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## HIRSCHSPRUNG'S DISEASE

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## **FOREWORD**

Hirschsprung's disease is characterized by the absence of myenteric ganglion cells in the large bowel. Even though Hirschsprung's description of congenital megacolon was published in 1886, it was not until 1948 that Orvar Swenson proposed a curative operation based on a sound understanding of the disease pathophysiology. Although the etiology of the disease is unknown, recent molecular genetics discoveries have enhanced our understanding of the developmental biology of ganglion cells. In this issue of Current Problem in Surgery, Dr. Michael Skinner of the Department of Surgery at the Washington University School of Medicine has written an excellent monograph on Hirschsprung's disease. He gives a clear description of the clinical presentation of the disease and reviews the current methods of diagnosis and treatment. Moreover, his discussion is based within a scientific context that gives the reader a broad biologic perspective of the clinical entity. Samuel A. Wells, Jr., MD Editor-in-Chief

## IN BRIEF

Hirschsprung's disease is characterized by the absence of myenteric and submucosal ganglion cells in the distal alimentary tract and results in decreased motility in the affected bowel segment. The clinical outcome for affected patients has improved dramatically with the development of effective operative procedures. The first report of a patient with Hirschsprung's disease was in 1691 by Frederick Ruysch, who performed an autopsy on a 5-year-old child who died of unremitting constipation. Harald Hirschsprung's classic description of congenital megacolon was published in 1886. He described the autopsy findings of massively dilated colon with muscular hypertrophy proximal to a more normal contracted colon in two infants who had severe constipation and abdominal distension since birth. It was not until the twentieth century that the absence of myenteric ganglion cells was first noted, and for many years the significance of this histological finding was minimized. Instead, the absence of ganglion cells was thought to result from the proximal megacolon rather than to be responsible for the condition. Most clinicians reasoned that the intestinal dilatation in Hirschsprung's disease resulted from a neurologic imbalance between sympathetic and parasympathetic neurologic innervation of the bowel. Early treatments included surgical sympathectomy and the administration of parasympathomimetic agents. Investigators continued to confirm the absence of ganglion cells within the distal contracted colon segment and in 1948 Orvar Swenson and Alexander Bill presented their insightful elucidation of the pathophysiology of Hirschsprung's disease. These investigators demonstrated conclusively that the aganglionic segment fails to relax during peristalsis, acting as a functional obstruction to the passage of fecal material. In 1948 Dr. Swenson described his pioneering definitive procedure for Hirschsprung's disease, in which he removed the distal aganglionic rectosigmoid colon and performed an anastomosis between proximal ganglionic colon and the anus. The first series of patients with congenital megacolon treated by Dr. Swenson's operation was published in 1949. Since then other operations have been developed to treat patients with Hirschsprung's disease. The Duhamel procedure was devised in 1956 to minimize complications associated with the anterior rectal dissection and disruption of autonomic nerves. The endorectal pull-through operation originally described by Ravich and Sabiston was modified by Soave in 1964 for use in children with Hirschsprung's disease. Each of these procedures has undergone modifications to simplify them and improve outcome, and the vast majority of children with Hirschsprung's disease are currently treated by one of these procedures. In recent population-based studies, the incidence of Hirschsprung's disease has been shown to be approximately 1 per 6000 live births. Approximately 80% of the patients are male. No association exists between incidence of aganglionosis and race. In approximately 8% of cases a history of Hirschsprung's disease is present in other family members. Hirschsprung's disease is known to be a genetically heterogeneous condition with autosomal-dominant, autosomal-recessive, and polygenic subtypes. Associated congenital anomalies are found in approximately 20% of patients with Hirschsprung's disease and include cardiac, central nervous system, genitourinary, and other gastrointestinal defects. Down's syndrome is also a frequent finding in patients with Hirschsprung's disease, occurring in approximately 8% of patients. The cause of congenital aganglionosis is unknown. Sophisticated molecular and embryologic

techniques have been used to elucidate the embryology of the enteric nervous system. Inbred strains of mice with congenital aganglionosis have been particularly useful in this regard. These studies have established that the aganglionosis results from a failure of cells derived from the neural crest to populate the embryonic colon during development. This failure results from a fundamental defect in the microenvironment of the bowel wall that prevents ingrowth of neuroblasts. Specific genetic defects known to be associated with Hirschsprung's disease include mutations to the endothelin-B receptor gene and the RET protooncogene. However, because of the polygenic nature of Hirschsprung's disease, there is variable penetrance of the condition in patients with these mutations. Multiple environmental and genetic factors determine the expression of Hirschsprung's disease. The mean age at diagnosis of Hirschsprung's disease is approximately 10 months, but in 5% of patients the diagnosis may not be established until after the age of 5 years. In neonates, the presenting signs for patients with Hirschsprung's disease may include abdominal distension, bilious emesis, and the failure to pass meconium within 24 hours of birth. This last finding is encountered in approximately 60% of patients. In addition, neonates with Hirschsprung's disease may have enterocolitis, which can be life-threatening. Clinical findings that suggest this diagnosis include abdominal distension and tenderness, diarrhoea, fever, and hematochezia. Significant risk factors for having enterocolitis include the presence of Down's syndrome and the delay in diagnosis of aganglionosis beyond the age of 1 week. Older children with Hirschsprung's disease usually have chronic constipation but may also have enterocolitis. In approximately 80% of patients with Hirschsprung's disease, a contrast enema will demonstrate proximally dilated bowel with a transition zone to contracted distal intestine. Anorectal manometry may also be used to aid in establishing the diagnosis; the diagnostic accuracy of this test is nearly 90%. The definitive diagnosis of Hirschsprung's disease is established by rectal biopsy to demonstrate the congenital absence of ganglion cells in Meissner's (submucosal) plexus or Auerbach's (myenteric) plexus. Hypertrophic nerve fibres are also usually seen in the affected region of the intestine, although this finding is not consistent enough to be diagnostically useful. Although the most definitive means of obtaining tissue for histologic examination is a full-thickness rectal biopsy, the suction rectal biopsy can be used to establish the diagnosis of Hirschsprung's disease in more than 95% of cases. Moreover, the diagnostic accuracy of a suction rectal biopsy may be increased by the addition of acetylcholinesterase staining to standard histologic evaluation. Congenital aganglionosis begins at the anus and extends proximally for a variable distance; in approximately 75% of cases ganglion cells may be found at the level of the rectum or rectosigmoid colon. The anatomic extent of aganglionosis extends into the more proximal colon in approximately 20% of cases and involves the entire colon or portions of the small intestine in 5% to 8% of patients. Once the diagnosis of Hirschsprung's disease is established, the basic principle of surgical management includes the removal of the poorly functioning aganglionic bowel and an anastomosis of a normally innervated portion of the intestine to the distal rectum. Historically, because of the increased risk of major operations on smaller children, patients with Hirschsprung's disease were initially treated with a "levelling colostomy" to divert fecal flow from the aganglionic segment. Then, when the child became larger, a definitive pullthrough procedure was performed. Recently there have been several reports of patients who have undergone an immediate corrective procedure when the diagnosis was made. Although

the ultimate safety and effectiveness of this treatment strategy remains to be demonstrated, this approach is becoming more popular. In addition, to avoid placement of a preliminary colostomy, children with a new diagnosis of Hirschsprung's disease may be placed on a rectal washout protocol to allow continued passage of stool before a definitive operative procedure is undertaken. It should be emphasized that an increased risk of enterocolitis is probably present in these patients with untreated Hirschsprung's disease. The most commonly used definitive procedures for the management of Hirschsprung's disease include the Soave pull-through, the Duhamel procedure, and the Swenson procedure. No prospective studies have compared these procedures. It is generally thought that there are no important differences with regard to outcome and long-term function in patients treated with these surgical procedures. However, specific problems have been described for each of the three procedures. These include a reported increase in the incidence of enterocolitis after the Swenson operation, diarrhoea and incontinence after the Soave endorectal pull-through and constipation after the Duhamel procedure. The operative mortality in Hirschsprung's disease is increased in patients with total colonic aganglionosis and in patients with Down's syndrome. Ultrashort-segment Hirschsprung's disease is a controversial condition in which the length of aganglionosis extends for at most several centimetres proximal to the anus. This condition is usually somewhat more indolent than longer segment aganglionosis, and the diagnosis is usually made at an older age. The principal symptom of such patients is severe constipation. Enterocolitis or failure to thrive is unusual, and these children have usually been treated with laxatives or cathartic agents until the diagnosis is made. Although these patients can be treated by one of the definitive corrective pull-through operations, in many cases they will also have acceptable results after a procedure aimed directly at allowing relaxation of the distal rectum and anus. As one example, an anorectal myectomy may be indicated as an initial procedure in selected patients with ultrashortsegment Hirschsprung's disease. Total colonic aganglionosis is a severe form of Hirschsprung's disease and occurs in approximately 5% to 8% of patients. Signs and symptoms of this condition are more serious than those associated with other forms of Hirschsprung's disease. In particular, total colonic aganglionosis is more commonly recognized in the neonatal period and is more likely to be associated with enterocolitis. The contrast enema is not generally useful for establishing the diagnosis of total colonic aganglionosis because a transition zone is rarely identified. To establish the diagnosis of total colonic aganglionosis, the surgeon must have a high index of suspicion, and the condition should be considered in any neonate who has signs of intestinal obstruction. Although there have been reports of patients with total colonic aganglionosis managed with a primary pull-through, most paediatric surgeons perform a diverting enterostomy proximal to the aganglionic segment and defer definitive pull-through. Enterocolitis remains the most serious complication of Hirschsprung's disease. The risk of this complication remains even after a definitive corrective operation has been performed and may develop many years after the operation. The incidence of enterocolitis after operation is approximately 33%. The most accepted explanation for the persistent risk of enterocolitis after the corrective procedure is related to the persistently hypertonic anal sphincter associated with Hirschsprung's disease. This is thought to result in a functional obstruction that leads to infection and inflammation of the colon. Symptoms of enterocolitis associated with Hirschsprung's disease include abdominal distension, explosive diarrhoea, emesis, fever and lethargy. Radiographs are

