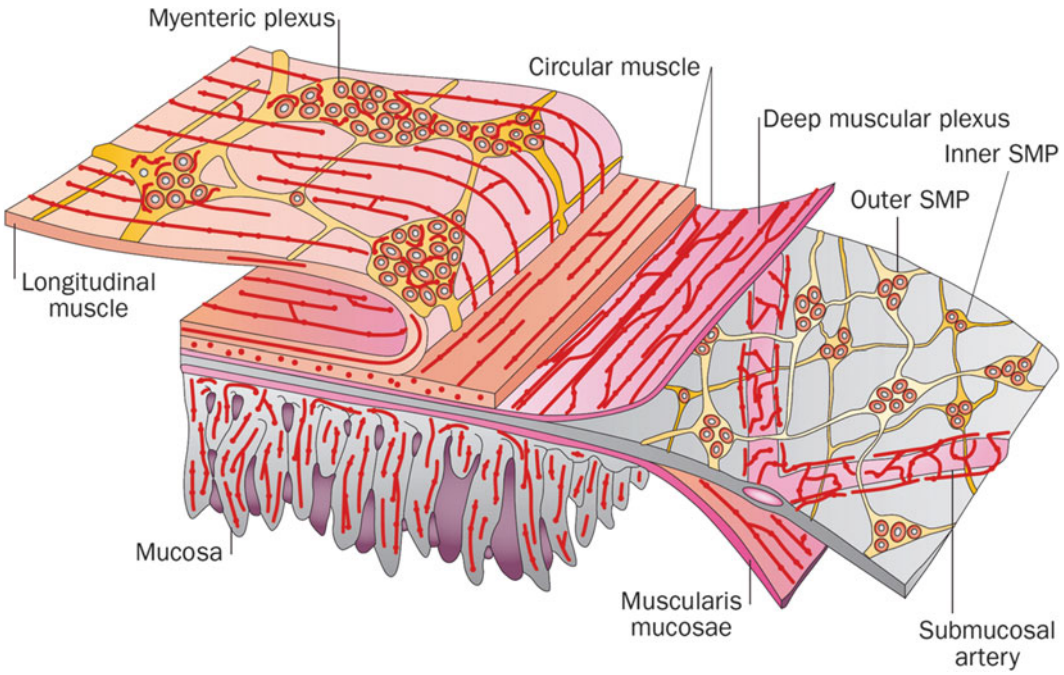

Fig. 1.1 The organization of the ENS of human and medium–large mammals. The ENS has ganglionated plexuses, the myenteric plexus between the longitudinal and circular layers of the external musculature, and the SMP that has outer and inner components. Nerve fiber bundles connect the ganglia and also form plexuses that innervate the longitudinal muscle, circular muscle, muscularis mucosae, intrinsic arteries, and the mucosa. Innervation of gastroenteropancreatic endocrine cells and gut-associated lymphoid tissue is also present, which is not illustrated here. *Abbreviations*: *ENS* enteric nervous system, *SMP* submucosal plexus (From Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012;9(5):286–94. Reprinted with permission from Nature Publishing Group)

mucosal plexus present between the mucosa and the inner circular muscle layer. The ENS comprises neurons and glia organized into aggregates of cell bodies or ganglia. These are interconnected by bundles of nerve fibers that run along the individual plexuses as well as those that run between them. The real complexity of the ENS is revealed at the ultrastructural level where an intricate circuitry is evident (Fig. 1.2). A variety of neuronal subtypes partakes in this and can be classed in terms of functional and structural characteristics. Subclasses include sensory and motor, excitatory, and inhibitory. There are other neuronal subtypes and neurotransmitters present within the ENS (Table 1.1) akin to and aligned with those present in the CNS befitting the title conferred upon the ENS as the "second brain."

The development of the ENS is similarly complex (Chap. 2). The neurons and glia of the ENS all arise from precursor cells derived from the vagal, sacral, and rostral trunk neural crest [5, 6]. These cells migrate into the oral and anal ends of the embryo and enter the foregut and hindgut [7], colonizing the entire gastrointestinal tract. ENS maturity results from an adequate number of correctly differentiated neurons with sufficient axon outgrowth and branching. Several lines of evidence show that enteric neuronal development is not completed at birth. Indeed, in the murine gut, changes in morphology of the plexuses [8] and in the total number of neurons have been reported between the first 4 weeks of life [9]. Submucosal plexuses appear later than myenteric plexuses, and the number of submucosal neurons also increases during the same time period [10]. New postmitotic neurons continue to appear until 3 weeks of postnatal life in the rat gut [11]. Although the pan neuronal marker PGP9.5 is present very early in the embryonic gut (E10.5 in the mouse) [12, 13], neurochemical phenotypic differentiation occurs later during embryonic development and even in postnatal life for cholinergic and peptidergic neurons [14, 15]. ENS neurochemical maturation reaches an adult pattern only at 1 month of postnatal life. In infants, data on functional maturation of the ENS are lacking but it has been reported that the number of cell bodies present within ganglia appears to change according to the age of the individual between 1 day of age and 15 years [16].

