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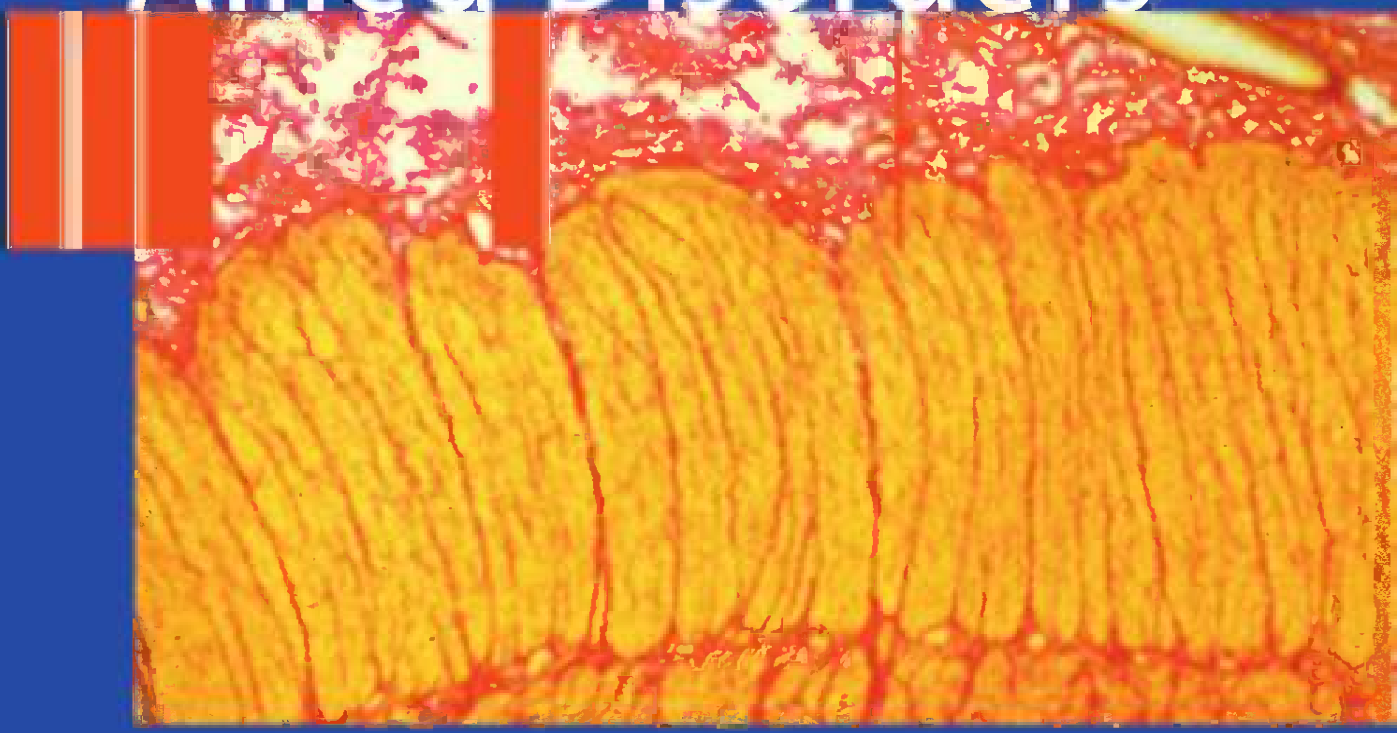
Editors

Hirschsprung's Disease and Allied Disorders



Third Edition

Springer

A. M. Holschneider · P. Puri (Eds.)

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Third Edition

With 318 Figures and 49 Tables

Springer

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Foreword

Drs. Holschneider and Puri have again given me the honor of writing the foreword to this magnificent new edition of their book.

This book will continue to be recognized as the most comprehensive and well-documented text ever written on this subject. This new edition expands the horizons of our knowledge of difficult and challenging conditions such as Hirschsprung's disease.

Dr. Grosfeld, a prestigious professor of pediatric surgery, was invited to write on the historical perspective of Hirschsprung's disease, and he has done so with a characteristically masterful style.

The chapter on the pathophysiology of Hirschsprung's disease is now written by Dr. Puri and Dr. Montedonico.

Dr. Moore has written a very interesting chapter on congenital anomalies and genetic associations in Hirschsprung's disease. The chapter on radiological diagnosis is now written by Dr. Kelleher.

This edition of the book characteristically continues to expand upon the genetic basis of the condition. Dr. Puri has been working in this particular area in the laboratory for many years, and we all grateful for his efforts and his contribution.

The chapter on immunohistochemical studies written by Dr. Rolle and and Dr. Puri summarizes the very exciting advances in this type of diagnosis.

An additional chapter by Dr. Milla on adynamic bowel syndrome expands our knowledge on the spectrum of motility disorders of the bowel and urinary tract.

Finally, Dr. Somme and Dr. Langer have written an additional chapter on the transanal pull-through procedure for the treatment of Hirschsprung's disease. There is no question that this new therapeutic approach represents a very important contribution to the treatment of this condition.

Again, we applaud the efforts of the editors in selecting a group of talented experts and innovators to contribute to what is still the best book on the subject.

Alberto Peña, MD

Preface

Hirschsprung's disease is one of the most important and most fascinating diseases in paediatric surgery. Our understanding of Hirschsprung's disease is developing rapidly, not only in relation to its pathophysiology and the development of new surgical techniques, but especially in relation to new genetic findings. A first comprehensive description of the pathophysiology, clinical symptoms, diagnosis and therapy of Hirschsprung's disease was outlined in 1970 by Theodor Ehrenpreis, Professor of Pediatric Surgery at the Karolinska Institute, Stockholm, Sweden, in a booklet entitled "Hirschsprung's Disease". The booklet of 176 pages was dedicated to Harald Hirschsprung (1830–1916) of Copenhagen, Denmark, and to Ovar Swenson of Chicago, Illinois, USA, the two pioneers in the study of Hirschsprung's disease. Harald Hirschsprung was a paediatrician, and Ovar Swenson a paediatric surgeon, who performed the first successful resection of an aganglionic bowel segment. That first book, published by Yearbook Medical Publishers, mainly discussed questions of postoperative continence based on the results of a large series of patients treated successfully at the Karolinska Institute.

In 1978 Ehrenpreis permitted one of the editors of the present edition to prepare an update of his internationally recognized book. Therefore, in 1982, a new book on Hirschsprung's disease by Alexander Holschneider was published by Hippokrates (Thieme-Stratton) with a foreword by Th. Ehrenpreis. It was a multiauthored textbook with particular prominence given to the results of an international clinical research study of the postoperative results in Hirschsprung's disease, undertaken from 1976 to 1978 by the author himself and a technical assistant, with special regard to the underlying surgical techniques. The follow-up studies were performed with the help of the Volkswagen Foundation in 16 paediatric surgical departments in Europe and the United States over a period of 3 years. The most interesting and unique aspect of this study was the fact that all clinical and electromanometrical investigations were performed by the same research team, independent of the staff of the individual hospital. As a result of this study concept, a most objective comparison of the results of Swenson's, Soave's, Duhamel's and Rehbein's techniques was achieved.

However, as our understanding of Hirschsprung's disease and associated motility disorders of the gut increased, a second edition of this book was published in 2000, this time by Harwood Academic Publishers, part of the Gordon and Breach Publishing Group. The title of this new book was changed to "Hirschsprung's Disease and Allied Disorders", because we included other enteric plexus disorders and smooth muscle disorders of the gut. The editors of this again multiauthored edition were Alexander Holschneider and Prem Puri. The book was divided into three parts: Physiology and Pathophysiology, Clinical Aspects, and Treatment and Results. As well as discussion of normal colonic motor function and the pathophysiology of classical Hirschsprung's disease, the book included special chapters on the development of the enteric nervous system, the functional anatomy of the enteric nervous system, animal models of aganglionosis, the molecular genetics of Hirschsprung's disease and the RET protein in human fetal development and in Hirschsprung's disease. New areas of special interest included intestinal neuronal dysplasia, particular forms of intestinal neuronal malformations, enterocolitis, megacystis-microcolon-intestinal hypoperistalsis syndrome, degenerative hollow visceral myopathy mimicking Hirschsprung's disease, and newer diagnostic techniques such as special neuronal markers, electron microscopy and anal sphincter achalasia. This second edition was the most comprehensive book ever published on Hirschsprung's disease and allied disorders.

With the passage of time, our understanding of enteric plexus disorders has exploded. Ehrenpreis in his preface of 1970 cited the President of the Swedish Nobel Prize Committee who stated that there are more scientists living today than during all past centuries. After having reviewed the recent literature on Hirschsprung's disease and allied disorders we are convinced that this is even more relevant today. Therefore, a new edition of Hirschsprung's disease and allied disorders was realized with the help of Springer. The previous chapters

"Clinical Generalities of Hirschsprung's Disease", "Disorders and Congenital Malformations associated with Hirschsprung's Disease", "Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome", "Degenerative Hollow Visceral Myopathy Mimicking Hirschsprung's Disease" and "Diagnosis of Hirschsprung's Disease and Allied Disorders" have been updated. A new separate chapter on "NAPDH-Diaphorase Histochemistry" has been introduced in the part "Diagnosis", next to the updated chapters "Histopathological Diagnosis and Differential Diagnosis of Hirschsprung's Disease", "Immunohistochemical Studies" and "Electron Microscopic Studies of Hirschsprung's Disease". For reasons of clarity, previously separated chapters such as the former chapters 5 and 6 "Molecular Genetics of Hirschsprung's Disease" and "Ret-Protein in Human Foetal Development and in Hirschsprung's Disease" have been brought together and concentrated in a new chapter. Chapter 3 "Functional Anatomy of the Enteric Nervous System" by M.D. Gershon and chapter 6 "Normal Colonic Motor Function and Relevant Structure" by J. Christensen have been reproduced. Chapter 12 "Particular Forms of Intestinal Neuronal Malformations" and chapter 14 "Megacolon in Adults" have become part of the new chapter 8 "Hirschsprung's Disease: Clinical Features" and chapter 18 "Neurocristopathies and Particular Associations with Hirschsprung's Disease". Chapter 17 "Intestinal Obstructions Mimicking Hirschsprung's Disease" has become chapter 21 "Adynamic Bowel Syndrome".

The chapters referring to the different surgical techniques have been updated too, but the concept of the previous editions, to compare the detailed description of one of the pioneer surgeons with the experience of a second author with the same technique, was given up. In the third edition of the book both parts of each chapter dealing with a specific surgical technique have been brought together to create new contributions for each of the different surgical approaches. The chapter "Laparoscopically Assisted Anorectal Pull-through" has been updated and a new chapter "Transanal Pull-through for Hirschsprung's Disease" has been introduced. Finally, the previous chapters dealing with early and late complications have also been brought together and the contribution of Teitelbaum and Coran on long-term results and quality of life has been updated.

The new edition is again a multiauthored book, and we have to thank all the internationally well-known authors and coauthors for their excellent and sophisticated contributions. It is their interest, help and effort that has again made possible the drawing together in one volume of the collective wisdom of many of the leading experts in Hirschsprung's disease and related disorders. Their contributions to this volume again provide a step forward in the elucidation of the genetic basis, and the correct diagnosis and treatment of this interesting disease and its allied disorders.

Besides the authors and coauthors, we would like to thank Mrs. Elisabeth Herschel of the Children's Hospital of Cologne, and the Children's Medical and Research Foundation, Our Lady's Children's Hospital, Dublin, for their support. Finally, we wish to thank the editorial staff of Springer, Heidelberg, Germany, particularly Ms. Gabriele Schroeder, for their interest and encouragement to publish a third edition of this book on a most important subject in paediatric surgery.

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1 Hirschsprung's Disease: A Historical Perspective — 1691–2005

J. L. Grosfeld

Hirschsprung's disease is a common cause of neonatal intestinal obstruction that is of great interest to pediatric surgeons throughout the world. Prior reports concerning the historical origins ascribe the initial description of this condition to Fredericus Ruysch, a Dutch anatomist in Amsterdam in 1691 [20, 33, 91, 137]. He described a 5-year-old girl with abdominal pain who did not respond to the "usual treatment of the day to relieve pain, pass wind and kill worms". She eventually died. The information regarding the patient was incomplete in regard to the events that occurred at the time of her birth and except for enormous dilatation of the colon, the autopsy findings were not clearly described. Although this may have represented a case of Hirschsprung's disease there was inadequate evidence to be sure of the actual diagnosis [33]. Similarly, Domenico Battini in Italy in 1800 described a child whom he followed for 10 years with severe constipation who eventually died and demonstrated severe colonic dilatation at autopsy consistent with, but not pathognomonic of, megacolon [39]. An additional report by Ebers in 1836 noted a 17-year-old boy with a history of constipation "since early youth" who died [33]. In 1869, Jacobi was the first to describe two newborn infants with intestinal obstruction that may have been attributable to congenital megacolon. One recovered after the administration of enemas; the other required a colostomy, that completely resolved the symptoms, but died of subsequent peritonitis [73]. No obstruction was found at autopsy and the colonic dilatation had disappeared.

Scattered reports concerning the autopsy findings in anecdotal cases of constipation in older children and adults that started at birth or early youth and progressed to intestinal obstruction appeared in the literature during the next 15 years [20, 33]. In 1884, Gee (as reported by Cass [20]) considered it possible, based on the findings of an autopsy of a 4-year-old child, that the condition was related to the presence of "spasm" of the sigmoid colon since the rectum was not involved in the typical dilatation and hypertrophy noted in his patient. In 1885, Bristowe described the course of an 8-year-old girl who died of intestinal obstruction after longstanding constipation. Her autopsy demonstrated dilatation of the colon and upper rectum that ceased abruptly 2 inches from the anus. No anal stricture or stenosis was observed [14]. This may have represented an instance of low segment Hirschsprung's disease.