helpful for establishing the diagnosis of enterocolitis. Characteristic findings include the presence of bowel dilation with multiple air fluid levels. The treatment of patients with enterocolitis associated with Hirschsprung's disease includes intravenous fluid resuscitation, bowel rest, nasogastric tube drainage, rectal tube drainage, and broad-spectrum antibiotics. In addition, gentle rectal irrigations with warm saline solution should be used to wash out retained stool and gas. Recently it had been suggested that routine rectal irrigations in the postoperative period after a definitive pull-through operation may prevent enterocolitis. The long-term functional outcome after definitive corrective operation for Hirschsprung's disease is difficult to determine, and there are conflicting data in the literature. In general, it is thought that in more than 90% of patients, the outcome will be satisfactory after one of the three most common operations for Hirschsprung's disease. In approximately 1% of cases, a permanent colostomy may be necessary. A poor functional outcome has been associated with the presence of Down's syndrome and total colonic aganglionosis. The reported incidence of rectal incontinence has ranged from 2% to 27% and the incidence of constipation has been approximately 10% in most reports. The great variability in the reported outcomes results from the retrospective nature of most of these surveys and argues strongly for additional prospective studies of the long-term functional outcome in patients with Hirschsprung's disease.

## INTRODUCTION

Hirschsprung's disease is one of the more common conditions treated by paediatric surgeons. Characterized by the absence of myenteric and submucosal ganglionic cells of the distal alimentary tract, Hirschsprung's disease results in decreased motility in the affected bowel segment. Patients with untreated Hirschsprung's disease may present for medical attention with symptoms ranging from severe constipation to life-threatening sepsis related to enterocolitis. The clinical outcome for affected patients has improved dramatically with the development of effective surgical procedures for managing this disease.

## HISTORICAL ASPECTS

The first report of a patient with Hirschsprung's disease was in 1691 by Frederick Ruysch in an autopsy report of a 5-year-old girl who died with unremitting constipation. His description, translated from the Latin text, was that of a "...five year-old girl (who) had been complaining for a long while of abdominal cramps. Whatever remedies have the ability to ease pain, dispel flatus, or kill worms were tried several times and found useless; for the pains continued and finally she died. When the small body was opened, I could see (to my amazement) hardly any abdominal viscus except that part of the colon where the rectum begins. The other viscera were hidden under an enormous extension of that part." Several more cases of the disease were noted before the classical description of congenital megacolon by Harald Hirschsprung, published in 1886. In this report he described the autopsy findings of massively dilated colon with muscular hypertrophy proximal to more normal colon in two infants who had severe constipation and abdominal distension since birth. The pathophysiologic features of Hirschsprung's disease remained in question until 1901, when Tittel noted the histologic finding of absent ganglionic cells in the bowel wall of a 15-month-old infant with congenital constipation. He also speculated that this abnormality may be responsible for the altered bowel motility. For many years the significance of this histologic finding was minimized and the absence of ganglion cells was generally thought to be a result of the proximal megacolon rather than responsible for the condition. Early in this century, most clinicians thought that the colonic dilatation in Hirschsprung's disease resulted from a neurologic imbalance between the sympathetic and parasympathetic neurologic innervation of the colon. In 1908, several theories for neuropathic dilation of the colon were advanced, and for many years, it was thought that the motility abnormality was primarily related to the proximally dilated portion of the bowel. Moreover, no differentiation was made of the various causes of megacolon, and pharmacologic and surgical treatment was directed specifically at the dilated segment. Specific treatment modalities included surgical sympathectomy and the administration of parasympathomimetic agents. By 1940, several more reports had noted the absence of ganglion cells in the colons of affected patients when Tiffen and colleagues concluded that the proximally dilated colon resulted from pseudoobstruction caused by absent peristalsis in the distal segment. This notion was not widely accepted and during the early 1940s it was still generally recommended that children with congenital megacolon undergo sympathectomy or subtotal colectomy. Investigators continued to confirm the absence of ganglion cells within the distal

contracted colon segment, and in 1948, Orvar Swenson and Alexander Bill presented their insightful elucidation of the pathophysiologic makeup of Hirschsprung's disease. This finally allowed the development of operative procedures to treat the condition definitively. Swenson's conclusion that the proximal megacolon results from an absence of distal peristalsis was made after he studied a 5-year-old child in whom the placement of a sigmoid colostomy resulted in marked improvement in the patient's condition. When the colostomy was closed 1 year later, the symptoms of malnutrition and chronic constipation recurred. The child improved again after an other diverting colostomy was created. Dr. Swenson believed that the child was behaving as if he had a distal colon obstruction, and manometry demonstrated the absence of peristaltic activity. He then performed his pioneering definitive procedure for Hirschsprung's disease by removing the distal rectosigmoid colon and performing a colo-ana anastomosis. The first series of patients with congenital megacolon treated with Swenson's operation was published in 1949. Other surgical procedures were then developed to treat patients with Hirschsprung's disease. The Duhamel procedure was devised to prevent the anterior dissection required by the Swenson operation. There have since been several modifications described that simplify the Duhamel procedure and aim to decrease the frequency of postoperative complications. The endorectal pull-through operation originally described by Ravitch and Sabiston was modified by Soave for use in children with Hirschsprung's disease. The Boley modification of the Soave procedure, in which a formal anastomosis is constructed at the anus, was described in 1964. Most paediatric surgeons performing the endorectal pull-through procedure use the Boley modification, but by convention it is usually still termed the Soave procedure. Today, approximately 35% of paediatric surgeons treat patients with the Soave procedure; roughly the same number use the modified Duhamel procedure and a slightly lower percentage use the Swenson operation.

## EPIDEMIOLOGY

In recent population-based studies, the incidence of congenital aganglionosis or Hirschsprung's disease has been shown to range from approximately 1 per 5400 to 1 per 7200 live births. In large clinical series approximately 80% of patients are male and 20% are female. The male preponderance for the disease is slightly reduced when only patients having long-segment aganglionosis are considered. Several studies have failed to demonstrate an association between the incidence of aganglionosis and race. In approximately 8% of cases, a history of Hirschsprung's disease is present in other family members. A familial component is more likely in patients with long-segment aganglionosis when compared with those whose aganglionic segment is short. The risk of a subsequent sibling having Hirschsprung's disease is approximately 5%. In a parent who has Hirschsprung's disease, the risk of having an affected child is approximately 2% in those who have short segment disease but may be as high 30% if the aganglionic segment is long. Hirschsprung's disease has been demonstrated by segregation analysis to be a genetically heterogeneous condition with autosomal-dominant, autosomal-recessive, and polygenic subtypes. Moreover, there are a number of inherited syndromes in which the incidence of Hirschsprung's disease is increased, including the multiple endocrine neoplasia syndrome (MEN) type 2A, Waardenberg's syndrome, and Cartilage-hair hypoplasia. In familial forms of the disease, a greater likelihood exists that patients will have aganglionosis involving the entire colon. Associated congenital anomalies are relatively common in patients with Hirschsprung's disease. In one report of 179 cases, 39 patients with Hirschsprung's disease (22%) also had other associated anomalies. A listing of these anomalies is presented in Table 1. Down's syndrome is also a frequent finding in patients with Hirschsprung's disease, occurring in approximately 8% of patients. Cardiac defect are especially common in those who have Hirschsprung's disease and Down's syndrome, occurring in approximately 50% of such patients.

## EMBRYOLOGY, CAUSE, AND GENETICS

The congenital absence of ganglion cells in the distal alimentary tract is the pathologic *sin quo non* of Hirschsprung's disease. The anus is always involved, and a variable length of distal intestine may be involved as well. Both the myenteric (Auerbach) and the submucosal (Meissner) plexuses are involved, and the absence of innervation results in reduced bowel motility. Although the exact cause of aganglionosis remains uncertain, three possible explanations have been postulated for the developmental defect: (1) either the precursor neuroblasts did not migrate into the affected portion of the bowel during embryonic development, (2) the neuroblasts were present at one time and then failed to develop into mature functioning ganglia, or (3) the cells developed normally and then underwent degradation through some undefined mechanism, perhaps because of microenvironmental factors or as a result of an ischemic insult. To study the pathophysiologic makeup of Hirschsprung's disease further, investigators have explored the embryonic development of the enteric nervous system. The embryology of the enteric nervous system has been studied most completely in the murine model. Recent advances in molecular probes and immunohistochemical techniques have allowed investigators to gain a much greater understanding of neural development. In particular, because undifferentiated neuroblasts are morphologically indistinguishable from the surrounding mesenchymal cells in the early period of enteric development, sensitive molecular markers have been used to follow enteric nerve cells through the various stages of migration. The neural and glial cells that form the ganglia of the alimentary tract originate from the vagal and sacral neural crest populations. Vagal enteric neural crest cells arise in the cranial portion of the neural tube and normally migrate throughout the gut in a cranial to caudal direction. The sacral neural crest cells arise from the caudal neural tube and probably migrate for a distance cranially from the distal end of the alimentary tract. It is thought that this process also occurs during human development. A dual gradient of enteric nerve cell maturation has been described in human embryos, where maturation in the esophagus and the rectum proceeded ahead of that of the ileum. The exact lineages of human enteric ganglia cells, however, have not been formally proven. There are two mutant strains of mice affected by congenital aganglionosis of the distal bowel that have been particularly useful in elucidating the embryology of Hirschsprung's disease. These are the homozygous lethal spotted and the piebald lethal strains, whose recessive genetic mutations initially arose in laboratory animals. These mice exhibit a clinical condition that is very similar to Hirschsprung's disease. Specifically, these mice have a variable length of distal aganglionic bowel with morphologically normal proximal bowel. The mice have dilated bowel proximal to a functional distal obstruction, a condition that is usually lethal. It is interesting that these animals also have areas of decreased skin pigmentation that result from an absence of cutaneous melanocytes, which also derive from the neural crest. Similar syndromes of bowel dysmotility related to an absence of ganglion cells in conjunction with abnormalities in skin pigmentation have been described in the rat and the horse (Fig. 1). These findings suggest that there may be a maturation or colonization defect in a particular population of cells derived from the neural crest that ultimately differentiate into melanocytes and gut neurons. With regard to the enteric ganglia, embryologic studies have shown that the distal gut of the lethal spotted embryo never contains cells with