Enteric Muscle Coats

The smooth muscle of the gastrointestinal tract, although present within the mucosa and the blood vessels of the submucosa, is primarily organized into three discrete muscle layers. The innermost, muscularis mucosa, sitting between the mucosa and submucosa, is the least developed of these layers, being only a few cells in thickness. The other two, grouped

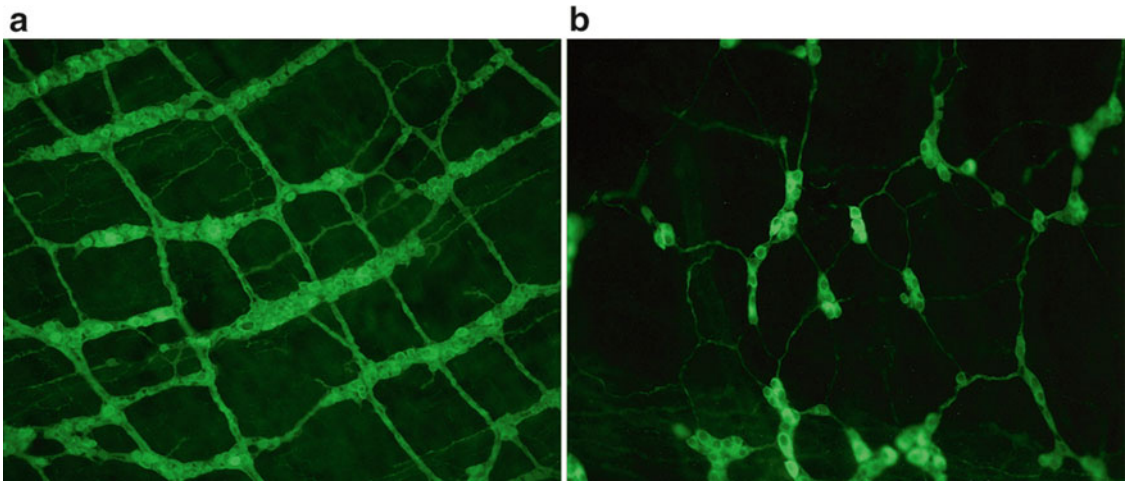

Fig. 1.2 Whole mount preparation of rat myenteric (**a**) and submucosal (**b**) plexuses (immunofluorescent staining with an antibody to the neuronal marker PGP9.5). Neuronal cells are grouped together in ganglia that interconnect both within and between the myenteric and submucosal plexuses. The neuronal cells of the plexuses comprise the enteric nervous system, and along with the glial cells, smooth muscle cells and interstitial cells of Cajal are the intrinsic components of the enteric neuromusculature

Table 1.1 Multiple transmitters of neurons that control digestive function

Type of neuron	Primary transmitter	Secondary transmitters, modulators	Other neurochemical markers
Enteric excitatory muscle motor neuron	ACh	Tachykinin, enkephalin (presynaptic inhibition)	Calretinin, γ-aminobutyric acid
Enteric inhibitory muscle motor neuron	Nitric oxide	VIP, ATP, or ATP-like compound, carbon monoxide	PACAP, opioids
Ascending interneuron	ACh	Tachykinin, ATP	Calretinin, enkephalin
ChAT, NOS descending interneuron	ATP, ACh	ND	Nitric oxide, VIP
ChAT, 5-HT descending interneuron	ACh	5-HT, ATP	ND
ChAT, somatostatin descending interneuron	ACh	ND	Somatostatin
Intrinsic sensory neuron	ACh, CGRP, tachykinin	ND	Calbindin, calretinin, IB4 binding
Interneurons supplying secretomotor neuron	ACh	ATP, 5-HT	ND
Noncholinergic secretomotor neuron	VIP	PACAP	NPY (in most species)
Cholinergic secretomotor neuron	ACh	ND	Calretinin
Motor neuron to gastrin cells	GRP, ACh	ND	NPY
Motor neurons to parietal cells	ACh	Potentially VIP	ND
Sympathetic neurons, motility inhibiting	Noradrenaline	ND	NPY in some species
Sympathetic neurons, secretion inhibiting	Noradrenaline	Somatostatin (in guinea pig)	ND
Sympathetic neurons, vasoconstrictor	Noradrenaline, ATP	Potentially NPY	NPY
Intestinofugal neurons to sympathetic ganglia	ACh	VIP	Opioid peptides, CCK, GRP