While a number of other physicians reported instances of severe constipation and colon dilatation in children that eventually led to their demise, Harald Hirschsprung, a Danish pediatrician from Queen Louise Children's Hospital, Copenhagen, presented the most telling and concise description of congenital megacolon at the Society of Pediatrics in Berlin in 1886. His treatise was entitled "Constipation in newborns due to dilatation and hypertrophy of the colon" [33, 56]. At the time, he was unaware of the previous reports concerning the subject [33]. He presented the pathologic colon specimens and case reports of two infant boys who had symptoms of constipation soon after birth and who eventually died at 11 and 8 months, respectively. The first patient failed to pass stool at birth and required repeated enemas to relieve his obstruction. Constipation continued in the ensuing months despite breast feeding and was managed by laxatives. He was hospitalized for a 2-month period when he was 8 months old. Spontaneous bowel motions never occurred and the boy's abdomen was enormously distended. After a bowel motion was provoked, the distension decreased. Following discharge from the hospital he developed abdominal distension and frequent loose stools. He experienced rapid weight loss and was readmitted to the hospital and died the same day at 11 months of age. At autopsy, the sigmoid and transverse colon was enormously dilated and the muscle wall of the bowel was hypertrophied. The rectum was described as not being dilated and there was no site of narrowing. The second patient basically had the same presenting history of constipation from birth. He died at 8 months of age following the onset of severe abdominal distension and diarrhea (probably enterocolitis). At autopsy, the colon appeared similar to that of the first patient, but the appearance of the rectum was not described, although it was noted that the rectum was empty on digital examina-

tion. Hirschsprung's presentation was published in 1888 [56]. He neither offered a method of treatment nor proposed an etiology for this condition.

In 1898, Treves described a patient with idiopathic dilatation of the colon. He treated the patient with colon irrigations and performed a rectosigmoid resection and colostomy [171]. He documented the presence of a "narrow distal rectum" and presumed that this was the cause of the obstruction (a fact that went unrecognized for many years) [171]. A year later (1899), Griffith published a collective review of 55 similar cases in the literature [48]. In 1900, Fenwick attributed the findings in infants with hypertrophy and dilatation of the colon to "spasm of the anal sphincters" [38]. The same year, Lennander was the first to suggest a neurogenic origin for this condition. He observed megasigmoid in the absence of mechanical obstruction in a 4-year-old boy and interpreted the findings as due to "deficient innervation" and treated the boy successfully with faradic (electric) enemas [92]. In 1901, Tittel in Austria is credited with the first histologic study suggestive of Hirschsprung's disease noting sparse development of plexuses throughout the colon, but normal findings in the ileum [169]. Brentano corroborated these findings in a patient three years later [13].

In 1904 Hirschsprung described his personal experience with ten patients with this condition that he now referred to as "congenital dilatation of the colon". Nine of the ten patients were boys and five had died at the time of his report between 2 and 11 months of age. The other patients continued to have significant problems with constipation. The bowel was dilated and hypertrophied in each of the patients autopsied. There was no evidence of mechanical obstruction. The mucosa of the colon showed inflammatory changes and ulceration that Hirschsprung interpreted as the result of fecal retention. While he now considered the condition to be congenital in nature, he continued his fixation on the abnormally dilated and hypertrophied colon and still did not speculate on the etiology nor offer specific treatment. Hirschsprung's observations were published in 1904 as the first textbook chapter devoted to congenital dilatation of the colon in *Traite des maladies de l'enfance* (2nd edition) edited by Grancher and Comby. Shortly after, Hirschsprung retired from active practice because of cerebral stenosis and ultimately died in 1916 at 86 years of age.

Ehrenpreis indicated that Mya had actually originated the term megacolon congenita in 1894, and some years later the term Hirschsprung's disease was brought into use to describe the condition that Harald Hirschsprung so carefully described and brought into focus [33]. Although Hirschsprung was not a pediatric surgeon, in addition to his acclaim regarding congenital megacolon, he made other important contributions to the field of children's surgery in the areas of esophageal and intestinal atresia, pyloric stenosis and the non-operative management of intussusception [57, 58, 125, 170]. Interested readers are referred to additional publications concerning this unusual personality [12, 20, 40, 75, 93, 125, 134, 170].

With the world now more aware of this common condition, additional reports describing similar clinical findings began to appear in the literature. Many of these reports concerned adult patients with a short history of constipation and atypical or inadequate autopsy studies that likely had other diagnoses. In regard to surgical interventions, Perthes described transanal resection of the rectal folds and valves in 1905, and Finney in 1908 and Barington-Ward in 1915 reported "temporary success" following resection of the dilated bowel [6, 20, 33]. Patients continued to do poorly and the etiology of this condition remained elusive. In 1920, Dalla Valla shed new light on the subject when he reported the absence of ganglion cells in the sigmoid colon in two brothers who had normal ganglion cells in the proximal colon [24]. These observations were corroborated by Cameron 8 years later [15]. In 1923, Ishikawa noted the absence of parasympathetic nerves in the pelvic colon in a 4-year-old girl and he and others induced experimental megacolon in laboratory animals by resecting the parasympathetic nerves to the distal colon [1, 33, 70]. In 1927, Wade and Royle performed a lumbar sympathectomy to reduce sympathetic tone in the affected bowel in a patient who relapsed after a sigmoid resection [177]. Other reports appeared documenting the use of sympathectomy for this condition [2, 76, 126]. In the 1930s spinal anesthesia was also employed to treat the sympathetic hyperfunction that was presumed to be the cause of symptoms in patients with megacolon with some improvement noted [53]. In 1931, Irwin provided a careful description of Auerbach's plexus [69]. In the late 1930s and early 1940s clinical reports described some improvement in symptoms after administration of parasympathomimetic drugs to patients with megacolon [80]. In 1940, Tiffin and associates described local absence of ganglion cells in the myenteric plexus in a patient with congenital megacolon with ganglia present above and below the area in question [168].

Despite these observations, many authors including Ehrenpreis, refuted the evidence regarding sympathetic hyperfunction and for that matter any neurogenic disturbance as the cause of the disease [1, 32]. In 1943, Whitehouse et al. suggested that both medical and surgical attempts to ablate sympathetic tone were equally unsuccessful and recommended segmental resection of the dilated intestine as the most appropriate therapy [183]. In 1945, Grimson and colleagues similarly recommended a one-stage resection for "obstinate megacolon and ileosigmoidostomy" [49]. Ehrenpreis considered the loss of ganglion cells reported by others as a secondary event resulting from persistent colonic dilatation and stasis and in 1946, he defined Hirschsprung's disease as "a dysfunction of evacuation of the colon of as yet unknown origin,

occurring in the absence of morphological and mechanical causations giving rise secondarily to a characteristic dilatation of the colon" [32, 33].

Following the end of World War II in 1945, further light was shed on the subject that would dramatically change the course for children with Hirschsprung's disease. In 1948, Drs. Swenson, Neuhauser (a radiologist) and Pickett in Boston using a barium enema and fluoroscopy, recognized an area of spasm in the rectum or rectosigmoid that defined the site of obstruction in patients with congenital megacolon [155]. This established the barium enema as a useful diagnostic tool in Hirschsprung's disease. In six patients, Swenson and Bill performed a life-saving proximal colostomy that relieved obstructive symptoms. This improvement following colostomy was similar to the observations made by Jacobi in 1869 and Treves in 1898 [73, 154, 158, 171]. Closure of the colostomy in three of the infants resulted in recurrence of obstructive symptoms. These astute clinical observations led to the decision to resect the colon from a point proximal to the abnormal area of obstruction identified on the barium studies and the narrow distal rectum (now recognized as the site of physiologic obstruction) and perform a coloanal anastomosis above the dentate line to preserve continence. This was a historic landmark event, the first successful operative procedure for Hirschsprung's disease—the Swenson procedure [154]. The procedure was initially developed in the experimental surgical laboratory at Boston Children's Hospital and then applied in the clinical setting. The operation was undertaken based on careful clinical observations and thoughtful deduction ignoring the controversy at the time regarding the influence of bowel innervation and the presence or absence of ganglion cells in this disorder [155, 158, 159].

That same year, Zuelzer and Wilson described the autopsy findings in 11 infants who died of Hirschsprung's disease [193]. No mechanical cause of obstruction was noted. All 11 had absence of ganglion cells in the distal segment with six having a recognizable definitive level of obstruction. They suggested that Hirschsprung's disease was a functional intestinal obstruction that had a congenital neurogenic basis and that an enterostomy should be considered [193]. Also in 1948, Whitehouse and Kernohan described the autopsy findings in 11 children who died of megacolon [184]. None had ganglion cells present and nonmyelinated nerve trunks between the longitudinal and circular muscle layers were identified in the distal bowel. They noted variations in the length of the transition zone between the aganglionic distal rectum and when normal ganglion cells were noted proximally [184].

In 1949, Bodian et al. reviewed 73 patients who presented with findings consistent with congenital megacolon [7]. In 39 patients he confirmed the diagnosis of Hirschsprung's disease by recognizing the presence of a spastic segment in the rectosigmoid and noting absence of ganglion cells in the spastic distal segment. The 34 patients who did not fit these criteria were labeled as "idiopathic cases" [7]. These findings may explain the controversy noted in early reports concerning the presence or absence of ganglion cells, and finally separated patients with Hirschsprung's disease from those with other motility disturbances and causes of colonic dilatation. In 1951, Bodian reported the first instance of aganglionosis affecting the entire bowel from the duodenum to the rectum [8]. All of these studies reaffirmed the importance of Dalla Valla's original report in 1920 describing absence of ganglion cells [24]. In 1951, Hiatt performed manometric studies in patients with Hirschsprung's disease and confirmed that the abnormal distal segment was the area of obstruction. The rectum lacked peristaltic activity but showed mass contraction and there was loss of anorectal relaxation of the internal anal sphincter [55].

Although Swenson's operation now provided surgeons with a satisfactory method to treat Hirschsprung's disease, some considered this a tedious operation and the results were not quite as good in other people's hands. Alternative procedures were sought. In 1952, State (Minneapolis, Minnesota) described the use of a low anterior resection to manage this condition [151]. The operation left considerable residual aganglionic tissue in place frequently causing recurrence of symptoms and was ultimately abandoned. In 1953, Sandegard in Sweden reported the first successful operation in a patient with total colonic aganglionosis (TCA) by performing a total colectomy and an ileoanal anastomosis [138]. In 1956, Bernard Duhamel of St Denis, France, described the retrorectal transanal pull-though procedure for the treatment of Hirschsprung's disease [30]. This concept was developed to preserve the nerves to the bladder and nervi erigente and left the aganglionic rectum in place. The normal proximal bowel was brought down to the perineum through an incision 1.0 cm above the dentate line in the posterior rectal wall. Since that time numerous modifications have been employed to alter the location of the anal incision to preserve part of the internal anal sphincter to avoid incontinence and to ablate the residual blind aganglionic rectal pouch to avoid the development of an obstructing fecaloma.

In 1960, Grob in Zurich, Switzerland, used a different location for the posterior incision. He made the incision 2.0–2.5 cm above the pectinate line, but this resulted in constipation [50]. Pagès in Paris made the rectal incision 1.5 cm above the pectinate line to avoid incontinence and constipation [116]. A variety of clamps and subsequently stapling devices were employed to divide the colorectal spur comprising the posterior wall of the aganglionic rectal stump and the anterior wall of the normally innervated pull-through segment by Martin, Ikeda, Soper and Miller and Steichen et al. [67, 100, 101, 150, 152]. In 1958, Rehbein of Bremen, Germany, reported his experience with low anterior resection taking the anastomosis

down to 3–4 cm above the pectinate line [128]. This procedure was associated with an increased anastomotic leak rate and significant constipation, but is still used in some German-speaking countries.

In 1963, Soave of Genoa, Italy, described the endorectal pull-through procedure bringing the innervated bowel down to the perineum through a muscular sleeve of the aganglionic rectum [149]. Performing the mucosal stripping dissection within the muscle wall reduced the risk of injury to the nerves to the bladder and nervi erigentes. The original Soave procedure left the pulled through bowel segment extending from the anal opening. After a period to allow adherence of the bowel to the anal tissues, the protruding segment was resected [149]. The preservation of the muscular sleeve was not an original technique as it had been described by Hochenegg in Austria in 1898, and was used by Ravitch in an adult patient with a benign colonic conditions in 1948 [59, 127]. Similarly, Kiesewetter used the concept during repair of high anorectal malformations [78]. Pellerin in France (1962) and Cutait in Brazil (1965) modified the endorectal technique by performing a delayed anastomosis, and in 1964 Boley (New York) further modified the procedure by performing a primary anastomosis at the time of the pull-through procedure [10, 23, 119].

Recognizing that the barium enema was not always diagnostic particularly in the neonate, in 1959 Swenson et al. described the full-thickness rectal biopsy to obtain material for a tissue diagnosis [156]. Shandling reported his experience with a simple punch biopsy to obtain tissue in 1960 [144]. That same year, Gherardi noted that the level of aganglionosis was similar in the submucosal and myenteric plexuses [45]. Bodian was the first to use a submucosal biopsy for the diagnosis of Hirschsprung's disease [9]. In 1965 Dobbins and Bill employed a suction rectal biopsy instrument to obtain tissue for diagnosis [29]. This was successfully employed by Campbell and Noblett in 1969, and was modified by Noblett later that year using a special suction biopsy tube [16, 114]. In 1968, Meir-Ruge confirmed the effective use of submucosal rectal biopsy in Europe [103]. In the current era suction rectal biopsy remains the preferred technique used to diagnose Hirschsprung's disease particularly in neonates and infants [165].

During the same period other investigators evaluated the diagnostic efficacy of anorectal manometrics in infants with Hirschsprung's disease [90, 142, 143]. The techniques measures resting anal canal pressures and determines if the normal anorectal reflex resulting in relaxation of the sphincter is present when the rectum is distended. Loss of the anorectal response is interpreted as being consistent with Hirschsprung's disease [113]. These studies were inconsistent in premature infants and some neonates because of perceived immaturity of the anorectal response and limitations in equipment sensitivity in this age group [63, 71, 94]. However, additional studies using advanced semiconductor technology and miniature probes have demonstrated a normal anorectal reflex in premature and full-term neonates [162].

Despite the ability of clinicians to histologically diagnose Hirschsprung's disease by confirming the absence of ganglion cells on rectal biopsy, there remained a significant number of children with conditions that resembled aganglionic megacolon but who had ganglion cells present on their specimens. This was the condition that Bodian referred to as "idiopathic megacolon" in his observations on the histology of Hirschsprung's disease in 1949 [7]. In 1971, Meier-Ruge in Switzerland published his classic article describing colonic neuronal dysplasia [103, 104]. The following year he described the benefit of acetylcholinesterase staining of the hypertrophied nerve fibers in the lamina propria and muscularis in the diagnosis of Hirschsprung's disease [105]. Special staining techniques that were employed to identify instances of hypoganglionosis, immaturity of the submucosal and myenteric plexuses and anorectal achalasia became commonplace in evaluating conditions that mimicked Hirschsprung's disease [141, 142].