neurogenic potential, supporting the hypothesis that intestinal aganglionosis results from the absence of neural colonization, rather than from the degradation of neurons. Recently a series of elegant experiments has been described that suggests that in lethal spotted and piebald lethal mice, the congenital aganglionosis is caused by an alteration in the microenvironment of the intestinal wall of the affected area, which in some way inhibits the colonization of the distal gut with neuroblasts. In these experiments, co-culture of embryonic hindguts from the mouse strains with embryonic neuroblasts from affected and wild-type animals revealed that the affected enteric segments did not allow the ingrowth of normal neural crest cells. In contrast, the hindgut of normal animals was able to support the growth of neuroblasts from both affected and wild-type animals. From these *in vitro* data, the investigators concluded that the essential defect in these mice strains is in the milieu of the gut wall, which prevents normal development of the enteric nervous system. The notion that the fundamental defect is in the microenvironment of the bowel wall, preventing ingrowth of neuroblasts, rather than intrinsically within the neuroblasts, is further supported by another line of *in vivo* evidence. A series of wild type/lethal spotted chimeric mice were created in which a genetic marker that allowed the investigators to distinguish the origin of the neuroblasts was present. In phenotypically normal animals, in which no megacolon was present, ganglion cells that were derived from the lethal spotted species were found in the gut. Thus no intrinsic defect was present in these cells. Moreover, the aganglionic phenotype was only seen in mice in which more than 80% of the mesenchymal cells were derived from the lethal spotted genome. Presumably, the microenvironmental defect can be compensated for if only approximately 20% of the cells are normal. These investigators concluded that in the lethal spotted mouse, the primary defect responsible for the absence of enteric ganglia in the distal colon is not autonomous to the migrating neuroblasts, but rather results from a primary defect in the surrounding mesenchyme of the intestinal wall. In another study these investigators demonstrated that the migration pattern of enteric neuroblasts in the colon differs from that in the small intestine. Moreover, there is a delay of transit through the ileocecal region, which may be responsible for the inability of the neuroblasts to colonize the entire colon. More recently, the nature of the genetic mutation responsible for the piebald lethal strain of mice was elucidated. In these mice there is complete absence of the endothelin-B receptor (EDNRB) gene. Moreover, when the EDNRB gene was disrupted in knockout mice, the animals exhibited a phenotype indistinguishable from piebaldism. When such mice were cross-bred with piebald lethal mice, there was no complementation of the aganglionic phenotype, proving that EDNRB is the responsible gene for the piebald lethal syndrome. To further investigate how EDNRB affects migration of enteric neuroblasts into the distal colon, the same investigators created mice in which there was deletion of the endothelin-3 ligand gene. This is the ligand that interacts with the EDNRB receptor, and its absence results in the development of mice with the recessive phenotype of aganglionic megacolon with coat spotting, identical to the murine lethal spotting phenotype. Moreover, in lethal spotting mice the endothelin-3 gene is mutated, completely preventing its activation. These studies have demonstrated conclusively in the murine model that the interaction between the EDNRB receptor and the endothelin-3 ligand is essential for migration of enteric neuroblasts into the distal colon and the disruption of either of these genes results in failure in this migration, with the subsequent development of clinical findings similar to Hirschsprung's disease. In

human beings, several different genes have been shown to be responsible for the development of Hirschsprung's disease. First, linkage data localized the causative gene to chromosome 10 in one kindred demonstrating autosomal-dominant inheritance of Hirschsprung's disease. The gene was further localized to the pericentromeric region of the chromosome. The responsible gene was subsequently found to be the RET protooncogene, which was found to possess missense mutations in affected patients. There is incomplete penetrance of the aganglionic trait in the kindred's with the RET mutation. As is the case with other familial types of Hirschsprung's disease, there is a higher incidence of long-segment aganglionosis in the affected patients, although short-segment disease also may be associated with RET mutations. Moreover, the length of aganglionosis may vary within a family. Mutations to the RET protooncogene, a gene that encodes for a receptor tyrosine kinase protein, have also been found to have arisen de novo in some sporadic (nonfamilial) cases of Hirschsprung's disease. Mutations in this gene have also been associated with the MEN 2A and MEN 2B syndromes, in which affected individuals have neoplasms of tissues. Indeed, in the RET-knockout transgenic mouse, there is a complete absence of enteric neurons throughout the alimentary tract and renal agenesis or dysgenesis. Several conditions are associated with mutations in the RET protooncogene. The specific phenotype depends on the position and type of mutation and, in the case of Hirschsprung's disease, other genes or environmental factors account for the variable penetrance and the differing lengths of the aganglionic bowel segment. The MEN 2 syndromes are caused by mutations in the RET gene that result in constitutive tyrosine kinase activity, increasing the signal for vulnerable cells to undergo mitosis. In Hirschsprung's disease, however, the missense and nonsense mutations in RET result in an inactivated or truncated protein. This decrease in total RET protein dosage apparently plays a critical role in the development of enteric neurons. Autosomally inherited aganglionosis is relatively unusual; approximately 80% of Hirschsprung's disease cases can be ascribed to the inheritance of recessive genes or are polygenic in origin. Recently the genes that confer susceptibility to Hirschsprung's disease in affected members of a Mennonite kindred were elucidated with segregation analysis. The major genetic locus responsible for the disease was found to reside at chromosome 13q22. Evidence was also found in the kindred for the existence of a genetic modifier for Hirschsprung's disease located on chromosome 21. This genetic locus may account for the greater incidence of the disease in patients with Down's syndrome. Further study of this Mennonite pedigree revealed that the major genetic lesion responsible for Hirschsprung's disease is a missense mutation in the EDNRB, a situation that is analogous to the piebald-lethal mouse strain. In the Mennonite kindred the mutation was neither completely autosomal nor completely dominant; instead, there was apparently a dosage effect in that the penetrance of Hirschsprung's disease was 74% in those who had homozygous mutation of EDNRB but only 21% in heterozygotes. The marked variation in the penetrance of the disease and the significant sex-related difference in disease expression support the muligenic nature of the disease. Yet another tyrosine kinase growth factor has been implicated in the pathogenesis of Hirschsprung's disease. Mutation of the c-kit protooncogene has recently been shown to be responsible for human piebaldism, which is a dominant trait characterized by patches of hypopigmented skin and hair and may be related to Waardenberg's syndrome. The trait is thought to result from defective melanocyte migration out of the neural crest. Other cell lines are affected as well. The

coincidence of piebaldism and Hirschsprung's disease has been described in a number of individuals, suggesting the presence of a general defect in migration of cells derived from the neural crest. The different clinical syndromes associated with human piebaldism may be associated with different c-kit mutations, which is reminiscent of the different conditions resulting from mutations in the RET protooncogene. It is interesting that in mice the c-kit protein has also been implicated to play an important role in the development of the autonomic pacemaker system of the gut. Recent studies in human beings have documented a reduced c-kit protein level in aganglionic bowel relative to normal bowel. Thus c-kit is another gene that may be important in some cases of Hirschsprung's disease. The microenvironment of the bowel wall in patients with Hirschsprung's disease has been evaluated in multiple studies. When aganglionic intestine has been compared with normal intestine, differences have been found in the levels of laminin, NAPH-diaphorase, and neural cell adhesion molecule. Furthermore, many neuropeptides thought to be important in gut innervation have also been investigated. In these studies, alterations have been found in the levels of nerve growth factor, neuropeptide-Y, vasoactive intestinal peptide, substance P, met-enkephalin, and gastrin releasing peptide when ganglionic bowel has been compared with aganglionic bowel. The specific mechanisms by which gut motility is affected by alterations in the levels of these various substances remains to be elucidated. Recently much attention has been directed toward the possible role of nitric oxide in the altered gut motility associated with Hirschsprung's disease. This substance was originally known as endothelium-derived relaxing factor, a smooth-muscle relaxant present ubiquitously within the body. Nitric oxide is used as a chemical messenger by the nonadrenergic noncholinergic nerves of the intestine and is thought to be an important mediator of gut relaxation. Nitric oxide synthase is reduced within the aganglionic portions of intestine in patients with Hirschsprung's disease, and this phenomenon is postulated to account for the inability of these portions of the gut to relax during peristalsis. Further support for this notion is provided by experiments in which isolated muscle strips from aganglionic bowel exhibited dose-dependent relaxation when incubated in the presence of exogenously applied nitric oxide. The relaxation was abrogated in the presence of methylene blue, which is known to block the action of nitric oxide. Thus the nonadrenergic noncholinergic enteric nervous system is likely important in normal bowel relaxation, and deficiency of these nerves may be responsible for the altered gut motility seen in patients with Hirschsprung's disease. To summarize what is known about the genetic cause of Hirschsprung's disease, the condition probably results from a failure of enteric neuroblasts to populate a variable length of the distal alimentary tract. Most of the data from animal models with aganglionosis support the assertion that the basic defect is in the microenvironment of the bowel wall; there is apparently a congenital absence of a factor or factors that are necessary for normal migration and development of the gut ganglion cells. The different animal models for congenital aganglionosis suggest that several specific molecular or genetic pathways may be altered to result in the absence of enteric ganglion cells. Most of the known genes thought to be responsible for Hirschsprung's disease (or aganglionosis in the complementary animal model) are from the family of genes encoding for receptor tyrosine kinase molecules or for the ligands to such molecules. Thus there are apparently defects in embryonic tissues derived from the neural crest either within the growth-signalling pathway or with cell to cell communication that

