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

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1

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 consti-

pation. 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 man-

agement 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.

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