Over the next three decades, numerous articles appeared in the literature regarding intestinal neuronal dysplasia (IND). The condition seemed to be common in Europe, but was a rare entity on the North American continent. Puri and associates and Scharli were advocates of Meir-Ruge's observations regarding IND and reported series of cases with this condition and other variants of Hirschsprung's disease [122–124, 140, 141]. IND is divided into two subtypes, A and B, with the former being quite rare and the latter far more common and can be treated conservatively in most cases. Puri and colleagues noted that IND can coexist with Hirschsprung's disease and might be responsible for the persistence of motility disturbances seen in some patients following pull-through operations [122]. Controversy surrounds this condition regarding whether it is a distinct primary entity or a secondary phenomenon resulting from stasis or obstruction.

Recently, Meir-Ruge and colleagues (2004) have reported follow-up studies in patients with IND-B [106]. IND–B was identified in 6% of their patients with Hirschsprung's disease and 2.3% of other children evaluated for chronic constipation. The criteria for diagnosis were a rectal biopsy obtained 8–10 cm above the pectinate line in which 15–20% of the ganglia were giant-sized and there were more than eight nerve cells in 30 sections of the same biopsy [106]. He considered the findings consistent with delayed maturation of the enteric nervous system (ENS) and recommended conservative management up to 4 years of age. In contrast, the authors suggested that children with hypoganglionosis required surgical intervention [106]. The precise management of IND in association with Hirschsprung's disease remains unclear.

In regard to anal achalasia, in 1934, Hurst considered that this was related to parasympathetic underactivity [65]. Others suggested this was a manifestation of very low segment Hirschsprung's disease. Thomas (1967) and Holschneider et al. (1976) performed a posterior sphincterotomy and Thomas (1970) and Lynn and van Heerdon (1975) recommended a transanal posterior rectal myectomy for those with low-segment disease [64, 95, 166, 167]. In 1990, Neilson and Yazbeck described five children with "ultra-short segment Hirschsprung disease" [110]. Each of the children had loss of anorectal reflex relaxation on manometry but ganglion cells were found on rectal biopsy. They responded to posterior sphincterotomy [110]. In 1994, Krebs and Acuna noted that internal sphincter pressures initially are reduced following sphincter myotomy, but with time they return to above normal levels [82]. Currently, the diagnosis of anal achalasia requires both a rectal biopsy showing the presence of ganglion cells and absence of anorectal reflex relaxation on manometric studies [165]. Puri and Rolle suggested this condition is associated with nitrergic nerve depletion and can be treated with internal sphincter myectomy [124]. Prato and associates have reported the benefit of myectomy in anal achalasia using a posterior sagittal approach [121]. This approach is the author's personal preference as well.

As experience was obtained, it became clear that Hirschsprung's disease is more common in boys and in 80–85% of patients aganglionosis is limited to the rectum and rectosigmoid. However, in 10% of patients aganglionosis extends to more proximal areas of the colon, and in 5–8% TCA is noted with proximal extension of the aganglionic segment to various levels of the small intestine. As noted above, Bodian documented the first instance of aganglionosis of the entire bowel in 1951 [8]. Talwalker's review on the subject in 1976 identified 11 patients [160]. Sporadic reports have documented even more rare extension of aganglionosis to the stomach and esophagus [178]. In 1985, Caniano et al. described an additional patient and noted that no intestinal distension, evidence of bowel obstruction or transition zone could be detected at laparotomy. In addition, a review of similar patients in the literature indicated that 33% pass meconium at birth and 25% do not demonstrate hypertrophied nerve fibers on histologic study [18]. In 1986, Rudin et al. described three neonates with absence of the entire ENS and described 13 additional patients from the literature [136].

As noted above, Sandegard performed the first successful operative repair of TCA with colon resection and ileoanal anastomosis in 1953 [138]. The morbidity and mortality with TCA was greater than in those with the typical rectosigmoid involvement [60, 68, 153]. In an effort to improve the absorptive capacity of the colon, in 1968, Martin described a modification of the Duhamel procedure utilizing a side-to-side anastomosis to the aganglionic colon up to the level of the splenic flexure [98]. In 1981, Kimura used an aganglionic right colon patch inserted in the antimesenteric surface of the ileum to slow transit and improve absorption following ileostomy. The patch was left in place at the time of the pull-through procedure [79]. Boley used the left colon as a patch in 1984 [11]. In 1982, Martin further revised his procedure for TCA by using the entire aganglionic colon [99]. This latter procedure was associated with severe enterocolitis and has subsequently been abandoned by most pediatric surgeons [36, 37, 165, 187]. Most recent reports suggest that reasonably good results can be achieved in TCA affecting the distal ileum up to the mid-small bowel using a standard modification of the Duhamel procedure, endorectal pull-through or a Swenson operation [37, 111, 153, 159, 165, 187]. Rintala and Lindahl and Lal et al. have suggested that an ileoanal J pouch or S pouch may also be of benefit in these patients [85, 133].

The outlook for extension of aganglionosis into the more proximal small bowel remains guarded. These children essentially have short bowel syndrome and frequently require long-term support with total parenteral nutrition (TPN). Escobar et al. [37], Kimura [79], Kottmeier et al. [81] and Nishijima et al. [112] have found the aganglionic patch procedure beneficial in this subset of patients; however, iron deficiency anemia is a late complication. In 1987, Ziegler described the concept of myotomy/myectomy of aganglionic bowel for patients with near total aganglionosis (NTAG) with less than 40 cm of normally innervated small bowel [191]. The concept of myotomy in Hirschsprung's disease was first described by Martin-Burden in 1927 [33] using the procedure in the rectosigmoid, and by Kasai et al. in 1971 [77] who performed myotomy of the intact aganglionic rectal segment following proximal colon resection. In 1993, Ziegler et al. reported the outcomes of 16 myotomy/myectomies for NTAG that had been performed at multiple centers [192]. At the time, 10 of 16 patients were still alive; however, only two were enterally independent. They suggested that myectomized aganglionic bowel has the capacity to adapt and absorb nutrients, and that the procedure may be viewed as a bridge to intestinal transplantation [192]. In 2000, Saxton et al. described their experience with seven patients with NTAG of the bowel. Only two of the seven survived despite the use of myectomy and aganglionic patch procedures. These adjunctive procedures were associated with a high complication rate [139].

In the 1990s intestinal transplantation became an option in the management of patients with NTAG of the small intestine. Instances complicated by TPN-induced liver failure are candidates for combined liver and bowel transplantation. In 1995, Tzakis et al. from Dr. Starzl's group in Pittsburgh, described a 16-month-old girl with extensive aganglionosis who had a successful combined liver/bowel transplantation and a Soave endorectal pull-through using donor descending colon [172]. In 1998,

Reyes et al. found that 4 of 55 children undergoing small bowel transplantation had Hirschsprung's disease [131]. In 1999, Goulet et al. described preliminary experience with small-bowel transplantation at the Enfants Malades Hospital in Paris. Four of 20 patients had Hirschsprung's disease with aganglionosis extending to the proximal jejunum [47]. In 2003, Revillon et al. from the same institution, reported an improved quality of life in three children with extensive aganglionosis who underwent successful combined liver/bowel transplantation and a subsequent pull-through procedure (two had a Duhamel procedure; one a Swenson procedure) [130]. Also in 2003, Sharif et al. from Birmingham, UK, reported a successful outcome in four of five infants with extensive aganglionosis (between 10–50 cm of normal jejunum remaining) and TPN-related liver failure following combined liver/bowel transplantation in four and an isolated small-bowel graft in one [145]. The authors stressed preservation of the aganglionic bowel and avoidance of extensive enterectomy to preserve the size of the abdomen for subsequent graft insertion. At present this group is recommending transplantation in patients with NTAG and severe TPN-related liver disease [145]. The long-term outcomes of children with Hirschsprung's disease and NTAG who undergo organ transplantation will have to be further assessed over time.

One of the major complications observed in children with Hirschsprung's disease, both prior to and after a pull-through operation, is enterocolitis. This was probably the cause of the demise of both of the infants described by Hirschsprung in his original report in 1886, and continued to be a problematic cause of morbidity and mortality over the next century. Swenson was the first to key in on the significance of this complication in babies with Hirschsprung's disease [157]. Enterocolitis is likely the result of functional obstruction and stasis [17, 163, 165]. The reported incidence of enterocolitis varies considerably, but is in the range 14–40% depending on the diagnostic criteria used [52, 163]. Enterocolitis is associated with explosive diarrhea (70%), vomiting (50%), fever (34%) and lethargy (27%) [163]. The diarrhea is often associated with abdominal distension suggesting an obstructive cause. Acute inflammatory infiltrates have been noted in the anal crypts and colon mucosa that may lead to crypt abscesses and mucosal ulceration. The exact etiology is still unknown, but impaired mucosal defense mechanisms have been implicated with deficiency in secretory IgA, absence of mucin precursors and muc-2 gene [4,163, 188]. Although enterocolitis has been observed after all of the procedures used to treat Hirschsprung's disease, the incidence is higher after a Soave pull-through (presumably because of a tight anastomosis or snug aganglionic muscular cuff), in patients with TCA (especially after a long Martin modification of the Duhamel procedure), and in infants with Down syndrome probably related to immunologic factors. These observations led to further operative modifications such as division of the posterior muscular cuff in the Soave procedure and abandoning the long Martin modification of the Duhamel procedure.

Aside from the availability of intestinal transplantation as a treatment option, the 1990s and the first few years of the 21st century has been the era of continued technical modifications with a trend toward one-stage procedures earlier in life using advances in minimally invasive technology, employing the transanal approach and managing treatment failures. In addition, this has been a time characterized by significant advances in understanding the ENS in general and the genetic basis of Hirschsprung's disease in particular due to a veritable explosion of new information especially following the elucidation of the human genome.

In 1981, So and colleagues were the first to report a one-stage pull-through procedure in neonates with Hirschsprung's disease without a preliminary colostomy [148]. In 1982, Carcassone and associates from Marseilles similarly described a favorable experience with a one-stage procedure in the first 3 months of life [19]. These reports refuted Swenson's contention that a definitive procedure in early infancy is associated with an increased morbidity and mortality. The one-stage approach became increasingly popular in the 1990s [51, 88, 164]. Georgeson et al. described a laparoscopically assisted Soave endorectal pull-through procedure avoiding an open laparotomy [42]. He adapted this to a primary procedure in 1999 [43]. Successful application of the laparoscopic technique has also been reported by pediatric surgeons performing the Swenson procedure [22, 61, 83] and modified Duhamel operation [25, 46, 147, 173]. In 1993, Rinatala and Lindahl of Helsinki described a predominantly transanal pull-through operation but performed a laparotomy to mobilize the proximal colon [132]. In 1998, de la Torre-Mondregon and Ortega-Salgado of Mexico were the first to perform a one-stage totally transanal pull-through procedure [26]. Results with the transanal endorectal pull-through were favorable when compared to the open procedure [27]. Since then, the transanal operation has been used extensively in the neonatal period by Langer et al. [86], Albanese et al. [3] and Teitelbaum et al. [164]. Three multicenter studies in Europe [62], North America [89] and Egypt [34] have supported the use of this approach.

The Swenson, modified Duhamel and Soave endorectal pull-through procedures all give satisfactory results and each has its advocates and detractors [30, 36, 89, 116, 129, 149, 154, 158, 159, 165, 175]. Each of the procedures has required modification since their inception in attempts to deal with subsequent postoperative complications [10, 54, 79, 100, 101, 157, 165, 166, 176, 179, 191]. Although most patients do well over time, aside from the previously mentioned instances of enterocolitis and IND, there are a subset of patients who have other recurring problems [36,

165, 174]. These include instances of "acquired" aganglionosis following a pull-through performed with normally innervated proximal bowel. These problems are likely related to ischemia of the pull-through segment and respond to a second pull-through procedure [21, 28, 182]. Similarly, occasional poor outcomes related to persistent postoperative stricture or severe obstipation also require a re-do pull-through procedure [83, 87, 174, 181, 185]. Persistent stooling problems have been treated with partial internal sphincterotomy, rectal myotomy/myectomy, botulinum toxin injections and topical nitric oxide [36, 107, 108, 157, 186].

While the exact etiology of Hirschsprung's disease is still unknown, the last two decades have provided new insights into the complexities of this condition and its variants. Hirschsprung's disease has been observed to co-exist with anorectal malformations, ileal atresia, colon atresia, achalasia of the esophagus and the Currarino syndrome [5, 41, 66, 74, 78, 146, 180]. A better understanding of the ENS and the molecular genetic basis of this disorder has provided a wealth of new information. Since the early studies of Okamoto and Ueda [115] on the embryogenesis and migration of the intraneural ganglia of the gut in 1967, many investigators have focused on uncovering the mysteries surrounding the ENS through genomic analysis of ENS and neural crest development, and migration and colonization of enteric neurons. The association of Hirschsprung's disease with other neurocristopathies is linked to various genetic disturbances. These include instances of Ondine's curse (Congenital central hypoventilation syndrome; PHOX-2B), Waardenburg-Shah syndrome (SOX-10), Mowat-Wilson syndrome (ZFHX1B), Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, MEN-2A and B, neuroblastoma, and ganglioneuromatosis of the bowel [97, 109, 120, 161, 165, 190].

While early studies by Passarge [118] and Engum and Grosfeld [35] identified familial instances of Hirschsprung's disease, it was the elucidation of the human genome that opened the door to the genetic basis of the disease. Collaboration between basic scientists, medical geneticists and pediatric surgeons led the way to these discoveries. In 1992 Martucciello et al. of Genoa reported the association of TCA with interstitial deletion of the long arm of chromosome 10 [102]. This was confirmed in 1993 by Angrist et al. [96] and Yin et al. [189] who described the close linkage of the RET protooncogene in autosomal dominant Hirschsprung's disease and by Pasini et al. in 1995 [117]. Mutations were identified in 50% of the patients from families with Hirschsprung's disease. Romeo et al. in 1994 identified point mutations affecting the tyrosine kinase domain of the RET protooncogene [135]. That same year Edery et al. [31] reported that loss of function of the RET protooncogene led to Hirschsprung's disease, whereas gain of RET function led to MEN-2B. Additional studies have uncovered genetic linkages involved in the development of the ENS. Most belong to the RET and endothelin signaling pathways. In 1995 Gershon demonstrated that endothelin and the endothelin-B receptor are necessary for the development of the ENS in the colon [44]. In 1997, Kusafuka et al. identified mutations in endothelin-B and endothelin-B receptor in isolated cases of Hirschsprung's disease [84]. Iwashita et al. noted that the glial cell line-derived neurotropic factor receptor (GDNF) RET is necessary for neural crest stem cell migration in the gut [72]. Gene expression profiling, reverse genetics and analysis of stem cell function have implicated neural crest stem cell function as the likely cause of Hirschsprung's disease [72]. These studies suggest that Hirschsprung's disease is a genetically complex and heterogeneous inborn error of neural crest cell development that may involve a number of mutations affecting different genes and signaling pathways and other biologic and molecular factors yet to be determined.