prevents the proper growth and migration of the enteric neuron cells. This is an especially attractive hypothesis in the case of patients with a mutated RET protooncogene, because the RET protein has a cadherin-like domain known to be important in intracellular signalling. The differences between normal gut and the Hirschsprung's intestine with regard to the presence of neuropeptides and other putative neural-receptor ligands such as nitric oxide probably reflect the different neural milieu present in the aganglionic bowel. The decreased number of nerves synthesizing nitric oxide may be the final common pathway responsible for the decreased gut relaxation. The challenge for the future is the further elucidation of the molecular mechanisms responsible for the altered intestinal physiologic makeup associated with Hirschsprung's disease. The ultimate aim remains the rational correction or management of the altered intestinal motility.

## DIAGNOSIS AND PATHOLOGIC FEATURES

Hirschsprung's disease is increasingly recognized earlier in childhood, so that currently the diagnosis is usually established during the first year of life. In recent reports the mean age of diagnosis has been approximately 10 months. The ages at diagnosis from two large series of patients with Hirschsprung's disease are presented in Table 2, demonstrating the recent improvement in recognition. In approximately 5% of patients, the diagnosis may not be established until after the age of 5 years; in very rare cases, patients may reach adulthood before their aganglionosis is recognized. In neonates the presenting signs associated with Hirschsprung's disease are relatively specific for intestinal obstruction and are tabulated from a series of patients in Table 3. At the C. S. Mott Children's Hospital, from which these data were obtained, aganglionosis is the second most common diagnosis associated with the clinical and radiographic diagnosis of bowel obstruction. The most common cause of obstruction in these patients was necrotizing enterocolitis. Bilious emesis or gastric drainage was present in 35% of the children, which is always suspicious for malrotation with volvulus, but may be seen in intestinal obstruction from any cause. Finally, although it has been taught that the failure to pass meconium within the first 24 hours of life is a sensitive and specific sign for aganglionosis, this finding was encountered in only 58% of the subjects in this study. In addition, more than one half of the babies had documented meconium passage by 48 hours of life. Neonates with Hirschsprung's disease may have enterocolitis that can be life-threatening. Clinical findings that suggest this diagnosis include abdominal distension, diarrhoea, fever, and hematochezia. On rectal examination there may be an explosion of diarrhoea when the examining finger is removed. There may also be more general signs of sepsis such as lethargy and poor tissue perfusion. Fortunately, as the aganglionosis is recognized earlier in infancy, fewer children are allowed to have development of the enterocolitis associated with untreated Hirschsprung's disease. Significant risk factors for enterocolitis include the presence of Down's syndrome and the delay in diagnosis of Hirschsprung's disease beyond the age of 1 week. In recent studies the frequency of enterocolitis as the presenting condition for Hirschsprung's disease in newborns has only been approximately 6%, whereas in previous reports this incidence has been as high as 20%. This earlier recognition and management of aganglionosis is an important advance, because the mortality of neonatal enterocolitis associated with Hirschsprung's disease may be as high as 30%. In rare cases neonates with Hirschsprung's disease may have intestinal perforation as the first manifestation. Older children with Hirschsprung's disease usually have chronic constipation but may also present with enterocolitis. Fortunately it is now rare for Hirschsprung's disease to remain unrecognized for years until the diagnosis is made in a chronically malnourished child with marked abdominal distension, as shown in Fig. 2. The differential diagnosis of chronic constipation in childhood is broad, but in most cases the paediatric surgeon will be asked to differentiate between behavioural or psychogenic constipation and a neurogenic dysmotility syndrome such as Hirschsprung's disease. Historic factors may help in distinguishing these diagnoses, and in retrospective studies more than 90% of children with Hirschsprung's disease were found to have had symptoms develop within the first 3 months of life. Children with Hirschsprung's disease have usually had constipation since birth and may be

chronically ill with evidence of poor weight gain. Moreover, these patients will usually have a markedly distended abdomen, owing to the tight anal sphincter and the inability to release gas. In contrast, children with chronic behavioural constipation may have infrequent huge bowel movements and occasional encompresis and will typically have a relatively flat abdomen on physical examination. Abdominal radiographs are indicated to evaluate children and infants suspected of having Hirschsprung's disease. In neonates, dilated loops of bowel extending to the level of the functional obstruction may be seen (Fig. 3). This is consistent with the diagnosis of a distal bowel obstruction, and the differential diagnosis of this condition is listed in Table 4. Whenever bilious emesis is encountered, strong consideration should be given to obtaining at least a limited upper gastrointestinal contrast study to document proper location of the ligament of Treitz to exclude the possibility of malrotation with volvulus. To exclude the syndromes of meconium plugging, a contrast enema should usually be obtained. A water-soluble contrast study can be therapeutic and diagnostic in cases of meconium ileus. It is important to refrain from performing a digital rectal examination or any manipulation of the anus before this diagnostic study, because this interference may distort the radiographic transition zone suggestive of Hirschsprung's disease. Patients who are found to have meconium plug disease of the newborn should undergo rectal biopsy, because some of these patients will also have Hirschsprung's disease. In older children with Hirschsprung's disease, there will in most cases be the classic radiographic finding of markedly dilated colon proximally with a transition zone into a contracted distal segment, as shown in Fig. 4. In neonates, however, the findings from the contrast enema are not necessarily diagnostic. Recent reports have shown that the diagnostic accuracy of the barium enema in newborn patients with aganglionosis is approximately 80%. Frequently, there will be retention of barium in the colon on delayed radiographs obtained 24 hours after the initial study, and this finding is suspicious INSERT FIG. 4 HERE INSERT FIG. 5 HERE for Hirschsprung's disease. These delayed fills may demonstrate the classic transition zone between dilated and contracted bowel, as shown in Fig. 5. Finally, in patients with total colonic Hirschsprung's disease, the barium enema findings are usually nondiagnostic and should not be relied on for establishing the diagnosis. Anorectal manometry is used in some paediatric centres to aid in establishing the diagnosis of Hirschsprung's disease. This test is based on the presence of altered anal reflexes in persons with aganglionosis. In particular, these patients do not exhibit normal anal sphincter relaxation in response to increased rectal ampullary pressure. Moreover, the resting anal sphincter pressure is significantly increased, INSERT FIG 6A HERE although there may be substantial overlap in this parameter between affected and normal individuals. Several studies regarding the usefulness of anorectal manometry in the diagnosis of hirschsprung's disease have shown a diagnostic accuracy rate of approximately 90% INSERT FIG 6C HERE This technique is somewhat less accurate in the neonatal population and is technically demanding, which renders it less useful than other methods for establishing the diagnosis of Hirschsprung's disease. Furthermore it has been suggested that the normal anorectal reflexes are underdeveloped in very young and prematurely born infants, although this is a controversial issue. In any case many experienced paediatric centres, especially in Japan, place strong reliance on anorectal manometry testing in the diagnosis of Hirschsprung's disease. The definitive diagnosis of Hirschsprung's disease is established by rectal biopsy to demonstrate the congenital