5-HT 5-hydroxytryptamine, *Ach* acetylcholine, *CCK* cholecystokinin, *ChAT* choline acetyltransferase, *CGRP* calcitonin gene-related peptide, *GRP* gastrin-releasing peptide, *ND* not determined, *NPY* neuropeptide Y, *NOS* nitric oxide synthase, *PACAP* pituitary adenylate cyclase-activating polypeptide, *VIP* vasoactive intestinal peptide

Adapted from Furness JB. The enteric nervous system and Neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012;9(5):286–94. Reprinted with permission from Nature Publishing Group

within the muscularis propria, are much thicker and comprise the inner circular muscle layer, with its cells arranged concentrically, placed between the submucosa and the myenteric plexus of the ENS, and the outer longitudinal muscle layer, with its cells running along the long axis of the gut, placed between the myenteric plexus and the outermost serosal layer. In the small intestine, the circular muscle appears well developed in sequential segments along its length giving the appearance of concentric rings. In the large intestine, bands of smooth muscle and connective tissue (taenia coli) run on its outside along its length. Their functional role is not completely clear. The enteric smooth muscle is organized in syncytia of cells that are electrically coupled to elicit upon activation contractile activity of the muscle layers. The circular and longitudinal muscles work in concert by contracting to result in segmentation and shortening to execute peristalsis and aboral propulsion of gastrointestinal luminal contents. Contraction of smooth muscle cells derives from two basic patterns of electrical activity across the membranes of smooth muscle cells: slow waves and spike potentials. The membrane potential of smooth muscle cells fluctuates spontaneously. These fluctuations spread to adjacent cells, resulting in "slow waves" which are waves of partial depolarization. The frequency of slow waves varies according to the localization in the GI tract: in the stomach, they occur at a frequency of 3 per min, in the duodenum jejunum 12–15 per min, and in the ileum 8 per min. Slow-wave activity is an intrinsic property of smooth muscle cells independent of intrinsic innervation. "Spike potentials" which result from exposition to excitatory transmitters occur at the crest of the slow waves and provoke muscle contractions at a maximal rhythm dependent upon slow-wave frequency.

Interstitial Cells of Cajal

In 1893, a Spanish physician and professor of pathology provided the first description of a distinct group of cells that appeared to reside in the "interstitium" between enteric nerves and smooth muscles. These cells, now termed interstitial cells of Cajal (ICC), are now established as critical components of the enteric neuromusculature regulating gastrointestinal motility, playing roles as pacemakers and as mediators of enteric motor neurotransmission. They are present in a number of subtypes and morphologies throughout the layers of the GI tract, each of which may relate to distinct physiological functions. One of the key ICC subtypes, ICC-MY, is present in highly branching networks within the myenteric plexus of the small intestine and appears to initiate slow waves that are spread passively to the adjacent electrically coupled smooth muscle cells. Depolarization of neighboring smooth muscle cells leads to activation of the contractile apparatus. There has been considerable recent interest in the potential role of ICC disorders in the pathogenesis of human gut motility disorders (reviewed by Burns [17]), and loss and reduced ICC numbers have been implicated in Hirschsprung's disease, slow transit constipation, chronic intestinal pseudo-obstruction, and esophageal achalasia. Some debate exists over whether there is true loss of ICCs, dedifferentiation, or loss of the cell surface receptor that defines ICCs c-kit. ICCs appear capable of transdifferentiation to smooth muscle cells, a cell type with which they share the same mesenchymal progenitor. Regeneration of ICCs also appears possible [18]. Further studies are required to understand the role of ICCs in disease.