Since the clinical presentations by Harald Hirschsprung in Berlin in 1886, the condition that bears his name has had a rich history. The seminal events that influenced progress in the understanding and management of this complex congenital disorder have been briefly covered in this historical review. More than 100 years ago, the condition was considered incurable and uniformly fatal over time [20, 33]. Mortality rates continued to be high in the 1940s (70%) and remained high even in the 1970s (25%). By the 1990s more than 90% of patients survived [129]. At the time of writing (2005) the survival in most advanced medical environments is greater than 95% [165]. While mortality has improved, there remains much to be learned. Why some patients with Hirschsprung's disease do poorly following operative repair remains an enigma. Similarly, the proper management of many patients with variants of Hirschsprung's disease needs to be more clearly elucidated. Continued study of the ENS and the molecular genetics of these conditions may shed further light on these issues and provide a better understanding of the choice of management in the future for affected children.

Most of the early major contributors to the care of infants and children with Hirschsprung's disease are recognized herein posthumously with the exception of Dr. Orvar Swenson who is currently 98 years of age. He and his wife Melva reside in Charleston, South Carolina. Dr. Swenson remains alert and well and continues to publish his views regarding Hirschsprung's disease with the same fervor and passion that led to the performance of the first successful operation for this condition 59 years ago [154, 158, 159]. Similarly, Dr. Lester Martin is 82 years of age, in good health, living with his wife Joan in Washington Courthouse, Ohio, 43 years following his important modifications of Duhamel's retrorectal pull-through procedure [100, 101]. Space limitations prevent individual mention of many other deserving physicians who have made significant contributions to the care of children with Hirschsprung's disease.

References

1. Adamson WAD, Aird I (1932) Megacolon: evidence in favor of a neurogenic origin. Br J Surg 20:220–223
2. Adson A (1937) Hirschsprung's disease: indications for and results obtained by sympathectomy. Surgery 1:859–877
3. Albanese CT, Jennings RW, Smith B, Bratton B, Harrison MR (1999) Perineal one-stage pull-through for Hirschsprung's disease. J Pediatr Surg 34:377–380
4. Aslam A, Spicer RD, Corfield AP (1998) Turnover of radioactive mucin precursors inn the colon of patients with Hirschsprung's disease correlates with the development of enterocolitis. J Pediatr Surg 33:103–105
5. Baltogiannis N, Mavridis G, Soutis M, Keramidas D (2003) Currarino syndrome associated with Hirschsprung's disease. J Pediatr Surg 38:1086–1089
6. Barington-Ward LE (1915) Colectomy for Hirschsprung's disease. Br J Surg 2:655
7. Bodian M, et al (1949) Hirschsprung's disease and idiopathic megacolon. Lancet 1:6–11
8. Bodian M, et al (1951) Hirschsprung's disease. Lancet 1:32
9. Bodian M (1960) Pathological aids in the diagnosis and management of Hirschsprung's disease. In: Recent advances in clinical pathology. Churchill Livingstone, London
10. Boley SJ (1964) New modification of the surgical treatment of Hirschsprung's disease. Surgery 56:1015–1017
11. Boley SJ (1984) A new operative approach to total colonic aganglionosis. Surg Gynecol Obstet 159:481–484
12. Breathnach CS (1987) Biographical sketches. Hirschsprung. Ir Med J 80:437
13. Brentano A (1904) Uber einen Fall von Hirschsprungscher Krankheit. Verh Dtsch Ges Chir 1:265–268
14. Bristowe JS (1885) The consequences of long continued constipation. BMJ 1:1085–1088
15. Cameron JAM (1928) On the etiology of Hirschsprung's disease. Arch Dis Child 3:210–211
16. Campbell PE, Noblett HR (1969) Experience with rectal suction biopsy in the diagnosis of Hirschsprung's disease. J Pediatr Surg 4:410–415
17. Caneiro P, Brereton R, Drake D, et al (1992) Enterocolitis in Hirschsprung's disease. Pediatr Surg Int 7:356–360
18. Caniano D, Ormsbee HS 3rd, Polito W, Sun CC, Barone FC, Hill JL (1985) Total intestinal aganglionosis. J Pediatr Surg 20:456–460
19. Carcassonne M, Morisson-Lacombe G, Letourneau JN (1982) Primary corrective operation without decompression in infants less than three months of age with Hirschsprung's disease. J Pediatr Surg 17:241–243
20. Cass D (1986) Hirschsprung's disease: an historical review. Prog Pediatr Surg 20:199–214
21. Cohen, Moore SW, Neveling U, Kaschula RO (1993) Acquired Hirschsprung's disease: a report of five cases during a 33 year experience with pull through procedures. Histopathology 22:163–168
22. Curran TJ, Raffensperger JG (1996) Laparoscopic Swenson pull-through: a comparison with the open procedure. J Pediatr Surg 31:1155–1156
23. Cutait DE (1965) Technique of rectosigmoidectomy for megacolon. Dis Colon Rectum 151:107–114
24. Dalla Valla A (1920) Richerche istologiche su di un caso di megacolon congenito. Pediatria 28:740–752
25. de Lagausie P, Berrebi D, Geib G, Sebag G, Aigrain Y (1999) Laparoscopic Duhamel procedure: management of 30 cases. Surg Endosc 13:972–974
26. de la Torre-Mondregon L, Ortega-Salgado JA (1998) Transanal endorectal pull-through for Hirschsprung's disease. J Pediatr Surg 33:1283–1286
27. de la Torre-Mondregon L, Ortega-Salgado JA (2000) Transanal vs. open endorectal colon pull-through for Hirschsprung's disease. J Pediatr Surg 35:1630–1632
28. Dimler M (1981) Acquired Hirschsprung's disease. J Pediatr Surg 16:844–845
29. Dobbins WO, Bill AH (1965) Diagnosis of Hirschsprung's disease excluded by rectal suction biopsy. New Engl J Med 272:990–993
30. Duhamel B (1956) Une nouvelle operation pan le megacolon congenital l'abaisement retrorectal et transanal du colon of san application possible au traitement de quelques autres malformation. Presse Med 64:2249–2250
31. Edery P, Lyonnet S, Mulligan LM, Pelet A, Dow E, Abel L, Holder S, Nihoul-Fekete C, Ponder BA, Munnich A (1994) Mutations of the RET proto-oncogene in Hirschsprung's disease. Nature 367:378–380
32. Ehrenpreis Th (1946) Megacolon in the newborn. A clinical and roentgenological study with special regard to the pathogenesis. Acta Chir Scand [Suppl] 94:112
33. Ehrenpreis T (1970) Hirschsprung's disease. Year Book Medical Publishers, Chicago
34. Elhalaby EA, Hashish A, Elbarbary MM, Soliman HA, Wishahy MK, Elkholy A, Abdelhay S, Elbehery M, Halawa N, Gobran T, Shehata S, Elkhouly N, Hamza AF (2004) Transanal one-stage endorectal pullthrough for Hirschsprung's disease: a multicenter study. J Pediatr Surg 39:345–351
35. Engum SA, Grosfeld JL (2004) Long-term results of treatment of Hirschsprung's disease. Semin Pediatr Surg 13:273–285
36. Engum SA, Petrites M, Rescorla FJ, Grosfeld JL, Morrison AM, Engles D (1993) Familial Hirschsprung's disease: 20 cases in 12 kindreds. J Pediatr Surg 28:1286–1290
37. Escobar MA, Grosfeld JL, West KW, Scherer LR, Rouse TM, Engum SA, Rescorla FJ (2005) Long-term outcomes in total colonic aganglionosis: a 32-year experience. J Pediatr Surg 40:955–961
38. Fenwick W (1900) Hypertrophy and dilatation of the colon in infants. BMJ 2:564–567
39. Fiori MG (1998) Domenico Battini and his description of congenital megacolon: a detailed case report one century before Hirschsprung. J Periph Nerv Syst 3:197–206
40. Frenckner B (1983) The man behind the syndrome: Harald Hirschsprung. A pioneer in pediatric research — a popular clinician but less valued lecturer. Lakartidningen 80:4664–4665
41. Gauderer MW, Rothstein FC, Izant RJ Jr (1984) Ileal atresia with long segment Hirschsprung disease in a neonate. J Pediatr Surg 19:15–17
42. Georgeson KE, Fuenfer MM, Hardin WD (1995) Primary laparoscopic pullthrough for Hirschsprung's disease in infants and children. J Pediatr Surg 30:1017–1022

43. Georgeson KE, Cohen RD, Hebra A, Jona JZ, Powell DM, Rothenberg SS, Tagge EP (1999) Primary laparoscopic-assisted endorectal colon pull through for Hirschsprung's disease: a new gold standard. Ann Surg 229:678–682
44. Gershon M (1995) Neural crest development: do developing enteric neurons need endothelin? Curr Biol 1:601–604
45. Gherardi GJ (1960) Pathology of the ganglionic-aganglionic junction in congenital megacolon. Arch Pathol 69:520–523
46. Goh DW, Ford WD, Little KE (1995) Primary neonatal Duhamel procedure using the ENDO GIA stapler. Aust N Z J Surg 65:120–121
47. Goulet O, Jan D, Lacaille F, Colomb V, Michel JL, Damotte D, Jouvet P, Brousse N, Faure C, Cezard JP, Sarnacki S, Peuchmaur M, Hubert P, Ricour C, Revillon Y (1999) Intestinal transplantation in children: preliminary experience in Paris. JPEN J Parenter Enteral Nutr 23 [5 Suppl]:S121–125
48. Griffith C (1899) Congenital idiopathic dilatation of the colon. Am J Med Sci 118:283
49. Grimson KS, Vandergrift L, Datz HM (1945) Surgery in obstinate megacolon: one stage resection and ileosigmoidostomy. Surg Gynecol Obstet 80:164
50. Grob M (1960) Intestinal obstruction in the newborn infant. Arch Dis Child 35:40–50
51. Hackam DJ, Superina RA, Pearl RH (1997) Single stage repair of Hirschsprung's disease: a comparison of 109 patients over five years. J Pediatr Surg 32:1028–1031
52. Hackam DJ, Filler RM, Pearl RH (1998) Enterocolitis after the surgical treatment of Hirschsprung's disease: factors and financial impact. J Pediatr Surg 33:830–833
53. Hawksley M (1943/1944) Spinal anaesthesia in the treatment of Hirschsprung's disease. With reports of 12 cases. Br J Surg 31:245–253
54. Hedlund H (1997) Posterior sagittal resection for rectal aganglionosis: preliminary results of a new approach. J Pediatr Surg 32:1717–1720
55. Hiatt RB (1951) The pathological physiology of congenital megacolon . Ann Surg 133:313–320
56. Hirschsprung H (1888) Struhltragheit Neugeborener in folge von Dilatation and Hypertrophie des colons. Jahrbuch Kinderheilkunde 27:1–7
57. Hirschsprung H (1895) Tilfaelde af medfodt Tillukning af Spiseroret. Hospitalstidende 38:1037–1041
58. Hirschsprung H (1901) Stenosis pylori congenital. Hospitalstidende 44:1169–1175
59. Hochenegg J (1898) Beitrage zur Chirurgie des rectum und der Beckenorgane. Wien Klin Wochenschr 2:515
60. Hoehner JC, Ein SH, Shandling B, Kim PC (1998) Long-term morbidity in total colonic aganglionosis. J Pediatr Surg 33:961–965
61. Hoffmann K, Schier F, Waldschmidt J (1996) Laparoscopic Swenson's procedure in children. Eur J Pediatr Surg 6:15–17
62. Hollwarth ME, Rivosecchi M, Schleef J, Deluggi S, Fasching G, Ceriati E, Ciprandi G, DePeppo F (2002) The role of transanal endorectal pull through in the treatment of Hirschsprung's disease: a multicenter study. Pediatr Surg Int 18:344–346
63. Holschneider AM, Kellner E, Streibl P, Sippell WG (1976) The development of anorectal continence and its significance in the diagnosis of Hirschsprung's disease. J Pediatr Surg 11:151–156
64. Holschneider AM, Shauer A, Meister P (1976) Results of sphincteromyotomy in anal-sphincter achalasia. Histology and postoperative continence (in German). Chirurg 47:294–300
65. Hurst AF (1934) Anal achalasia and megacolon (Hirschsprung's disease: idiopathic dilatation of the colon. Guys Hosp Rep 84:317–350
66. Hyde G Jr, de Lorimier AA (1968) Colon atresia and Hirschsprung's disease. Surgery 64:976–978
67. Ikeda K (1967) New technique in the surgical treatment of Hirschsprung's disease. Surgery 61:503–508
68. Ikeda K, Goto S (1986) Total colonic aganglionosis with or without small bowel involvement : an analysis of 137 patients. J Pediatr Surg 21:319–322
69. Irwin DA (1931) The anatomy of Auerbach's plexus. Am J Anat 49:141
70. Ishikawa N (1923) Experimentelle und klinische Untersuchungen uber die Pathogenese und das Wesen des megacolons. Mitt med Fak kaiserl, Kyushu Univ 7:339
71. Ito Y, Donahoe PK, Hendren WH (1977) Maturation of the rectoanal response in premature and perinatal infants. J Pediatr Surg 12:477–481
72. Iwashita T, Kruger GM, Pardal R, Kiel MJ, Morrison SJ (2003) Hirschsprung disease is linked to defects in neural crest stem cell function. Science 301:972–976
73. Jacobi A (1869) On some important causes of constipation in infants. Am J Obstet 2:96
74. Janik JP, Wayne ER, Janik JS, Price MR (1997) Ileal atresia with total colonic aganglionosis. J Pediatr Surg 32:1502–1503
75. Jay V (2001) The legacy of Harald Hirschsprung. Pediatr Dev Pathol 4:203–204
76. Judd ES, Adson AW (1928) Lumbar sympathetic ganglionectomy and ramisection for congenital idiopathic dilatation of the colon. Ann Surg 88:479–498
77. Kasai M, Suzuki H, Watanabe K (1971) Rectal myotomy with colectomy: a new radical operation for Hirschsprung's disease. J Pediatr Surg 6:36–41
78. Kiesewetter WB, Sukarochana K, Sieber WK (1965) The frequency of aganglionosis in association with imperforate anus. Surgery 58:877–880
79. Kimura K (1981) A new surgical approach to extensive aganglionosis. J Pediatr Surg 16:840–849
80. Klingmann W (1938) The treatment of neurogenic megacolon with selective drugs. J Pediatr 13:805
81. Kottmeier PK, Jongco B, Velcek FT, Friedman A, Klotz DH (1981) Absorptive function of the aganglionic ileum. J Pediatr Surg 16:275–278
82. Krebs C, Acuna R (1994) Transanal internal sphincter myomectomy: indications, operative procedure and results. Eur J Pediatr Surg 4:151–157
83. Kumar R, Mackay A, Borzi P (2003) Laparoscopic Swenson procedure—an optimal approach for both primary and secondary pull through for Hirschsprung's disease. J Pediatr Surg 38:1440–1443