absence of ganglion cells in Miessner's (submucosal) and in Auebach's (myenteric) plexus. Hypertrophic nerve fibres are usually present in the affected region of the intestine, although this finding is not consistent enough to be diagnostically useful. Representative histologic sections of normal and aganglionic colon are shown in Fig.6. The most definitive method for obtaining tissue for histologic examination is by full-thickness rectal biopsy. The specimen must be obtained at least 1.5cm above the pectinate line, because there is normally hypoganglionsis below this level. Care should be taken to orient the resected specimen correctly for the pathologist, and in most paediatric centres the treatment plan can reliably be based on a frozen section interpretation. Surgical complication such as infection or bleeding after a full thickness rectal biopsy are uncommon. Over the last 2 decades suction rectal biopsy has been used more commonly as a simpler method for obtaining rectal tissue for definitive histologic evaluation. This technique uses a simple device in which rectal mucosa is sucked into the side port of the instrument, and a self-contained cylindrical knife cuts off the tissue. Advantages of this method include its simplicity and the fact that the procedure does not require general anaesthesia. The principal disadvantage is that the tissue obtained is quite small and in most cases is only partial thickness bowel, requiring that the diagnosis be established without evaluating the myenteric neural plexus. Moreover, in patients older than infants, the mucosa is thicker so that the specimen obtained with the suction rectal biopsy device does not even include submucosal tissue, which usually renders the specimen inadequate to diagnose aganglionsis. In addition, because of difficulty in orienting the tiny piece of tissue and owing to distortion, frozen-section evaluation of suction rectal biopsy specimens is not recommended. Although complication from the procedure are rare, there have been a few reports of bowel perforation with sepsis, excessive bleeding requiring transfusion and even a case in which the iliac artery was injured. When an adequate piece of tissue is obtained with suction rectal biopsy, submucosal ganglion cells, but not the myenteric ganglia, can usually be identified on histologic examination. The absence of submucosal ganglion cells does not necessarily prove the diagnosis of Hirschsprung's disease, but the presence of such cells in the submucosa effectively excludes aganglionsis. In a series of 302 children younger than 1 year of age, the initial tissue specimens were inadequate to make a diagnosis in 2.3% of cases, but the diagnostic accuracy was 100% in the patients who had adequate specimens. In 142 children older than 1 year of age, the incidence of suction biopsy yielding an inadequate tissue specimen, no false-positive or false-negative diagnoses were made. In this study definitive treatment of aganglionsis was based on a confirmatory full thickness biopsy as recommended by most paediatric surgeons. Thus suction rectal biopsy is an accurate and safe method for establishing the diagnosis of Hirschsprung's disease; in cases where the diagnosis remains in doubt, definitive open full-thickness biopsy should be performed. Moreover, the definitive biopsy should be obtained before undertaking definitive surgical treatment. Difficulty in obtaining a conclusive diagnosis of Hirschsprung's disease based on excluding the presence of ganglion cells, this provided the impetus to devise a positive diagnostic method. This has been especially important since the wider adoption of suction rectal biopsy over definitive full-thickness biopsy. Because it is known that cholinergic innervation is increased in the aganglionic intestine in patients with Hirschsprung's disease, pathologists in many centres use histochemical staining for acetylcholinesterase activity to improve the diagnostic accuracy of suction

rectal biopsy. There is increased staining of this moiety in affected patients INSE4RT

FIGURE 7 HERE The diagnostic accuracy of acetylcholinesterase staining has been evaluated in many studies but the results have been conflicting. In one study of 154 suction rectal biopsy specimens from children with constipation, there were 25 cases of which the tissue stained with hematoxylin-eosin was inadequate to make the diagnosis. In 23 patients with acetylcholinesterase staining enabled an accurate diagnosis that was confirmed either by repeat biopsy or by repeated clinical evaluation. Thus the use of acetylcholinesterase staining in conjunction with standard microscopic evaluation allowed the correct histologic diagnosis to be made in 99% of cases and these investigators concluded in the test was useful and that it prevented repeat rectal biopsies. In other studies acetylcholinesterase staining of rectal biopsies have produced misleading results in many 10 % of cases . The conflicting results are probably related to a different levels of experience with the test, although even pathologists with extensive experience acknowledge that the false-negative and false positive acetylcholinesterase staining test results occur. In summary the diagnosis of Hirschsprung's disease can either be established or excluded in most cases with suction rectal biopsy with standard hematoxylin-eosin staining. The addition of acetylcholinesterase staining increases the diagnostic accuracy, but the procedure is technically complicated and the interpretation can be misleading unless there is extensive experience with the technique. In some patients the biopsy may need to be repeated. A properly performed full-thickness rectal biopsy is still regarded as the definitive method for evaluating the ganglion cells in the alimentary tract to establish the diagnosis of Hirschsprung's disease. However for patients who have the typical clinical findings and a radiographic picture demonstrating the classic transition zone in the colon the surgeon may elect not to perform a rectal biopsy, instead, biopsies of the colon may be obtained at the time of laparotomy for colostomy placement. at some point in the treatment of the patient with Hirschsprung's disease the extend of the affected intestine must be determined. The aganglionosis begins at the anus and extends proximally for a variable distance; in approximately 75% of cases, ganglion cells may be found at the level of the rectum or rectosigmoid colon. the anatomic extend of aganglionosis in nearly 1000 patients with Hirschsprung's disease taken from a survey of members of the surgical section of the American Academy of Paediatrics, is tabulated in table 5 Insert table 5 here Because the treatment and outcome of patients with Hirschsprung's disease may depend on the extend of aganglionosis, this condition has been classified accordingly. When the ganglionic portion of the intestine extends into the sigmoid or rectum then it may be termed "short segment" Hirschsprung's disease. "Long Segment" disease is present when the ganglionated intestine extends into the colon proximal to the sigmoid. The term "total colonic" is used to describe cases in which the entire colon and perhaps some of the small intestine is involved. Finally "ultrashort segment" disease describes the controversial condition in which there is at most a few centimetres of aganglionic rectum adjacent to the anus. Although this terminology is useful when studying the various treatment options for Hirschsprung, it is probably preferable simply to describe the anatomic level at which the ganglionated segment ends. It should also be noted that although aganglionosis is the most common neuropathic cause of altered bowel motility, other very rare conditions can exist in conjunction with Hirschsprung's disease or present with clinical features reminiscent of aganglionosis. These conditions are known collectively as Neuronal intestinal dysphasia (NID)

## TREATMENT

The basic principle in the surgical management of Hirschsprung's disease is the removal or bypass of the poorly functioning aganglionic bowel, with anastomosis of normally innervated intestine to the distal rectum. In most cases this restores nearly normal motility and enables most affected individuals to have normal bowel function. For technical reasons the standard treatment has been to create a diverting colostomy at the time of diagnosis. A definitive pull-through procedure is performed some months later when the child is grown to at least 10kg in weight. This approach evolved during the 1950s when the risk of major operations in neonates was thought to be prohibitive, but this probably remains the approach for most paediatric surgeons. Recently with the development of safer anaesthetic methods, hemodynamic monitoring, and modern antibiotics, other approaches have been explored in which the condition is treated without the preliminary diverting colostomy. In general, the treatment plan will vary according to the extent of aganglionosis and the age of the patient. The choices available for treatment of patients with Hirschsprung's disease are illustrated in fig 8

## INITIAL TREATMENT

The principal reason for creating a diverting colostomy, rather than simply performing a definitive pull-through when Hirschsprung's disease is first diagnosed, has been the difficulty in performing these procedures in small infants. Moreover, when the initial presenting condition is enterocolitis the results in the diagnosis of aganglionosis, is probably wise to allow the inflammation in the intestine to resolve before subjecting the patient to a major abdominal operation. Finally in many children marked distension is present and this renders the pull-through procedure more difficult. The operation to create a diverting colostomy usually begins with a transverse left lower quadrant abdominal incision. Most paediatric surgeons use loop colostomies in children with Hirschsprung's disease and in most cases it is acceptable to bring the ostomy through the incision. The term "levelling colostomy" is often used for this procedure to denote the fact that one of the aims of the operation is to determine the level of aganglionosis, so that the colostomy will be created in normally innervated and normally functioning bowel. If there has not been a full-thickness rectal biopsy obtained before the laparotomy, then it may be wise to establish the diagnosis of Hirschsprung's disease definitively by performing an extramucosal colon biopsy at the peritoneal reflection. Similarly, biopsy specimens must be obtained and sent for frozen section histologic analysis to determine where there is a ganglionic bowel in which to place the ostomy. In approximately 80% of cases, this will be hypertrophied bowel wall that has developed in most of the distal pseudo obstructed segment (FIG (9)). If ganglionated colon can not be identified through the initial incision then the incision should probably be close and a right sided incision should be performed to find the level to create the ostomy. Biopsy specimens of the right colon should be obtained and consideration should be given to removing the appendix to determine whether the proximal colon has ganglion cells. In addition, if ganglia are identified, this may serve as a "positive control" to aid the pathologist in identifying these cells elsewhere. The ostomy should be created in unequivocally normal intestine. An area of the bowel with decreased number of ganglionic cells may represent the transition zone and an ostomy placed in this region may not function well. As with any surgical procedure risks are associated with the diverting colostomy in children. In one large series of patients with Hirschsprung's disease, the reported incidence of ostomy prolapse or retraction was 26% and 13% of the patients' required stomal revision. In addition, the risk of having severe enterocolitis after undergoing a diverting colostomy but before the definitive pull-through procedure is approximately 10%. Another option for the initial treatment of patients with Hirschsprung's disease avoids a temporary colostomy and defers the definitive surgery. The child is placed on a regimen of rectal irrigations to encourage continued passage of fecal material. This is aided by the use of breast milk or pre-digested formula to reduce fecal bulk. In many cases infants taking only breast milk will have nearly normal bowel function until other foods are introduced into the diet. The goal of these manoeuvres is to offset the decreased motility of the distal colon and reduce the risk of enterocolitis, which can be life-threatening. Moreover, this technique of maintaining bowel function will prevent dilatation of the bowel proximal to the pseudo obstructed segment allowing accurate anastomosis without leakage. Finally, another obvious advantage of avoiding the placement of a diverting ostomy is the prevention of complications associated with this procedure. It should be noted that in sending a child