Control of the Enteric Neuromusculature and the Gut-Brain-Microbiota Axis

Although it has been recognized that the neuromusculature of the gut is capable of independent function, this largely relates to fairly rudimentary observations of the retention of basic functions such as contractility, which depend on the integrity of intrinsic reflex circuits that integrate sensory inputs and effector outputs, both excitatory and inhibitory. Thus, in the experimental setting, segments of isolated gut dissected out of the body and placed in a water bath in vitro are capable of efficiently propagating a bead introduced at its rostral end. However, as discussed above, it has long been recognized that the gastrointestinal tract is a portal for, and dependent on, a whole multitude of interactions that facilitate its many and varied functions.

In addition to the complex interactions with the CNS, it is clear that the autonomic nervous system (ANS) exerts critical control of gastrointestinal function. Like the ENS, the ANS is also part of the peripheral nervous system and traditionally further subdivided into the parasympathetic and sympathetic nervous systems with craniosacral and thoracolumbar outflows, respectively. Much of the parasympathetic innervation to the GI tract travels via the vagus nerve and sacral nerves and the sympathetic along mesenteric blood vessels from the prevertebral ganglia. These tracts carry both sensory and motor innervation. Akin to their other functions, these two subdivisions schematically function in opposition to each other with the parasympathetic primarily excitatory to gut function by promoting secretion and peristalsis and mainly mediating physiological (nature and composition of the intestinal content and motility and contractile tension of the smooth muscle) rather than harmful sensations and the sympathetic inhibitory by decreasing peristalsis and reducing perfusion of the GI tract and transmitting information on potentially noxious stimuli. As a consequence, disorders of the autonomic nervous system are related to disturbances in GI motility and sensing.

Beyond control by the CNS and ANS, the extrinsic modulation of the ENS is much more complex. This is reflected in the multiplicity of factors involved in its development

from connective tissue and through to functional interaction with other organ systems such as the immune and endocrine systems. In children, this process is further complicated by ongoing growth, development, and maturation of the gut and its immune system as well as their interaction and adaptation to postnatal life including psychosocial influences, environmental and dietary factors, as well as establishment and changes in the microbiome. This concept of integrated activity across biological and psychosocial systems is one of the most fundamental that has arisen in the field of neurogastroenterology and reflected in the recognition and study of what is now referred to as the gut-brain-microbiota axis, which also incorporates the neuro-immune interactions that occur within the gut itself (Chaps. 4 and 5) [19]. Using the example of childhood functional abdominal pain disorders, Fig. 1.3 illustrates the putative role of the bio-psycho-social model and gut-brain-microbiota axis in the pathogenesis of disease.

Not only does disruption of these factors and their interactions contribute to symptoms, its integrated working