84. Kusafuka T, Wang Y, Puri P (1997) Mutation analysis of the RET, the endothelin-B receptor, and the endothelin-3 genes in sporadic cases of Hirschsprung's disease. J Pediatr Surg 32:501–504
85. Lal DR, Nichol PF, Harms BA, Go LL, Lund DP (2004) Ileoanal S-pouch reconstruction in patients with total colonic aganglionosis after failed pull-through procedure. J Pediatr Surg 39:e7–9
86. Langer JC (1999) Repeat pull-through surgery for complicated Hirschsprung's disease: indications, technique and results. J Pediatr Surg 34:1136–1141
87. Langer JC, Fitzgerald PG, Winthrop AL, Srinathan SK, Foglia RP, Skinner MA, Ternberg JL, Lau GY (1996) One-stage versus two-stage Soave pull-through for Hirschsprung's disease in the first year of life. J Pediatr Surg 31:33–36
88. Langer JC, Minkes RK, Mazziotti MV, Skinner MA, Winthrop AL (1999) Transanal one-stage Soave procedure for infants with Hirschsprung's disease. J Pediatr Surg 34:148–151
89. Langer JC, Durrant AC, de la Torre L, Teitelbaum DH, Minkes RK, Caty MG, Wildhaber BE, Ortega SJ, Hirose S, Albanese CT (2003) One-stage transanal Soave pull-through for Hirschsprung's disease: a multicenter experience with 141 cases. Ann Surg 238:569–576
90. Lawson JON, Nixon HH (1967) Anal canal-pressure in the diagnosis of Hirschsprung disease. J Pediatr Surg 2:544–552
91. Leenders E, Sieber WK (1970) Congenital megacolon, observation by Frederici Ruysch 1691. J Pediatr Surg 5:1–3
92. Lennander KG (1900) Fall av medfodd (?) dilatation och hypertrofi av flexura simoides hos ett barn (malade de Hirschsprung?). Nord Med Ark 11:1
93. Lister J (1977) Hirschsprung: the man and the disease. J R Coll Surg Edinb 22:377–384
94. Loening-Bauke VA (1983) Anorectal manometry: experience with strain gauge pressure transducers for the diagnosis of Hirschsprung's disease. J Pediatr Surg 18:595–600
95. Lynn H, van Heerdon J (1975) Rectal myectomy in Hirschsprung's disease: a decade of experience. Arch Surg 110:991–994
96. Lyonnet S, Bolino A, Pelet A, et al (1993) A gene for Hirschsprung's disease maps to the proximal long arm of chromosome 10. Nat Genet 4:346–350
97. Maris JM, Chatten J, Meadows AT, Biegel JA, Brodeur GM (1997) Familial neuroblastoma: a three-generation pedigree and a further association with Hirschsprung disease. Med Pediatr Oncol 28:1–5
98. Martin LW (1968) Surgical management of Hirschsprung's disease involving the small intestine. Arch Surg 97:183–189
99. Martin LW (1982) Total colonic aganglionosis preservation and utilization of entire colon. J Pediatr Surg 17:635–637
100. Martin LW, Altemeier WA (1962) Clinical experience with a new operation (modified Duhamel procedure) for Hirschsprung's disease. Ann Surg 156:678–681
101. Martin LW, Caudill DR (1967) A method of elimination of the blind rectal pouch in the Duhamel operation for Hirschsprung's disease. Surgery 62:951
102. Martucciello G, Biocchi M, Dodero P, et al (1992) Total colonic aganglionosis associated with interstitial deletion of the long arm of chromosome 10. Pediatr Surg Int 7:308–310
103. Meier-Ruge W (1971) Causistic of colon disorder with symptoms of Hirschsprung's disease. Verh Dtsch Ges Pathol 35:506–510
104. Meier-Ruge W, Morger R (1968) Neve Gesichtspunkle zur pathogenese und klinik des morbus Hirschsprung. Schweitz Med Wochenschr 98:209
105. Meier-Ruge W, Lutterbeck PM, Herzog B, Morger R, Moser R, Scharli A (1972) Acetylcholinesterase activity in suction biopsies of the rectum in the diagnosis of Hirschsprung's disease. J Pediatr Surg 7:11–17
106. Meier-Ruge WA, Ammann K, Bruder E, Holschneider AM, Scharli AF, Schmittenbecher PP, Stoss F (2004) Updated results on intestinal neuronal dysplasia (IND B). Eur J Pediatr Surg 14:384–391
107. Millar AJ, Steinberg RM, Raad J, Rode H (2002) Anal achalasia after pull-through operations for Hirschsprung's disease – preliminary experience with topical nitric oxide. Eur J Pediatr Surg 12:207–211
108. Minkes RK, Langer JC (2000) A prospective study of botulinum toxin for internal anal sphincter hypertonicity in children with Hirschsprung's disease. J Pediatr Surg 35:1733–1736
109. Mowat DR, Wilson MJ, Goossens M (2003) Mowat-Wilson syndrome. J Med Genet 40:305–310
110. Neilson M, Yazbeck S (1990) Ultrashort Hirschsprung's disease: myth or reality. J Pediatr Surg 25:1135–1138
111. N-Fekete C, Ricour C, Martelli H, Jacob SL, Pellerin D (1986) Total colonic aganglionosis (with or without ileal involvement): a review of 27 cases. J Pediatr Surg 21:251–254
112. Nishijima E, Kimura K, Tsugawa C, Muraji T (1998) The colon patch graft procedure for extensive aganglionosis: long-term follow-up. J Pediatr Surg 33:215–219
113. Nixon HH (1972) Problems in the diagnosis of Hirschsprung's disease. Paediatr Paedol [Suppl] 2:21
114. Noblett H (1969) A rectal suction biopsy tube for use in the diagnosis of Hirschsprung's disease. J Pediatr Surg 4:406–409
115. Okamoto E, Ueda T (1967) Embryogenesis of the intraneural ganglia of the gut and its relation to Hirschsprung's disease. J Pediatr Surg 2:437–443
116. Pagès R (1969) Maladie Hirschsprung. In: Patel J, Leger L (eds) Nouveau traite de technique chirurgicale. Maison et cie, Paris, pp 636–652
117. Pasini B, Borrello MG, Greco A, Bongarzone I, Luo Y, Mondellini P, Alberti L, Miranda C, Arighi E, Bocciardi R, et al (1995) Loss of function effect of RET mutations causing Hirschsprung disease. Nat Genet 10:35–40
118. Passarge E (1967) The genetics of Hirschsprung's disease — evidence for heterogeneous etiology and a study of 63 families. New Engl J Med 276:138–143
119. Pellerin D (1962) The surgical treatment of Hirschsprung's disease by resection and exterior anastomosis. J Int Coll Surg 37:591–593

120. Pingault V, Bondurand N, Kuhlbrodt K, Goerich DE, Prehu MO, Puliti A, Herbarth B, Hermans-Borgmeyer I, Legius E, Matthijs G, Amiel J, Lyonnet S, Ceccherini I, Romeo G, Smith JC, Read AP, Wegner M, Goossens M (1998) SOX10 mutations in patients with Waardenburg-Hirschsprung disease. Nat Genet 18:171–173
121. Pini Prato A, Martucciello G, Torre M, Jasonni V (2004) Feasibility of perineal sagittal approaches in patients without anorectal malformations. Pediatr Surg Int 20:762–7
122. Puri P (2003) Intestinal neuronal dysplasia. Semin Pediatr Surg 12:259–264
123. Puri P, Rolle U (2004) Variant Hirschsprung's disease. Semin Pediatr Surg 13:293–299
124. Puri P, Lake BD, Nixon HH, Mishalany H, Claireaux AE (1977) Neuronal colonic dysplasia: an unusual association of Hirschsprung's disease. J Pediatr Surg 12:681–685
125. Raffensperger JG (1987) Hirschsprung's disease: an historical review. Bull Soc Sci Med Grand Duche Luxemb 124(Spec):31–36
126. Rankin FW, Learmouth JR (1930) Section of sympathetic nerves of the distal part of the colon and rectum in the treatment of Hirschsprung's disease and certain types of constipation. Ann Surg 92:710
127 Ravitch MM (1948) Anal ileostomy with sphincter preservation in patients requiring total colectomy for benign conditions. Surgery 24:170
128. Rehbein F (1958) Intraabdominalle Resektion oder rectosigmoidektomie (Swenson) bei der Hirschsprungschen Krankheit? Chirurg 29:366–369
129. Rescorla FJ, Morrison AM, Engles D, West KW, Grosfeld JL (1992) Hirschsprung's disease: Evaluation of mortality and long-term function in 260 cases. Arch Surg 127:934–941
130. Revillon Y, Yves A, Dominique J, Thierry Y, Olivier G, Florence L (2003) Improved quality of life by combined transplantation in Hirschsprung's disease with a very long aganglionic segment. J Pediatr Surg 38:422–424
131. Reyes J, Bueno J, Kocoshis S, Green M, Abu-Elmagd K, Furukawa H, Barksdale EM, Strom S, Fung JJ, Todo S, Irish W, Starzl TE (1998) Current status of intestinal transplantation in children. J Pediatr Surg 33:243–254
132. Rintala R, Lindahl H (1993) Transanal endorectal coloanal anastomosis for Hirschsprung's disease. Pediatr Surg Int 8:128–131
133. Rintala RJ, Lindahl HG (2002) Proctocolectomy and J-pouch ileo-anal anastomosis in children. J Pediatr Surg 37:66–70
134. Roed-Peterson K, Erichsen G (1988) The Danish pediatrician Harald Hirschsprung. Surg Gynecol Obstet 166:181–185
135. Romeo G, Ronchetto P, Luo Y, Barone V, Seri M, Ceccherini I, Pasini B, Bocciardi R, Lerone M, Kaariainen H, et al (1994) Point mutations affecting tyrosine kinase domain of the RET proto-oncogene in Hirschsprung patients. Nature 367:377–378
136. Rudin C, Jenny P, Ohnacker H, Heitz PU (1986) Absence of the enteric nervous system in the newborn: presentation of three patients and review of the literature. J Pediatr Surg 21:313–318
137. Ruysch F (1691) Observationum anatomico-chirurgicarum centuria. Amstelodami
138. Sandegard E (1953) Hirschsprung's disease with ganglion cell aplasia of the colon and terminal ileum. Report of a case treated with total colectomy and ileoanostomy. Acta Surg Scand 106:367–376
139. Saxton ML, Ein SH, Hoehner J, Kim PC (2000) Near-total intestinal aganglionosis: long-term follow-up of a morbid condition. J Pediatr Surg 35:669–672
140. Scharli A, Meir-Ruge W (1981) Localized and disseminated forms of neuronal intestinal dysplasia mimicking Hirschsprung's disease. J Pediatr Surg 16:164–70
141. Scharli AF, Sossai R (1998) Hypoganglionosis. Semin Pediatr Surg 7:187–191
142. Schnaufer L, Talbert JL, Haller JA, Reid NC, Tobon F, Schuster MM (1967) Differential sphincteric studies in the diagnosis of ano-rectal disorders of childhood. J Pediatr Surg 2:538–543
143 Schuster MM, Hendrix TR, Mendeloff AI (1963) The internal anal sphincter response: manometric studies on its normal physiology, neural pathways, and alteration in bowel disorders. J Clin Invest 42:196–207
144. Shandling B (1961) New technique in the diagnosis of Hirschsprung's disease. Can J Surg 4:298–305
145. Sharif K, Beath SV, Kelly DA, McKiernan P, van Mourik I, Mirza D, Mayer AD, Buckels JA, de Ville de Goyet J (2003) New perspective for the management of near total or total intestinal aganglionosis in infants. J Pediatr Surg 38:25–28
146. Siu KL, Kwok WK, Lee WY, Lee WH (1999) A male newborn with colon atresia and total colonic aganglionosis. Pediatr Surg Int 15:141–142
147. Smith BM, Steiner RB, Lobe TE (1994) Laparoscopic Duhamel pullthrough procedure for Hirschsprung's disease in childhood. Laparoendosc Surg 4:273–276
148. So HB, Schwartz DL, Becker JM, Daum F, Schneider KM (1980) Endorectal pull-through without preliminary colostomy in neonates with Hirschsprung's disease. J Pediatr Surg 15:470–471
149. Soave F (1964) A new surgical technique for treatment of Hirschsprung's disease. Surgery 56:1007–1014
150. Soper RT, Miller FE (1968) Modification of the Duhamel procedure: elimination of rectal pouch and colorectal septum. J Pediatr Surg 3:376–385
151. State D (1952) Surgical treatment for idiopathic congenital megacolon (Hirschsprung's disease). Surg Gynecol Obstet 95:201–212
152. Steichen FM, Talbert JL, Ravitch MM (1968) Primary side-to-side colorectal anastomosis in the Duhamel operation for Hirschsprung's disease. Surgery 64:475–483
153. Suita S, Taguchi T, Kamimura T, Yanai K (1997) Total colonic aganglionosis with or without small bowel involvement: a changing profile. J Pediatr Surg 32:1537–1544
154. Swenson O (1964) Partial internal sphincterectomy in the treatment of Hirschsprung's disease. Ann Surg 160:540–550
155. Swenson O (1999) How the cause and cure of Hirschsprung's disease was discovered. J Pediatr Surg 34:1580–1581
156. Swenson O (2004) Hirschsprung's disease — a complicated therapeutic problem: some thoughts and solutions based on data and personal experience over 56 years. J Pediatr Surg 39:1449–1453