home on a strict rectal irrigation regimen requires responsible parents or caretakers who are educated to recognize the signs and symptoms of enterocolitis and who can bring the child to the clinic for frequent follow up visits. If the social situation is such that these requirements can not be met, then it is probably safer to perform a diverting colostomy and to allow the child to grow for a few months before a definitive treatment. The risk of deferred treatment may be higher in children with total colonic aganglionosis. In one report of seven children with total colon Hirschsprung's disease managed with rectal irrigations protocol, there was severe enterocolitis or an iatrogenic perforation in five patients that necessitated an emergent diverting ileostomy. Orvar Swenson's early series with his procedure to treat children with Hirschsprung's disease documented a mortality rate of 28% in patients younger than 4 months of age. Understandably, these results for many years discouraged paediatric surgeons from attempting definitive surgical treatment in young infants with Hirschsprung's disease, however in the early 1980's surgeons reported a small selected series of neonates and infants treated for congenital megacolon at the time of diagnosis without the previous placement of diverting colostomy. Although the results appeared to be acceptable, the technique was not widely accepted. In the last several years, there have been a number of additional reports of successful treatment of children with Hirschsprung's disease without an initial diverting colostomy. In most cases the Soave procedure, as modified by Boley, is used. The Swenson procedure has also been used as a primary procedure, and with the development of smaller stapling devices initially designed for laparoscopic procedures, the Duhamel procedure has now been reported in the neonatal period. The complications associated with the primary correction of Hirschsprung's disease in recent reports are listed in Table 6. No controlled prospective studies have compared patients who had early primary management of their Hirschsprung's disease with those who were treated after a period of decompression with an enterostomy. Recently, to compare patients who had primary treatment of their megacolon with a concurrent group of children who had a colostomy before definitive treatment, the experience at Washington University and McMaster University Hospital Centre was reviewed. In this study, the results for 36 children with Hirschsprung's disease treated in the first year of life with a Soave pull-through were reviewed. This was the experience of seven paediatric surgeons over a period of 3 years. Twenty-three children initially underwent a diverting colostomy, and 13 patients underwent a single-stage pull-through without diverting colostomy. No significant differences were found between the two groups with regard to presenting symptoms, age at diagnosis, extent of aganglionosis, and associated anomalies. None of the patients had total colonic Hirschsprung's disease. The patients were not randomized and the treatment plan was made according to the surgeon's usual practice. The mean period of follow up for all patients was 17 months. The complications experienced by the patients are listed in Table 7. Although one death occurred in the group of patients treated with the single-stage approach, no significant differences were seen between the groups with regard to complications related to the definitive procedure. However, the complications related to the definitive procedure. However, the complication rate associated with the diverting colostomy in the patients having this procedure was 35% and three (13%) of the children required operative revision of the colostomy. It is interesting that all of the major complications in the single-stage group of patients occurred in infants who were less than 4 kg in weight. Thus in this study, although no advantage was clearly demonstrated by

using either the one-stage or the two-stage approach to treating Hirschsprung's disease, significant complications were associated with enterostomies. The authors therefore tentatively concluded that the single-stage approach may be acceptable for managing Hirschsprung's disease in infants. In summary, the decision regarding the timing of the definitive pull-through procedure for Hirschsprung's disease remains controversial. Most paediatric surgeons create a diverting enterostomy at the time of diagnosis and defer a definitive pull-through procedure until the child weighs 5 to 10 kg. In many children, it may be preferable to use the single-stage approach, placing small infants on a rectal washout protocol to allow them to gain weight before performing a definitive pull-through procedure when the child weighs more than 4 kg. In children with total colonic aganglionosis, an increased complication rate may be associated with the use of rectal irrigations before a primary definitive procedure is performed, and the two-stage approach may be preferred. If the social situation is such that uncertainty exists about the ability of caretakers to perform rectal washouts or if the patient cannot return regularly for follow-up, then it may be unsafe to send a child with Hirschsprung's disease home without a diverting enterostomy. IN addition, if there is any uncertainty about the diagnosis, then the definitive pull-through procedure should be deferred.

## DEFINITIVE SURGICAL CORRECTION

The three most commonly performed operations for definitive treatment of patients with Hirschsprung's disease are Swenson, Duhamel, and Soave procedures and their various modifications. Although no prospective trials have compared these operations, it is generally thought that there are no significant differences between them with regard to outcome or surgical complications. In most uncomplicated cases of Hirschsprung's disease, the choice of an operative procedure depends principally on the surgeon's personal preference. In some particular situations, however, one procedure may have some advantages over the others. For example, when the diagnosis is made in older children who have had multiple episodes of enterocolitis, the submucosal dissection associated with the Soave endorectal pull-through procedure can be very difficult and associated with excessive blood loss. In this case, it may be more rational to perform the technically simpler Duhamel operation. On the other hand, some surgeons prefer the Soave procedure because it allows the relatively straightforward Duhamel procedure to be performed if a second operation is needed. Moreover, particular operations may have theoretic and practical advantages in the case of ultrashort-segment disease or total colonic aganglionosis. Swenson's procedure was the first operation devised for the definitive management of Hirschsprung's disease and is illustrated in Fig. 10. This operation is generally performed with the patient in the lithotomy position, enabling operative access to both the abdomen and the perineum. If a levelling colostomy had been placed in a previous procedure, this is closed after a transverse abdominal incision is made. The gastrointestinal anastomosis (GIA) stapler is used to divide the bowel just proximal to the enterostomy and tissue at this level should be sent for frozen-section analysis to verify that ganglion cells are present. Blood vessels to the aganglionic bowel are ligated and divided, and the aganglionic segment is removed down to the level of the distal sigmoid colon. The GIA stapler is again used to divide the bowel at the distal sigmoid colon. The dissection must be performed right on the rectal wall to avoid injury to the parasympathetic nerve fibres. The dissection is performed circumferentially around the rectum down to the level of the internal sphincter. Complete hemostasis may be ensured with the electrocautery. The surgeon should be certain that there is enough length on the proximal ganglionic segment to ensure that this can be moved to the anus without tension. It may be necessary to divide one of the inferior mesenteric vessels to get enough length. The surgeon then moves to the perineum and inserts a long curved clamp through the anus to grasp the proximal rectal segment, and while the clamp is pulled out, the distal bowel is intussuscepted out through the anus. The intussuscepted rectal segment is then divided anteriorly approximately 2 cm distal to the dentate line and through this enterotomy a clamp is inserted and the ganglionic segment is pulled through. The staple line is then partially removed with the electrocautery, and the ganglionic neorectum is sutured to the distal rectal aganglionic segment with interrupted absorbable sutures. This procedure may be performed in either a single-layer or a two-layer fashion. As the suture line is constructed, more of the staple line and the aganglionic rectum is sequentially removed, so that approximately 1 cm of the cuff is on the aganglionic rectum posteriorly. After the anastomosis is completed, the suture line is allowed to recede into the anal canal. Continuing the operation intra abdominally, the mesenteric defect is closed to prevent internal herniation and the abdominal incision is closed. After the operation the

urinary catheter is left if the patient for several days and nasogastric drainage is used until there is return of bowel function. To perform the Soave Operation (figure 11) with a primary anastomosis (the boley modification), the patient is usually placed in the lithotomy position. After the abdomen is opened through a transverse incision the aganglionic rectum is mobilized and the blood supply is divided down to the level of the peritoneal reflection. The GIA stapler is used to divide the intestine at the transition zone, and a specimen is sent for frozen-section histologic analysis to document the presence of ganglia in the segment to be pull through. At the level of the peritoneal reflection, the seromuscular layer of the rectum is scored with the electrocautery and is separated from the underlying mucosa. The stripping of the muscular layer from the mucosal tube then continues distally down to a level of approximately 1 cm of proximal to the denate line. The preoperative transanal injection of methylene blue at 1 cm proximal to the denate line is helpful for recognizing when the dissection is completed. After the mucosal stripping is done, a long clamp is passed transanally and the mucosal tube is grasped and intussuscepted out though the anus. The mucosal tube is then partially divided anteriorly with the electrocautery. A clamp is inserted through this incision into the pelvis, and the ganglionic segment to be pulled through is brought down. Traction sutures placed on the muscular tube will be helpful in preventing this "funnel" form being disturbed by these manoeuvres. The staple line is then partially removed with electroautery, and serial interrupted poyglycolic sutures are placed between the intussuscepted rectal tissue and the ganglionic colon. the anastomosis is continued in the anterior to posterior direction circumferentially and is allowed to retract back into the anus. Continuing the operation intra abdominally, the peritoneal defect is repaired and the abdominal incision is closed. A closed suction drain is usually placed writing the muscular cuff, because so the extensive pelvic dissection, a urinary catheter is left in place for several days. Feedings are begun when there is return of the alimentary tract function, and the pelvic drain is removed when it is certain that there are no hematomas or abscesses to drain. To perform the Duhamel operation (fig12), the patient is usually placed in the lithotomy position. Aganglionic bowel is removed down to the level of the peritoneal reflection, and the ganglionic proximal bowel is mobilized to ensure an adequate length to reach the anal anastomosis . The retrorectal space is opened and the dissection is continued to the level of the anus posteriorly. Care is taken to remain directly posterior to the rectum. To perform the perineal portion of operation, the electrocautery is used to make a transverse incision inside the rectum approximately 1 cm proximal to the denate line. This incision extend for approximately one third of the circumference and in depth should extend all the way into the previously mobilized retrorectal space. Polyglycolic acid sutures are then placed around the posterior colostomy except at the 12'o clock position, where the GIA stapler will be used. The ganglionic neorectum is then pulled through this enterotomy, and the staple line is gradually removed while the suture line is completed in an anterior-to-posterior fashion. Then, the GIA stapler is inserted with one limb in each of the aganglionic and ganglionic segments and the stapler is discharged. Intra abdominally, the open upper end of the aganglionic rectum is sutured to the colon so there is no pouch superiorly. If this is not closed properly, there is a relatively high incidence of fecal material collecting within the blind-ending "spur," which can result in intestinal obstruction and necessitate another corrective procedure. Recently, there was a report in which the Duhamel procedure was performed entirely with automating stapling devices

for each aspect of the anastomosis. Finally, as with many other surgical procedures, the feasibility of minimally invasive surgery has been explored with regard to the treatment of patients with Hirschsprung's disease. Laparoscopic techniques have been used to perform the Swenson and the Duhamel procedures. The clinical follow-up period is short, and the ultimate usefulness of these procedures remains to be determined.