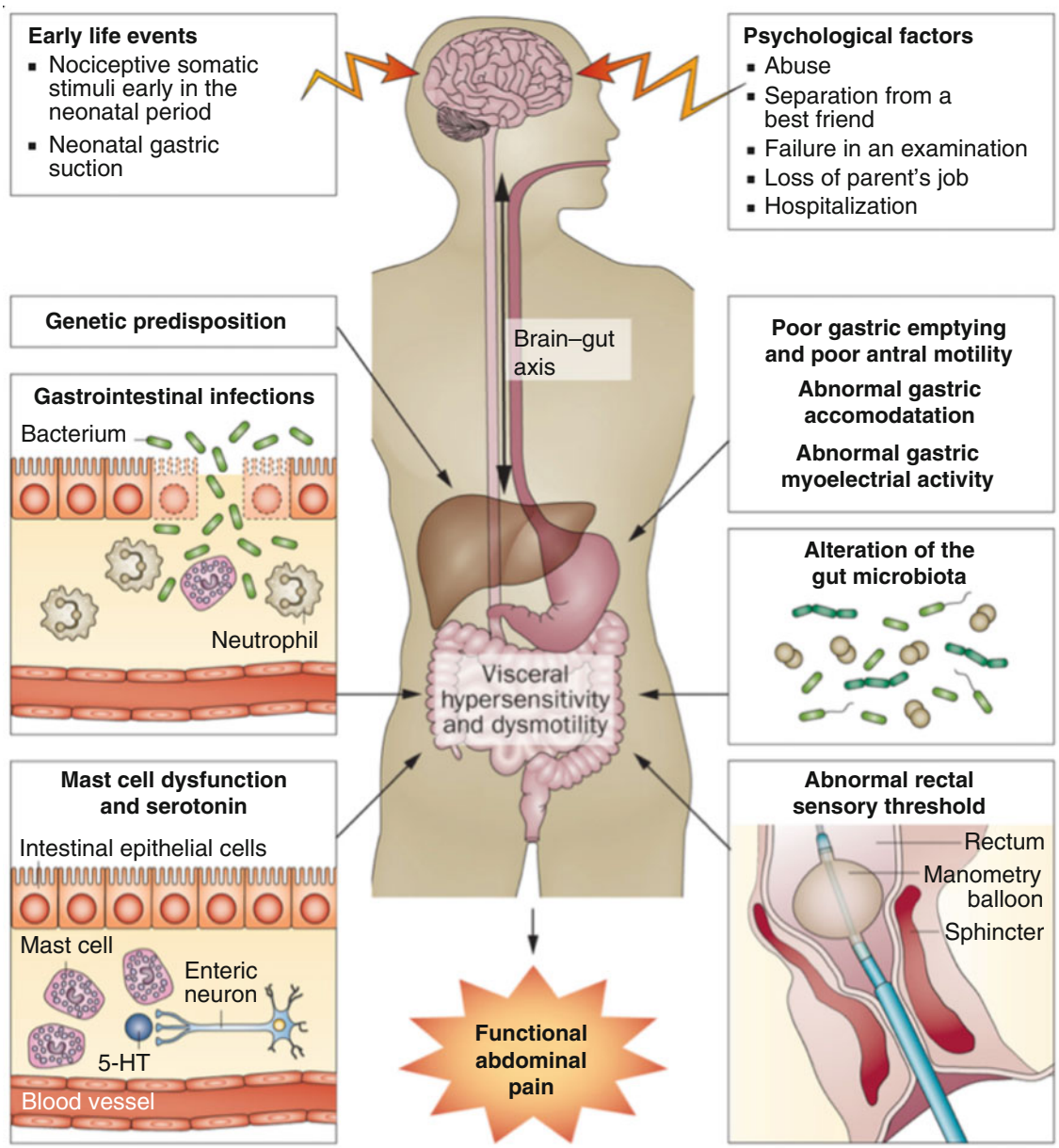

Fig. 1.3 Pathogenesis of childhood functional abdominal pain. Several risk factors are associated with changes in visceral hypersensitivity and motility and contribute to the development of functional abdominal pain. *Abbreviations*: *5-HT* 5-hydroxytryptamine, *FGID* functional gastrointestinal disorder (From Korterink J, Devanarayana NM, Rajindrajith S, et al. Childhood functional abdominal pain: mechanisms and management. *Nature Reviews Gastroenterology & Hepatology,* **12**, 159–171, 2015. Reprinted by permission from Macmillan Publishers Ltd.)

appears susceptible to being "programmed" especially at an early age to give rise to pathology later on in life. Of these, recurrent abdominal pain (Chaps. 36 through 38) appears to provide a key paradigm for such "programming" (Fig. 1.3). It follows, therefore, that there are an enormous range of potential etiopathogenic factors acting over a considerable time period of development that could result in gut motility disorders. This functionality is of course affected by noxious and genetic influences occurring during development that determine the structural and functional viability of its components.

Sensory Function and the Gastrointestinal Tract

Gut motility disorders are often seen as synonymous with dysfunction of motor activity of the GI tract. Certainly, the most severe disorders are predominated by disturbances or failure in propagation of luminal contents. It is clear, however, that sensory functions of the GI tract are similarly important and dysfunction often carries significant bearing on the ultimate impact of disease. Although particularly evident in functional GI disorders, sensory symptoms are present throughout the spectrum of GI motility disorders (Chap. 4).

Normally, most of the information originating from the GI tract does not reach the level of conscious perception and is processed in the brainstem. Other sensations such as hunger, fullness, satiety, bloating, and need to defecate that involve adapted behaviors do reach the cortex. As previously stated, extrinsic innervation of the GI tract is composed of vagal, spinal visceral (sympathetic), and sacral nerves. These nerves contain afferent (or sensory) fibers that transmit information from the viscera to the CNS and efferent fibers that transmit information from the CNS to the gut. At the level of the gastrointestinal tract, sensory neurons and entero-endocrine cells serve as transducers. The central processing of visceral sensitivity is complex and involves the somatosensory cortex which provides information about intensity and localization of the stimulus, the anterior cingulate cortex which mainly processes pain characteristics and cognitive aspects of the pain experience, the insula which integrates internal state of the organism, and the prefrontal cortex which is believed to play a key role in the integration of sensory information and in the affective aspect of the sensation. Therefore, it appears that, similar to motor disorders, visceral sensory disorders may result from multiple factors and are prone to be influenced by complex interactions with cognitive and behavioral components [20].

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