157. Swenson O, Bill AH (1948) Resection of rectum and rectosigmoid with preservation of the sphincter for benign spastic lesions producing megacolon. Surgery 24:212–220
158. Swenson O, Neuhauser EBD, Pickett LK (1949) New concepts of etiology, diagnosis, and treatment of congenital megacolon (Hirschsprung's disease). Pediatrics 4:201–209
159. Swenson O, Fisher JH, MacMahon HE (1959) Rectal biopsy as an aid in the diagnosis of Hirschsprung's disease. N Engl J Med 253:632–635
160. Talwalker VC (1976) Aganglionosis of the entire bowel. J Pediatr Surg 11:213–216
161. Tam PK, Garcia-Barcelo M (2004) Molecular genetics of Hirschsprung's disease. Semin Pediatr Surg 13:236–248
162. Tamate S, Shiokawa C, Yamada C, Takeuchi S, Nakahira M, Kadowaki H (1984) Manometric diagnosis of Hirschsprung's disease in the neonatal period. J Pediatr Surg 19:285–288
163. Teitelbaum DH, Coran AG (1998) Enterocolitis. Semin Pediatr Surg 7:162–169
164. Teitelbaum DH, Coran AG (2005) Hirschsprung disease and related conditions. In: Grosfeld JL, O'Neill JA, Fonkalsrud EW, Coran AG, Caldamone A (eds) Pediatric surgery, 6th edn. Elsevier, Philadelphia
165. Teitelbaum DH, Cilley RE, Sherman NJ, Bliss D, Uitvlugt ND, Renaud EJ, Kirstioglu I, Bengston T, Coran AG (2000) A decade of experience with the primary pull-through for Hirschsprung disease in the newborn period: a multicenter analysis of outcomes. Ann Surg 232:372–380
166. Thomas CG Jr (1967) Posterior sphincterotomy in Hirschsprung's disease. Surg Gynecol Obstet 124:365–366
167. Thomas CG Jr, Bream CA, DeConnick P (1970) Posterior sphincterotomy and rectal myotomy in the management of Hirschsprung's disease. Ann Surg 171:796–810
168. Tiffin ME, Chandler LR, Faber HK (1940) Localized absence of ganglion cells of the myenteric plexus in congenital megacolon. Am J Dis Child 59:1071–1082
169. Tittel K (1901) Uber eine angeborene Missbildung des Dickdarmes. Wien Klin Wochenschr 14:903–907
170. Touloukian RJ (1995) Pediatric surgery between 1860 and 1900. J Pediatr Surg 30:911–916
171. Treves F (1898) Idiopathic dilatation of the colon. Lancet 1:276–279
172. Tzakis AG, Nour B, Reyes J, Abu-Elmagd K, Furukawa H, Todo S, Starzl TE (1995) Endorectal pull-through of transplanted colon as part of intestinal transplantation. Surgery 117:451–453
173. van der Zee DC, Bax NM (1996) Duhamel-Martin procedure for Hirschsprung's disease in neonates and infants: one stage operation. J Pediatr Surg 31:901–902
174. van Leeuwen K, Teitelbaum DH, Elhalaby EA, Coran AG (2000) Long term follow up of re-do pull-through procedures for Hirschsprung's disease: efficacy of the endorectal pull-through. J Pediatr Surg 35:829–833
175. Vrsansky P, Bourdelat D, Pages R (1997) Early history of the therapy of Hirschsprung's disease: facts and personal observations over 50 years. J Pediatr Surg 32:935–936
176. Vrsansky P, Bourdelat D, Pages R (1998) Principal modifications of the Duhamel procedure in the treatment of Hirschsprung's disease. Analysis based on results of an international retrospective study of 2,430 patients. Pediatr Surg Int 13:125–132
177. Wade RB, Royle ND (1927)The operative treatment of Hirschsprung's disease: a new method. Med J Aust 14:137–141
178. Walker AW, Kempson RL, Ternberg JL (1966) Aganglionosis of the small intestine. Surgery 60:449–457
179. Wang G, Sun XY, Wei MF, Weng YZ (2005) Heart shaped anastomosis for Hirschsprung's disease: operative technique and long term follow up. World J Gastroenterol 11:296–298
180. Watanatittan S, Suwatanaviroj A, Limprutithum T, Rattanasuwan T (1991) Association of Hirschsprung's disease and anorectal malformation. J Pediatr Surg 26:192–195
181. Weber TR, Fortuna RS, Silen ML, Dillon PA (1999) Reoperation for Hirschsprung's disease. J Pediatr Surg 34:153–156
182. West KW, Grosfeld JL, Rescorla FJ, Vane DW (1990) Acquired aganglionosis: a rare occurrence following pull-through procedures for Hirschsprung's disease. J Pediatr Surg 25:104–109
183. Whitehouse FR, Kernohan JW (1948) Myenteric plexus in congenital megacolon. Arch Int Med 82:75–111
184. Whitehouse F, et al (1943) Congenital megacolon: favorable end-results of treatment by resection. Gastroenterology 1:922–937
185. Wilcox DT, Kiely EM (1998) Repeat pull-through for Hirschsprung's disease. J Pediatr Surg 35:1507–1509
186. Wildhaber BE, Pakarinen M, Rintala RJ, Coran AG, Teitelbaum DH (2004) Posterior myotomy/myectomy for persistent stooling problems in Hirschsprung's disease. J Pediatr Surg 39:920–926
187. Wildhaber BE, Teitelbaum DH, Coran AG (2005) Total colonic Hirschsprung's disease a 28 year experience. J Pediatr Surg 40:203–207
188. Wilson-Storey G, Scobie WG (1989) Impaired gastrointestinal mucosal defense in Hirschsprung's disease: a clue to the pathogenesis of enterocolitis? J Pediatr Surg 24:462–464
189. Yin L, Ceccherini I, Pasini B, Matera I, Bicocchi MP, Barone V, Bocciardi R, Kääriäinen H, Weber D, Devoto M, Romeo G (1993) Close linkage with the RET protooncogene and boundaries of deletion mutations in autosomal dominant Hirschsprung disease. Hum Mol Genet 2:1803–1808
190. Yomo A, Taira T, Kondo I (1991) Goldberg-Shprintzen syndrome: Hirschsprung disease, hypotonia, and ptosis in sibs. Am J Med Genet 41:188–91
191. Ziegler MM, Ross AJ 3rd, Bishop HC (1987) Total colonic aganglionosis: a new technique for prolonged survival. J Pediatr Surg 22:82–83
192. Ziegler MM, Royal RE, Brandt J, Drasnin J, Martin LW (1993) Extended myotomy-myectomy: a therapeutic alternative for total intestinal aganglionosis. Ann Surg 218:504–509
193. Zuelzer WW, Wilson JL (1948) Functional intestinal obstruction on a congenital neurogenic basis in infancy. Am J Dis Child 75:40–64

Development of the Enteric Nervous System

P. Puri and U. Rolle

2

2.1 Introduction

The enteric nervous system (ENS) is the largest and the most complex division of the peripheral nervous system [1]. The ENS contains more neurons than the spinal cord and is capable of mediating reflex activity in the absence of central nervous system. About 80–100 million enteric neurons can be classified into functional distinct subpopulations, including intrinsic primary neurons, interneurons, motor neurons, secretomotor and vasomotor neurons [2]. The ENS plays a crucial role in normal gastrointestinal motility. Therefore insights into the development of the gastrointestinal tract and the ENS are relevant for the understanding of the pathophysiology and treatment of infants and children with motility disorders.

2.2 Embryonic Origin of ENS

There are two major steps in the development of the gastrointestinal tract: (1) formation of the gut tube, and (2) formation of individual organs, each with their specialized cell types (Table 2.1) [3].

Gastrulation is an early step in the development of all multicellular organisms. During gastrulation the axes of the embryo are determined and the development of the gastrointestinal tract starts. Gastrulation gives rise to three germ layers, endoderm, mesoderm, and ectoderm [3]. The mammalian gastrointestinal system originates from all three embryonic germ layers. The epithelial lining of the gastrointestinal tube and the parenchymal cells of the liver and pancreas are formed by the endoderm. The mesoderm provides mesenchymal elements including smooth muscle and stromal cells. The neurons of the ENS which regulates gastrointestinal motility are derived from ectoderm.

The ectoderm divides into three types of cells; outer ectoderm, neural tube, and neural crest (NC). The NC arises from the dorsal region of the neural tube. Melanocytes, the adrenal medulla, the dentine of teeth, the sympathetic and parasympathetic arms of the peripheral nervous system, and the neurons of the ENS are derived form the NC. These tissues and cell types originate from

Table 2.1 Developmental milestones of human gastrointestinal tract

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

different regions of the NC, which means that the cells need to migrate to the site of the mature organs. The gene mutations that result in disrupted NC cell migration to one region also cause altered migration of other NC-derived tissues [4].

2.3 Origin and Development of Neural Crest-Derived Cells

The NC is located along the entire length of the body axis. Two groups of undifferentiated cells, derived from NCs, colonize the gut wall and migrate in craniocaudal and caudocranial directions.

The embryonic NC arises in the neural tube, originating with the central nervous system, but NC cells detach from this tissue via reduction of cell–cell and cell–matrix adhesion. The epitheliomesenchymal transformation allows NC cells to migrate along pathways of defined routes to various tissues, where they stop moving and differentiate into various cell types. Pathway selection is most likely achieved by balanced combinations of molecules that promote and reduce adhesions [5, 6]. NC cells give rise to neuronal, endocrine and paraendocrine, craniofacial, conotruncal heart, and pigmentary tissues. Neurocristopathies encompass tumors, malformations, and single or multiple abnormalities of tissues, mentioned above in various combinations [7].

In the human fetus, NC-derived cells first appear in the developing esophagus at the 5th week of gestation, and then migrate down to the anal canal in a craniocaudal direction during the 5th and 12th week of gestation. The NC cells first form the myenteric plexus just outside the circular muscle layer. The mesenchymally derived longitudinal muscle layer then forms, sandwiching the myenteric plexus after it has been formed in the 12th week of gestation. In addition, after the craniocaudal migration has ended, the submucous plexus is formed by the neuroblasts, which migrate from the myenteric plexus across the circular muscle layer and into the submucosa; this progresses in a craniocaudal direction during the 12th to 16th week of gestation [5]. The absence of ganglion cells in Hirschsprung's disease has been attributed to a failure of migration of NC cells. The earlier the arrest of migration, the longer the aganglionic segment is.

It is generally accepted that the enteric ganglion cells are derived primarily from the NC cells [8–11]. Studies in the avian system provide strong evidence for the contribution of the sacral NC to the hindgut ENS [12–14]. Whether the sacral NC contributes to the ENS in the mammalian hindgut is less clear. Failure of the vagal derived NC cells to colonize the hindgut results in failure of hindgut ENS development, suggesting that interaction between sacral and vagal enteric NC cells may be necessary for sacral NC cell contribution to the ENS [15].

Yntma and Hammond first performed NC ablations in chick embryos and identified the vagal NC (somites 1 to 7) as the source of the ENS stem cells [11]. Le Douarin and Teillet showed an additional source of NC stem cells originating from the lumbosacral region to colonize the gut [12]. Later the lumbosacral derived crest cells were found principally in the myenteric plexus, with very few in the submucous plexus. The number of these cells declines rostrally. Cells derived from the lumbosacral NC were never observed in any gut region above the umbilicus [14].

The colonization of the gut by sacral NC-derived cells and the contribution of the cells to the development of the ENS is controversial [16]. The dual origin of enteric neurons has been negated by studies on chick embryo as well as human embryo. Allen and Newgreen [17] isolated bowel segments from fowl embryos at various stages of development, and grew these segments in the chorioallantoic membrane and found that enteric neurons appeared in a craniocaudal sequence, showing a vagal source. Meijers et al. [18] transected the chicken bowel in ovo at an early stage, before the passage of NC cells had occurred, preventing craniocaudal migration of vagal NC cells. They found that the hindgut remained aganglionic, showing that there was no colonization by sacral NC cells.

Some studies have shown that sacral NC-derived cells migrate from the neural plate early in development and extraenteric pelvic ganglia. Later these cells are able to colonize the gut and contribute to the ENS, coincident with the migration of vagal NC-derived cells [14, 19–21]. In contrast, other studies suggest that sacral NC-derived cells invade the hindgut mesenchyme several days before the colonization of the hindgut by vagal NC cells and contribute to the development of ENS [13, 22–24].

In contrast the mouse ENS is derived embryologically from cells of the vagal, truncal, and sacral regions of the NC. The vagal NC originates in somites 1 to 5 in the mouse, the truncal NC from somites 6 and 7, and the sacral NC posterior to somite 28. Cells from each of these regions of the NC migrate into the developing gut by defined pathways. Cells of the vagal and truncal NC enter the foregut, migrating in a proximal to distal direction. Truncal NC cells populate only the foregut, whereas those of the vagal NC migrate more distally to colonize the rest of the gastrointestinal tract. Cells arising from the sacral crest seem first to colonize pelvic autonomic ganglia, from which they then migrate into the distal gut, colonizing it from distal to proximal [19].

The current concept is that the development of the ENS in humans is derived primarily from cells of the vagal segment of the NC [2, 12]. Fujimoto et al. [25] studied NC cell migration in the developing gut in the human embryo using antineurofilament protein triplet antibody and found that enteric ganglia originated from a single vagal NC source. The vast majority of studies have revealed that vagal NC cells provide the main source of enteric neurons and sacral NC additionally innervates the distal bowel [12–14, 26–28].

The final requirement for development and maturation of the ENS is the formation of ganglia. Several days after NC cells have colonized the gut these cells are evenly distributed, with no indication of cell clustering, except the cecum. As the gut later increases in length and diameter, the cells start forming ganglionic groups [29]. A previous study has shown that cells forming a ganglion do not arise from a single precursor cell [30]. A recent study used human fetal intestine to investigate nitrergic neurons in the developing myenteric plexus. The distribution of nitrergic neurons was found to change markedly between 14 and 22 weeks of gestation. Nitrergic neurons were randomly distributed at week 14 and were later aggregated in the plexus and within individual ganglia at week 19 [31]. It is currently not known what factors induce cells to cluster into ganglia.