## **OUTCOMES AND COMPLICATIONS**

It is difficult to make definitive recommendations regarding the different operations used to treat Hirschsprung's disease. No prospective trials have compared these operations, and the large series that have been published are not concurrent in time. In addition, these trials suffer from imprecise nomenclature when outcomes and complications are listed. However, specific difficulties have been described for each of the three procedures and include an increased incidence of enterocolitis after the Swenson operation, diarrhoea and incontinence after the Soave pull-through, and constipation after the Duhamel procedure.

## EARLY SURGICAL COMPLICATIONS

A tabulation of the early and intermediate surgical results from several large series of patients with Hirschsprung's disease is listed in Table 8. The mortality rate is apparently not influenced by the type of corrective procedure performed. The importance of infection and sepsis as causes of death has been noted by many authors. The mortality of enterocolitis ranges as high as 30%. In one report, sepsis related to enterocolitis accounted for 40% of the total mortality, and pneumonia or peritonitis was responsible for another 18% of the deaths. An increased mortality rate has been also noted in patients with total colonic aganglionosis, which may be related to the increased incidence of enterocolitis in this population. Finally, it has been well documented that children with Hirschsprung's disease who have Down's syndrome have a poorer outcome. These patients frequently have congenital cardiac disease and enterocolitis, and both of these factors may contribute to the increased mortality rate. Preoperative infections frequently complicate the clinical course of children undergoing a definitive operative procedure for Hirschsprung's disease (Table 8). The severity ranges from a superficial wound infection to intra abdominal abscess related to an anastomotic leak. The latter conditions at times necessitate a diverting colostomy until the infection subsides. Usually these complications are not associated with long-term patient morbidity, but on rare occasions a complete revision of the procedure may be required. Infections of the seromuscular cuff can occur after the Soave procedure is performed; these complications are usually related either to an anastomotic leak, to a large hematoma in the cuff, or to island of mucosa that have been left after the stripping procedure. In most cases cuff abscesses should be drained and the faecal flow should be diverted with a colostomy. It is important to recognise a pelvic infection early to prevent extension of the infection, systemic sepsis, and necrosis or scarring of the pull-through segment. Computed tomography is useful for assessing the presence of a pelvic or cuff abscess.

## ENTEROCOLITIS

Enterocolitis remains the most serious complication of Hirschsprung's disease, and the risk of this condition is present even after the corrective pull-through procedure is performed. In one series of patients monitored after undergoing an endorectal pull-through procedure, the incidence of enterocolitis was 33%. In this report, the mean length of time between the operation and the attack of enterocolitis was 29 months, and the longest period was 176 months. Parents and primary care physicians should be made aware of this possibility to ensure expeditious surgical referral when this condition occurs. If postoperative enterocolitis is unrecognized, a significant risk of death is present. The most prevalent explanation for the persistent risk of enterocolitis after the corrective procedure is related to the persistently hypertonic anal sphincter associated with the disease; this is thought to result in a functional obstruction causing infection and inflammation of the colon. There are many other theories regarding the pathogenesis of enterocolitis associated with Hirschsprung's disease, including an alteration in the intestinal mucins, a deficiency in the intestinal secretory immune system, and infection with *Clostridium difficile*. The histopathologic features of the enterocolitis associated with Hirschsprung's disease have been characterized microscopically. There is a progression of severity beginning with simple dilation of the intestinal crypts, extending to the development of crypt abscesses, with the ultimate progression to mucosal ulceration. In the most severe cases, there may be transmural necrosis or perforation. The clinical criteria required to establish the diagnosis of enterocolitis have not been well defined, and there is some disagreement among clinicians regarding this issue. The signs and symptoms of enterocolitis may be non-specific and it may be difficult to distinguish this condition from a postoperative adhesive bowel obstruction, a viral gastroenteritis, or simple constipation. The clinical features present in 119 episodes of enterocolitis that occurred in a reported series of 57 patients are tabulated in Table 9. In that report, the incidence of postoperative enterocolitis was 28%. Some patient factors associated with an increase in the risk of the enterocolitis included the presence of other congenital anomalies and that presence of long-segment aganglionosis. Other investigators have suggested that the presence of trisomy 21 is also a risk factor for enterocolitis. Radiographs are very helpful in establishing the diagnosis of enterocolitis when the clinical findings are equivocal. Characteristic findings on the plain abdominal radiograph include the presence of bowel dilation with multiple air-fluid levels (Fig. 13). The radiographic findings of mucosal spiculation and pneumatosis intestinalis are present only uncommonly. In one report by Blane and colleagues, the presence of the intestinal cut-off sign, defined as the presence of distended bowel loop along the left flank with an abrupt termination in the pelvis, was also a common finding. These investigators determined that the presence of this sign on the upright abdominal radiograph with two or more air-fluid levels had a sensitivity rate of 68% and a specificity rate of 83% for the diagnosis of enterocolitis. The positive predictive value was 0.71 and the over-all accuracy was 77%. The contrast enema did not add to the ability to make an accurate diagnosis of enterocolitis. Most patients with enterocolitis related to Hirschsprung's disease can be treated successfully with aggressive nonoperative measures that should include intravenous fluid resuscitation, bowel rest, nasogastric tube drainage, rectal tube drainage, and broad-spectrum intravenous antibiotics. In addition, gentle rectal irrigations

should be performed several times a day with 10 ml/kg of warm saline solution to wash out retained stool and gas. Enteric and viral stool cultures should be obtained and evaluation for the *C. difficile* organism and toxin should be performed. Several recent reports have documented the importance of this organism in the cause of enterocolitis, and consideration should be given to presumptive treatment with enteral vancomycin or metronidazole until culture results are available. If an episode of enterocolitis is the first manifestation of Hirschsprung's disease, the surgeon must decide whether to treat the condition with a levelling colostomy or with a primary pull-through procedure. Obviously, in a child who has sepsis and enterocolitis, the most conservative measure is to place a diverting colostomy. If excessive anal tone is present in a child who has already had definitive treatment for Hirschsprung's disease, then anal dilations may prevent recurrence of enterocolitis. Moreover, surgical sphincterotomy has been reported to be a successful method of managing recurrent enterocolitis, and in rare cases diverting colostomy must be used to prevent severe recurrent bouts of the condition. A recent report has suggested the usefulness of routine rectal irrigations in the postoperative period to prevent severe enterocolitis after the pull-through procedure. In 40 children treated with rectal irrigations for 6 months after a definitive corrective procedure (irrigations were done three times per day for 3 months and once per day for three months), there were three cases of enterocolitis and no related deaths. In a historic control group of 95 children not treated with routine rectal irrigation, 34 patients had enterocolitis, and the disease was fatal in five cases. Although the difference between the two groups was very significant ( $p < 0.001$ ), the study results must be confirmed in a prospective fashion before firm recommendations can be made regarding routine postoperative rectal irrigation in children with Hirschsprung's disease.

## **FUNCTIONAL RESULTS AND RECURRENT SYMPTOMS**

The long-term functional outcome after definitive corrective operation for Hirschsprung's disease is difficult to determine, and there are conflicting data in the literature. Although a number of reports suggest that patient satisfaction is very high, other investigators have found a high incidence of severe constipation and incontinence. It is usually believed that these problems resolve with time. In one study in which patients underwent serial anomanometric examinations and evaluations of anal sensation, some improvement was found as late as 10 years after pull-through surgery. In general, it is thought that in more than 90% of patients, the outcome will be satisfactory after one of the three most commonly used procedures for Hirschsprung's disease. In approximately 1% of cases, a permanent colostomy may be necessary, and the poorer functional outcome experienced by patients with trisomy 21 has been well documented. Moreover, the patients with total colonic aganglionosis also may be expected to have a poorer outcome. Retrospective surveys by the operating surgeons have been the rule for measuring these outcomes, and such studies may suffer from some bias on the part of the surgeon or some embarrassment in the patients that would prevent them from reporting negative information. Functional results from a number of clinical studies with long follow-up after surgery for Hirschsprung's disease are tabulated in Table 10. The great variability in reported outcomes argues strongly for additional study of the long-term functional outcome in patients with Hirschsprung's disease that uses a well-validated questionnaire of bowel habits and is free of any bias on the part of the investigator.