2.4 Functional Development of the ENS

The complexity of mature ENS is exemplified by many different functional types of neurons containing various neurotransmitters occurring in various combinations. Types of neurotransmitters vary according to the time of their appearance [29, 32]. The development of the human enteric nervous system is characterized by the early appearance (between 9 and 12 weeks' gestation) of adrenergic and cholinergic nerves. Strong evidence has emerged that the enteric nervous system is not only composed of adrenergic and cholinergic nerves but also nonadrenergic, noncholinergic (NANC) autonomic nerves, which contain different peptides. These peptides act as neurotransmitters, or neuromodulators, or both. These nerves have been termed *peptidergic nerves*. The development of peptidergic innervation occurs much later.

In recent years, pharmacologic and physiologic studies have provided evidence that nitric oxide (NO) is the most important mediator in nonadrenergic, noncholinergic relaxation of the gastrointestinal tract. By 12 weeks' gestation, nitrergic neurons appear in the myenteric ganglia, at all levels of the gut, and begin plexus formation. Nitrergic innervation in the submucous plexus becomes evident after 14 weeks. As gestational age increases, nitrergic innervation becomes richer and more organized. Increasing numbers of nitrergic nerve fibers are seen in the circular muscle; some of these fibers project from the myenteric plexus. Thus, the onset and pace of development of nitrergic innervation are similar to adrenergic and cholinergic innervation and occur before peptidergic innervation [33].

Serotonin (5-HT) together with glucagon, insulin, peptide XY, gastrin, and somatostatin are the earliest neurohumoral substances to be expressed at about 8 weeks of gestation. By 24 weeks of gestation, most of the known gastrointestinal neurohumoral substances can be identified.

Further contacts between enteric nerves and effectors are developed at 26 weeks and the first signs of motility can be detected at 25 weeks of gestation [3].

2.5 Development of Intestinal Motility

The innervation of the gastrointestinal tract in utero is accompanied by functional activity of increasing complexity. The first studies to measure intestinal transit in humans used amniography; aboral transport of contrast agent did not occur in the intestinal tract of fetuses younger than 30 weeks of gestation [34]. With increasing gestational age, increasing aboral transit and rate of propagation develops. Subsequent studies of gastrointestinal motility in premature infants have been performed using intraluminal catheters [35]. The data from these studies reveal no regular periodicity or rhythmicity at 25 weeks of gestation. Further development occurs during the next 15 weeks, so that by term, mature motor patterns of the gastrointestinal tract are well established. Responses to feeding vary considerably among preterm infants; in general, intestinal motility studies can predict feeding intolerance [36].

Enteric nerve cells continue to differentiate throughout the first couple of years of life, which means that the infant's nervous system is plastic and developing [37]. There is clear evidence that the development of the ENS continues after birth. In rats, NO synthase-expressing neurons are already present at birth but increase in number and location during the first 3 weeks of postnatal life [32]. Normal ganglion cell distribution is present at 24 weeks of gestation in humans. These ganglia continue to mature on into childhood. Previous studies on human bowel specimens have revealed that the density of NADPH-diaphorase-positive ganglion cells decreases in the submucous plexus of the human distal colon and the myenteric plexus of human small bowel, colon and rectum [38, 39].

2.6 Genes Involved in ENS Development

Normal development of ENS is related to migration, proliferation, differentiation and survival of NC-derived cells [40]. Several genes and signaling molecules have been identified that control morphogenesis and differentiation of the ENS. These genes, when mutated or deleted, interfere with ENS development (Table 2.2) [7, 42–44].

2.6.1 RET/GDNF/GFRα1 Signaling System

This signaling pathway is of importance for subpopulations of both peripheral and central neurons, having been shown by in vitro and in vivo assays to promote survival of neurons, mitosis of neuronal progenitor cells, and dif-

Table 2.2 Genes involved in the morphogenesis and differentiation of the ENS

Genes	Chromosomal assignment	Function
RET	10q11.2	Tyrosine kinase receptor
GDNF	5p12–13.1	Glial cell-derived neurotropic factor
NTN	19q13.3	Neurturin, RET ligand
GFRα	10q26	GDNF family receptor alpha 1
EDNRB	13q22	Endothelin-B receptor
EDN-3	20q13.2–13.3	Endothelin-B
ECE-1	1p36.1	Endothelin-converting enzyme
SOX 10	22q13.1	Sry/HMG box transcription factor
PHOX2B	4p12	Paired-like homeobox 2b
PAX3	2q35	Paired box gene 3
SIP1	2q22	Siah-interacting protein

ferentiation of neurons and neurite extension [41, 45, 46]. The RET receptor is the signaling component of receptor complexes with four ligands, glial derived neurotropic factor (GDNF), neurturin (NTN), artemin (ATM), and persephin (PSP) [45, 47]. The complete receptor complex includes the RET receptor tyrosine kinase and a glycosylphosphatidylinositol-anchored binding component (GFRα1, GFRα2, GFRα3, and GFRα4) [47–49]. In vivo the absence of GDNF/GFRα1-mediated signaling leads to the failure of ENS development, whereas the absence of NTN/GFRα2-mediated signaling leads to more subtle abnormalities in ENS development [47]. The importance of RET in mammalian organogenesis has been further illustrated by the generation of RET knockout mice [50]. These mice exhibit total intestinal aganglionosis and renal agenesis. The RET protooncogene has been demonstrated to be a major gene causing Hirschsprung's disease [51–55]. Mutations of RET account for 50% of familial and 15% to 20% of sporadic cases of Hirschsprung's disease [55, 56].

The development of the ENS is dependent upon the actions of GDNF, which stimulates the proliferation and survival of NC-derived precursor cells in the embryonic gut [57–60]. It has been reported that GDNF is the ligand of RET [61]. Mice carrying the homozygous null mutation in GDNF have been generated, and these mice demonstrate the lack of kidneys and ENS, confirming the crucial role of GDNF in the development of the ENS [62, 63]. Although a causative role for GDNF mutations in some patients with Hirschsprung's disease has been suggested, the occurrence of such cases is uncommon, and it is more likely that the GDNF mutations are involved in modulation of the Hirschsprung's disease phenotype via its interaction with other susceptibility loci such as RET [7, 64].

2.6.2 Endothelin Signaling Pathway

The endothelins (EDN1, EDN2, and EDN3) are intercellular local messengers that act via the cell surface receptors, EDNRA and EDNRB [45]. EDN is initially produced as an inactive preproendothelin that undergoes two proteolytic steps to produce an active peptide. The first cleavage produces inactive big endothelins, and these are finally cleaved by a specific protease, endothelin-converting enzyme (ECE) to produce biologically active EDN [7, 16, 45].

EDN3 and EDNRB have a role in the migration and development of the ENS [65–67]. In mice in which the EDN3 or EDNRB gene is disrupted, intestinal aganglionosis has been demonstrated experimentally. Several reports suggest that the downregulation of EDN3 expression may play a role in the pathogenesis of Hirschsprung's disease in the sporadic cases [68–74].

ECE1 knockout mice show craniofacial and cardiac abnormalities in addition to colonic aganglionosis [75].

2.6.3 SOX10

The SOX10 (sex determining region Y-box) gene is expressed in neuronal crest derivates that contribute to the formation of the peripheral nervous system during embryogenesis [76, 77]. The involvement of SOX10 in the development of enteric neurons was demonstrated in the Dom (dominant megacolon) mouse model of Hirschsprung's disease which exhibits distal intestinal aganglionosis [76]. Mutations in SOX10 have been identified as a cause of the dominant megacolon mouse and Waardenburg-Shah syndrome in humans, both of which include defects in the ENS and pigmentation abnormalities [78, 79].

2.6.4 PHOX2B

The PHOX2B gene is a homeodomain-containing transcription factor that is involved in neurogenesis and regulates RET expression in mice, in which disruption of the PHOX2B gene results in a Hirschsprung's disease-like phenotype [80, 81]. Enteric PHOX2B expression begins in vagal and truncal NC-derived cells as they invade the foregut mesenchyme and is contained in the adult submucosal and myenteric plexus [81].

2.6.5 HOX11L1

HOX11L1 is a homeobox gene involved in peripheral nervous system development and is reported to play a role in the proliferation or differentiation of NC cell lines. Two different HOX11L1 knockout mouse models have been generated [82, 83]. In both cases, homozygous

mutant mice were viable but developed megacolon at the age of 3 to 5 weeks. Histologic and immunohistochemical analysis showed hyperplasia of myenteric ganglia, a phenotype similar to that observed in human intestinal neuronal dysplasia.

2.7 Other Factors Implicated in the Control of ENS Development

Kit, another receptor with tyrosine kinase activity, is involved in the development of the interstitial cells of Cajal (ICCs) [84]. These are nonneuronal cells that serve as pacemaker cells and are responsible fro the spontaneous, rhythmic, electrical excitatory activity of gastrointestinal smooth muscle. Recent studies have found that the c-kit receptor is essential for the development of the ICCs. Mesenchymal ICC precursors that carry the c-kit receptor require the kit ligand (KL), which can be provided by neuronal cells or smooth muscle cells. According to the influence of the KL from either neuronal or smooth muscle cells, the ICCs develop as either myenteric ICCs or muscular ICCs [85]. These cells are also important in modulating communications between nerve and muscle. Mice with mutations in the KIT gene lack ICCs and have changes in skin pigment and abnormal intestinal motility [86]. No such mutations have been reported in humans so far, but several studies have shown disturbed expression of ICCs in patients with motility disorders [87–91]

Further studies have indicated the importance of the gut microenvironment during development of ENS. Mice lacking EDN-3 show increased expression of laminin, one of extracellular matrix (ECM) proteins, which leads to the conclusion that EDN-3 also affects the environment through which the NC cells migrate [92]. Altered ECM proteins such as tenascin, fibronectin and nidogen have been shown in patients with Hirschsprung's disease which suggests the importance of ECM molecules during development of ENS [93, 94].

2.8 Conclusions

During the past decade there has been an explosion of information about genes that control the development of NC. Molecular-genetic analysis has identified several genes that have a role in the development of Hirschsprung's disease. The major susceptibility gene is RET, which is also involved in multiple endocrine neoplasia type 2. Recently, genetic studies have provided strong evidence in animal models that intestinal neuronal dysplasia (IND) is a real entity. HOX11L1 knockout mice and endothelin B receptor-deficient rats demonstrated abnormalities of the ENS resembling IND type B in humans. These findings support the concept that IND may be linked to a genetic defect [95]. The development of the ENS requires the complex interaction of genes encoding transcription factors, signaling molecules, and their receptors. Normal ENS development is based on survival of NC-derived cells and their coordinated proliferation, movement and differentiation into neurons and glia. These processes are influenced by the microenvironment of the developing gut. Alterations in gene function, defects in NC cells or changes in the gut microenvironment may result in abnormal development of the ENS.

References

1. Gershon MD, Jerde SM (1981) The nervous system of the gut. Gastroenterology 80:1571–1594
2. Furness JB, Clere N, Vogalis F, Stebbing MJ (2003) The enteric nervous system and its extrinsic connections. In: Yamada T, Alpers DH (eds) Textbook of gastroenterology. Lippincott Williams & Wilkins, Philadelphia, pp 13–34
3. Montgomery RK, Mulberg AE, Grand RJ (1999) Development of the human gastrointestinal tract: twenty years of progress. Gastroenterology 116:702–731
4. Bates MD (2002) Development of the enteric nervous system. Clin Perinatol 29:97–114
5. Rolle U, Nemeth L, Puri P (2002) Nitrergic innervation of the normal gut and in motility disorders of childhood. J Pediatr Surg 36:551–567
6. Puri P, Ohsiro K, Wester T (1998) Hirschsprung's disease: a search for etiology. Semin Pediatr Surg 7:140–147
7. Amiel J, Lyonnet S (2001) Hirschsprung's, associated syndromes and genetics: a review. J Med Genet 38:729–739
8. Gershon MD, Chalazonitis A, Rothman TP (1993) From neural crest to bowel: development of the enteric nervous system. J Neurobiol 24:199–214
9 Goyal RK, Hirano I (1996) The enteric nervous system. N Engl J Med 334:1106–1115
10. Gershon MD (1999) The enteric nervous system: a second brain. Hosp Pract (Minneap) 34:31–2, 35–8, 41–2
11. Yntma CL, Hammond WS (1954) The origin of intrinsic ganglia of trunk viscera from vagal neural crest in the chick embryo. J Comp Neurol 101:515–541
12. Le Douarin NM, Teillet MA (1973) The migration of neural crest cells to the wall of the digestive tract in avian embryo. J Embryol Exp Morphol 30:31–48
13 Pomeranz HD, Gershon MD (1990) Colonization of the avian hindgut by cells derived from the sacral neural crest. Dev Biol 137:378–394
14. Burns AJ, Le Duoarin NM (1998) The sacral neural crest contributes neurons and glia to the post-umbilical gut: spatiotemporal analysis of the development of the enteric nervous system. Development 125:4335–4347
15. Caniano DA, Ormsbee HS III, Polito W (1985) Total intestinal aganglionosis. J Pediatr Surg 20:456–460
16. Gariepy CE (2004) Developmental disorders of the enteric nervous system: genetic and molecular bases. J Pediatr Gastroenterol Nutr 39:5–11
17. Allan IJ, Newgreen DF (1980) The origin and differentiation of enteric neurons of the intestine of the fowl embryo. Am J Anat 157:137–154
18. Meijers JHC, Tibboel D, Van der Kamp AWM (1989) A model for aganglionosis in the chicken embryo. J Pediatr Surg 24:557–561

19. Kapur RP (2000) Colonization of the murine hindgut by sacral crest-derived neural precursors: experimental support for an evolutionarily conserved model. Dev Biol 227:146–155
20. Burns AJ, Champeval D, le Douarin NM (2000) Sacral neural crest cells colonise aganglionic hindgut in vivo but fail to compensate for lack of enteric ganglia. Dev Biol 219:30–43
21. Young HM, Hearn CJ, Ciampoli D, Southwell BR, Brunet JF, Newgreen DF (1998) A single rostrocaudal colonization of the rodent intestine by enteric precursors is revealed by the expression of Phox2b, Ret, and p75 and by explants grown under the kidney capsule in organ culture. Dev Biol 202:67–84
22. Erickson CA, Goins TL (2000) Sacral neural crest cell migration to the gut is dependent upon migratory environment and not cell-autonomous migratory properties. Dev Biol 219:79–97
23. Serbedzija GN, Burgan S, Fraser SE, Bronner-Frases M (1991) Vital dye labelling demonstrates a sacral neural crest contribution to the enteric nervous system of chick and mouse embryo. Development 111:857–866
24. Pomeranz HD, Rothman TP, Gershon MD (1991) Colonization of the postumbilical bowel by cells derived from the sacral neural crest: direct tracing of cell migration using an intercalating probe and replication-deficient retrovirus. Development 111:647–655
25 Fujimoto T, Hata J, Yokoyama S, Mitomi T (1989) A study of the extracellular matrix protein as the migration pathway of neural crest cells in the gut: Analysis in human embryos with special reference to the pathogenesis of Hirschsprung's disease. J Pediatr Surg 24:550–556
26. Le Douarin NM, Dupin E, Ziller C (1994) Genetic and epigenetic controls in neural crest development. Curr Opin Genet Dev 4:685–695
27. Taraviras S, Pachnis V (1999) Development of the mammalian enteric nervous system. Curr Opin Genet Dev 9:321–327
28. Young HM, Hearn CJ, Newgreen DF (2000) Embryology and development of enteric nervous system. Gut 47 [Suppl 4]:iv12–iv14
29. Young HM, Newgreen DF (2001) Enteric neural crest-derived cells: origin, identification, migration, and differentiation. Anat Rec 262:1–15
30. Rothman TP, Le Douarin NM, Fontaine-Perus JC, Gershon MD (1993) Colonization of the bowel by neural crest-derived cells migrating from foregut backtransplanted to vagal or sacral regions of host embryos. Dev Dyn 196:217–233
31. Roman V, Bagyanszki M, Krecsmarik M, Horvath A, Resch BA, Fekete E (2004) Spatial pattern analysis of nitrergic neurons in the developing myenteric plexus of the human fetal intestine. Cytometry A 57:108–112
32. Matini P, Mayer B, Faussone-Pellegrini MS (1997) Neurochemical differentiation of rat enteric neurons during pre- and postnatal life. Cell Tissue Res 288:11–23
33. Brandt CT, Tam PKH, Gould SJ (1996) Nitrergic innervation of the human during early foetal development. J Pediatr Surg 31:661–664
34. Grand RJ, Watkins JB, Torti FM (1976) Development of the human gastrointestinal tract. A review. Gastroenterology 70:790–810
35. Dumont RC, Rudolph CD (1994) Development of gastrointestinal motility in the infant and child. Gastroenterol Clin North Am 23:655–671
36. Berseth CL, Nordyke CK (1992) Manometry can predict feeding readiness in preterm infants. Gastroenterology 103:1523–1528
37. Gershon MDV (1998) Genes, lineages, and tissue interactions in the development of the enteric nervous system. Am J Physiol 275:G869–873
38. Wester T, O'Briain S, Puri P (1998) Morphometric aspects of the submucous plexus in whole-mount preparations of normal human distal colon. J Pediatr Surg 33:619–622
39. Wester T, O'Briain S, Puri P (1999) Notable postnatal alterations in the myenteric plexus of normal human bowel. Gut 44:666–674
40. Wallace AS, Burns AJ (2005) Development of the enteric nervous system, smooth muscle and interstitial cells of Cajal in the human gastrointestinal tract. Cell Tissue Res 319:367–382
41. Montgomery RK, Mulberg AE, Grand RJ (1999) Development of the human gastrointestinal tract: twenty years of progress. Gastroenterology 116:702–731
42. Gariepy CE (2000) Intestinal motility disorders and development of the enteric nervous system. Pediatr Res 49:605–613
43. Parisi MA, Kapur RP (2000) Genetics of Hirschsprung's disease. Curr Opin Pediatr 12:610–617
44. Passarge E (2002) Dissecting Hirschsprung's disease. Nat Genet 31:11–12
45. Newgreen D, Young HM (2002) Enteric nervous system: development and developmental disturbances part 1. Pediatr Dev Pathol 5:224–247
46. Taraviras S, Pachnis V (1999) Development of the mammalian enteric nervous system. Curr Opin Genet Dev 9:321–327
47. Newgreen D, Young HM (2002) Enteric nervous system: development and developmental disturbances part 2. Pediatr Dev Pathol 5:329–349
48. Jing S, Wen D, Yu Y, Holst PJ, Fang M, Tamir R, et al (1996) GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-α, a novel receptor for GDNF. Cell 85:1113–1124
49. Jing S, Yu Y, Fang M, Hu Z, Holst PL, Boone T, et al (1997) GFRα-2 and GFRα-3 are two new receptors for ligands of the GDNF family. J Biol Chem 272:33111–33117
50. Schuchardt A, D'Agati V, Larsson-Blumberg L, Constantini F, Pachnis V (1994) Defects in the kidney and enteric nervous system of mice lacking the tyrosine kinase receptor Ret. Nature 367:380–383
51. Luo Y, Cecchernin I, Pasini B, Matera I, Bicochi MP, Barone V, et al (1993) Close linkage with the RET protooncogene and boundaries of deletion mutations in autosomal dominant Hirschsprung's disease. Hum Mol Genet 2:1803–1808
52. Romeo G, Ronchetto P, Luo Y, Barone V, Seti M, Ceccherini I, et al (1994) Point mutations affecting the tyrosine kinase domain of the RET proto-oncogene in Hirschsprung's disease. Nature 367:377–387
53. Edery P, Lyonnet S, Mulligan LM, Pelet A, Dow E, Abel L, et al (1994) Mutations of the RET proto-oncogene in Hirschsprung's disease. Nature 367:378–380

54. Kusafuka T, Puri P (1997) Altered RET gene mRNA expression in Hirschsprung's disease. J Pediatr Surg 32:600–604
55. Kusafuka T, Puri P (1997) The RET proto-oncogene: a challenge to understanding of disease pathogenesis. Pediatr Surg Int 12:11–18
56. Martucciello G, Ceccherini I, Lerone M, Jasonni V (2000) Pathogenesis of Hirschsprung's disease. J Pediatr Surg 35:1017–1025
57. Hellmich HL, Kos L, Cho ES, Mahon KA, Zimmer A (1996) Embryonic expression of glial-line derived neurotrophic factor (GDNF) suggests multiple developmental roles in neural differentiation and epithelial-mesenchymal interactions. Mech Dev 54:95–105
58. Worley DS, Pisano JM, Choi ED, Walus L, Hession CA, Cate RL, et al (2000) Developmental regulation of GDNF response and receptor expression in the enteric nervous system. Development 127:4383–4393
59. Fock PJ, Schiltz CA, Jones SE (2001) Enteric neuroblasts require the phosphatidylinositol 3-kinase pathway for GDNF-stimulated proliferation. J Neurobiol 47:306–317
60. Young HM, Hearn CJ, Farlie PG, Canty AJ, Thomas PQ, Newgreen DF (2001) GDNF is a chemoattractant for enteric cells. Dev Biol 229:503–516
61. Durbec P, Marcos-Gutierrez CV, Kilkenny C, Grigoriou M, Wartiowaara K, Suvanto P, et al (1996) GDNF signaling through the ret receptor tyrosine kinase. Nature 381:789–793
62. Sanchez M, Silos-Santiago I, Frisen J, He B, Lira SA, Barbacid M (1996) Renal agenesis and the absence of enteric neurons in mice lacking GDNF. Nature 382:70–73
63. Pichel JG, Shen L, Sheng HZ, Granholm AC, Drago J, Grinberg A, et al (1996) Defects in enteric innervation and kidney development in mice lacking GDNF. Nature 382:73–76
64. Angrist M, Bolk S, Thiel B, Puffenberger EG, Hofstra RM, Buys CH, et al (1995) Mutations analysis of the RET receptor tyrosine kinase in Hirschsprung disease. Hum Mol Genet 4:821–830
65. Baynash AG, Hosoda K, Giaid A, Richardson JA, Emoto N, Hammer RE, et al (1994) Interaction of endothelin-3 with endothelin-B receptor is essential for development of epidermal melanocytes and enteric neurons. Cell 79:1277–1285
66. Leibl MA, Ota T, Woodward MN, Kenny SE, Lloyd DA, Vaillant CR, et al (1999) Expression of endothelin-3 by mesenchymal cells of embryonic mouse caecum. Gut 44:246–252
67. Hosoda K, Hammer RE, Richardson JA, Baynash AG, Cheung JC, Giaid A, et al (1994) Targeted and natural (piebald-lethal) mutations of endothelin-B receptor gene produce megacolon associated with spotted coat color in mice. Cell 79:1267–1276
68. Kusafuka T, Wang Y, Puri P (1997) Mutation analysis of the RET, endothelin-B receptor, and the endothelin-3 genes in sporadic cases of Hirschsprung's disease. J Pediatr Surg 32:501–504
69. Kusafuka T, Wang Y, Puri P (1996) Novel mutations of the endothelin-B receptor gene in isolated patients with Hirschsprung's disease. Hum Mol Genet 5:347–349
70. Kusafuka T, Puri P (1997) Mutations of the endothelin-B receptor and endothelin-3 genes in Hirschsprung's disease. Pediatr Surg Int 12:19–23
71. Bidaud C, Salomon R, Pelet A, van Camp G, Attie T, Eng C, et al (1997) Endothelin-3 gene in isolated and syndromic Hirschsprung's disease. Eur J Hum Genet 5:247–251
72. Amiel J, Attie T, Jan D, Pelet A, Edery P, Bidaud C, et al (1996) Heterozygous endothelin receptor B (EDNRB) mutations in isolated Hirschsprung's disease. Hum Mol Genet 5:355–357
73. Oue T, Puri P (1999) Altered endothelin-3 and endothelin-B receptor mRNA expression in Hirschsprung's disease. J Pediatr Surg 34:1257–1260
74. Abe Y, Sakurai T, Yamada T, Nakamura T, Yanagisawa M, Goto K (2000) Functional analysis of five endothelin-B receptor mutations found in human Hirschsprung's disease patients. Biochem Biophys Res Commun 275:524–531
75. Yanagisawa H, Yanagisawa M, Kapur RP, Richardson JA, Williams SC, Clouthier DE, et al (1998) Dual genetic pathways of endothelin-mediated intercellular signalling revealed by targeted disruption of endothelin converting enzyme-1 gene. Development 125:825–836
76. Southard-Smith EM, Kos L, Pavan WJ (1998) Sox10 mutations disrupts neural crest development in Dom Hirschsprung mouse model. Nat Genet 18:60–64
77. Kuhlbrodt K, Herbarth B, Sock E, Enderich J, Hermans-Borgmeyer I, Wegner M (1998) Sox10, a novel transcriptional modulator in glial cells. J Neurosci 18:237–250
78. Pingault V, Bondurand N, Kuhlbrodt K, Goerich DE, Prehu MO, Puliti A, et al (1998) SOX 10 mutations in patients with Waardenburg-Hirschsprung's disease. Nat Genet 18:171–173
79. Kuhlbrodt M, Schmidt C, Sock E, Pingault V, Bondurand N, Goosssens M, et al (1998) Functional analysis of Sox 10 mutations found in human Waardenburgs-Hirschsprung's disease. J Biol Chem 273:23033–23038
80. Pattyn A, Morin X, Cremer H, Goridis C, Brunet JF (1997) Expression and interactions of the two closely related homeobox genes Phox2a and Phox2b during neurogenesis. Development 124:4065–4075
81. Pattyn A, Morin X, Cremer H, Goridis C, Brunet JF (1999) The homeobox gene Phox2b is essential for the development of autonomic neural crest derivates. Nature 399:366–377
82. Hatano M, Aoki T, Dezawa M, Yusa S, Iitsuka Y, Koseki H, et al (1997) A novel pathogenesis of megacolon in NCX/HOX11L1 deficient mice. J Clin Invest 100:795–801
83. Shirasawa S, Yunker AMR, Roth KA, Brown GA, Horning S, et al (1997) ENX (HOX11L1) deficient mice develop myenteric neuronal hyperplasia and megacolon. Nat Med 3:646–650
84. Huizinga JD, Thuneberg L, Kluppel M, Malysz J, Mikkelsen HB, Bernstein A (1995) W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. Nature 373:347–349
85. Wu JJ, Rothman TP, Gershon MD (2000) Development of the interstitial cell of Cajal: origin, kit dependence and neuronal and nonneuronal sources of kit ligand. J Neurosci Res 59:384–401
86. Maeda H, Yamagata A, Nishikawa S, Yoshinaga K, Kobayashi S, Nishi K, et al (1992) Requirement of c-kit for development of intestinal pacemaker system. Development 116:369–375

87. Feldstein AE, Miller SM, El-Youssef, Rodeberg D, Lindor NM, Burgart LJ, et al (2003) Chronic intestinal pseudoobstruction associated with altered interstitial cells of Cajal networks. J Pediatr Gastroenterol Nutr 36:492–497
88. Hagger R, Finlayson C, Kahn F, De Oliveira R, Chimelli L, Kumar D (2000) A deficiency of interstitial cells of Cajal in Chagasic megacolon. J Auton Nerv Syst 80:108–111
89. Kenny S, Connell MG, Rintala RJ, Vaillant C, Edgar DH, Lloyd DA (1998) Abnormal colonic interstitial cells of Cajal in children with anorectal malformations. J Pediatr Surg 33:130–132
90. Rolle U, Piotrowska AP, Nemeth L, Puri P (2002) Altered distribution of interstitial cells of Cajal in Hirschsprung's disease. Arch Pathol Lab Med 126:928–933
91. Tong WD, Liu BH, Zhang LY, Zhang SB, Lei Y (2004) Decreased interstitial cells of Cajal in the sigmoid colon of patients with slow transit constipation. Int J Colorectal Dis 19:467–473
92. Rothman TP, Chen J, Howard MJ, Costantini F, Schuchardt A, Pachnis V, et al (1996) Increased expression of laminin-1 and collagen (IV) subunits in the aganglionic bowel of ls/ls, but not c-ret -/- mice. Dev Biol 178:498–513
93. Parikh DH, Tam PK, Van Velzen D, Edgar D (1994) The extracellular matrix components, tenascin and fibronectin, in Hirschsprung's disease: an immunohistochemical study. J Pediatr Surg 29:1302–1306
94. Parikh DH, Leibl M, Tam PK, Edgar D (1995) Abnormal expression and distribution of nidogen in Hirschsprung's disease. J Pediatr Surg 30:1687–1693
95. Puri P, Shinkai T (2004) Pathogenesis of Hirschsprung's disease and its variants: recent progress. Semin Pediatr Surg 13:18–24