## EVALUATION

A number of possible reasons exist for an unsatisfactory outcome after an operation for Hirschsprung's disease. Postoperative manometric studies have documented that there is usually reduced rectal sensation, increased anal tone, and persistent absence of the anorectal reflex. Incontinence may be related to decreased neural sensation in the area resulting from the pull-through procedure or as a natural correlate of aganglionosis. Furthermore, increased anal tone may cause functional obstruction, resulting in rectal stasis and subsequent alteration in colon bacterial flora. It has also been suggested that incontinence may be related to a weakened internal anal sphincter, making it impossible to expel flatus selectively without passage of liquid stool. Finally, it is possible that in patients who have had a Soave procedure, the seromuscular cuff around the distal rectal segment functions to reduce the reservoir function of the bowel, so semiformed feces may be propelled rapidly from the colon into the anal canal without warning. These conditions are difficult to manage, but medications to decrease colonic motility (e.g., loperamide) may be useful. In addition, the bacterial flora may be modified with oral metronidazole. If the incontinence is related to fecal overflow from increased anal tone, then a procedure to relax the anus may be indicated. Chronic constipation in patients with corrected Hirschsprung's disease is usually related to a postoperative stricture, residual aganglionosis caused by a technical error, or the inability to relax the anal sphincter (anal achalasia), resulting from the underlying disease. One anomanometric study demonstrated that the absent rectosphincteric reflex in patients with Hirschsprung's disease is not restored after corrective surgery. The evaluation of a child who is having symptoms of constipation after definitive surgery for Hirschsprung's disease should begin with a contrast enema to define the anatomy of the rectal pull-through segment and to exclude the possibility of an obstructing fecaloma within a retained rectal "spur" after a Duhamel procedure. Moreover, the contrast study may reveal findings indistinguishable from those seen in an untreated patient with aganglionosis, suggesting an anal stricture or recurrent aganglionosis. A fixed stricture may respond to rectal dilation. If this conservative measure does not result in symptomatic improvement, then the evaluation should be continued with a biopsy of the rectum to exclude the possibility of acquired aganglionosis or neuronal intestinal dysplasia. Consideration should also be given to performing anorectal manometry to obtain an objective measure of the degree of anal achalasia, although the usefulness of this test in discriminating the cause of symptoms in patients with recurrent Hirschsprung's disease is controversial.

## **ACQUIRED AGANGLIONOSIS**

The possibility of acquired aganglionosis in the pull-through segment must be considered as a cause of persistent constipation. The incidence of this complication at one institution was 5 cases among 248 children treated for Hirschsprung's disease. Acquired aganglionosis was originally described nearly 3 decades ago and is thought to result from ischemia in the pull-through segment occurring at the time of the original operation. It is also possible that the condition results from recurrent episodes of enterocolitis. This complication has been associated with each of the three commonly used corrective procedures. The symptoms related to the acquired aganglionosis usually begin to occur approximately 2 years after the operation. The diagnosis must be established by a full-thickness rectal biopsy. Acquired aganglionosis is usually managed with a repeat pull-through procedure.

## NEURONAL INTESTINAL DYSPLASIA

Another rare cause of recurrent symptoms of Hirschsprung's disease after operative correction is the presence of neuronal intestinal dysplasia (NID) in the intestine proximal to the aganglionic segment. First described in 1971, NID is a controversial and poorly understood condition characterized most commonly by decreased intestinal motility of the distal colon. The actual incidence of NID is difficult to determine, but this condition can occur as an isolated condition or in association with aganglionosis. This condition has been recognized far more frequently in Europe than in the United States. The diagnostic criteria have been difficult to specify, owing to the absence of pathognomic histopathologic findings. In one large referral centre, NID was found in 45% of patients with Hirschsprung's disease, and aganglionosis was present in 65% of patients with NID. It should be emphasized that the high incidence of NID in the report is almost certainly a reflection of the special interest and referral patterns of the particular institution. These data probably cannot be generalized to all patients with Hirschsprung's disease. In other reports, the incidence of concurrent NID in patients with Hirschsprung's disease is approximately 10% to 20%. The disease usually presents with long-standing constipation (after pull-through procedure in patients with coincident Hirschsprung's Disease) or with recurrent episodes of pseudoobstruction. Moreover, NID can be associated with neonatal enterocolitis and, in rare cases, can cause intestinal strictures. There are two forms of the disease. NID-A is characterized histologically by rudimentary or absent sympathetic innervation of the gut, and NID-B is characterized by dysplasia of the submucosal plexus with defective neuron differentiation. Recently, sophisticated morphometric analysis of the enteric nervous system in neonates and children with severe chronic constipation has firmly established that histologic abnormalities are present in patients with NID. In this analysis, standard histologic and immunohistochemical methods were used to demonstrate that children with NID had significantly larger ganglia, with an increased number of nerve cells per ganglion. This has been an issue of controversy because the findings are relatively non-specific and variable and pathologists and other clinicians have disputed the existence of the diagnosis. Indeed, in this morphologic evaluation, some overlap occurred between the morphologic condition in normal patients and in those with NID, demonstrating the difficulty in establishing the diagnosis on histologic evaluation. The most constant findings are increased acetylcholinesterase staining and increased ganglion cell number. In several studies, no correlation has been found between the histologic abnormalities and disease severity. The NID associated with Hirschsprung's disease is difficult to diagnose with certainty but is being recognized more frequently. The diagnosis of NID is established by biopsy with histologic evaluation and acetylcholinesterase staining. Recent reports from specialized centres have suggested that colonic manometry can assist in differentiating neurogenic constipation from other disorders. In some patients, the manometric abnormalities in the colon proximal to a pull-through may correlate with areas having increased acetylcholinesterase staining on full-thickness biopsy. Such biopsies can be obtained with laparoscopy in children who continue to have difficulties after a pull-through procedure for Hirschsprung's disease (personal communication, Jacob C. Langer). The management of NID is controversial, and the correlation between treatment modality and outcome is poor. In many cases occurring without associated aganglionosis, the symptoms of chronic constipation

improve spontaneously with time. When the condition is found to coexist with surgically corrected Hirschsprung's disease, medical management is usually the first line of therapy. In one study, the patients with delayed intestinal transit time caused by NID demonstrated a 50% improvement after beginning the prokinetic agent cisapride. Enemas and cathartics may also be used in conjunction with anal dilation. If symptoms continue and the histologic findings are consistent with NID, a subtotal resection of the affected portion of the colon should be performed.

## **SPECIAL PROBLEMS**

### **ULTRASHORT-SEGMENT HIRSCHSPRUNG'S DISEASE**

In rare cases, the length of aganglionosis is very short and extends for only a few centimetres proximal to the dentate line. This condition has been termed ultrashort-segment Hirschsprung's disease or lower segment disease and was originally described as a specific entity in 1951. The existence of ultrashort Hirschsprung's disease is controversial, and some paediatric surgeons do not recognize this form of aganglionosis, which can be managed without a definitive pull-through operation. One point of contention is that some surgeons have described patients with severe chronic constipation who actually had ganglion cells on rectal biopsy specimen, calling this condition ultrashort Hirschsprung's disease. This is probably a misnomer; the condition more accurately should be termed anal achalasia. Another claim of those not recognizing the existence of ultrashort-segment aganglionosis is that there is a normal variability in the distribution of ganglion cells around the anus, and it is argued that the reported aganglionosis in such cases is due to sampling error. However, careful histologic studies have established that in children older than 1 year of age, the area of myenteric hypoganglionosis normally extends less than 1 cm proximal to the dentate line, and this area is avoided with standard methods of rectal biopsy. Although this issue remains controversial, the evidence on balance supports the existence of patients with Hirschsprung's disease whose aganglionosis extends for only a few centimetres or less proximal to the anus, and who may respond well to treatment less aggressive than is used to treat most patients with Hirschsprung's disease. Ultrashort-segment Hirschsprung's disease is usually somewhat more indolent than the condition associated with a longer segment of aganglionosis, and the diagnosis is usually made at an older age. In one recent report, the average age of the children was 6 years and ranged from 2 to 14 years. The principal symptom in these patients was severe constipation, and none of the children had a history of enterocolitis or failure to thrive. Typically, these patients have been treated with cathartic agents and frequent enemas to evacuate the rectum. Moreover, no radiographic transition zone was seen on contrast enema; this is a common characteristic of ultrashort-segment Hirschsprung's disease. Anorectal manometry is a useful test in children with chronic constipation; the anorectal reflex is absent for children with ultrashort-segment Hirschsprung's disease. As with all cases of Hirschsprung's disease, the definitive diagnosis is established by rectal biopsy. Because of the older age of children with ultrashort-segment disease, with the thickened rectal mucosa, suction rectal biopsy is often inadequate and the open full-thickness biopsy technique may be necessary to establish the diagnosis. Many reports have established that ultrashort-segment Hirschsprung's disease can be managed effectively and safely with a surgical myectomy. Of course, one of the rectal pull-through procedures would also be successful. The technique most commonly used is the transanal method described by Lynn and van Heerden. The patient is placed in the lithotomy position, and a transverse incision is made in the anal mucosa at the level of the dentate line. The internal sphincter muscle is freed from the overlying superficial mucosa, and a strip of muscle 5 to 10 mm in width is resected in the cephalad direction as far as possible. Depending on the size of the patient, the strip will be approximately 3 to 6 cm long. Special care should be taken to ensure that the most distal fibres of the internal sphincter are removed. The mucosa can be closed

with an absorbable suture. Another option is to perform the myectomy through the posterior sagittal approach, dividing the parasagittal muscle fibres and levator muscles to gain exposure to the distal rectum. The subjective results in three groups of children who had anorectal myectomy for ultrashort Hirschsprung's disease are tabulated in Table 11. In nearly every patient, there was significant improvement after the procedure, and most patients described their outcome as "excellent." In one report, 7 of the 14 patients were still using laxatives after a mean period of 37 months after the operation; 3 patients used them intermittently, and 4 were taking laxatives regularly to maintain bowel regularity. In these reports, the operative complications were minor and there were no reports of fecal incontinence. It is interesting that some of the patients, the resected muscle strip did not have ganglia at its most proximal margin, yet the procedure was still effective. These children presumably continue to have unrelaxed aganglionic bowel in the fecal stream, suggesting that in some patients with ultrashort-segment Hirschsprung's disease, relaxing of the anal musculature will be sufficient to allow acceptable bowel function even with abnormal peristalsis. In rare cases in which the anomyectomy was not effective in alleviating the symptoms associated with ultrashort Hirschsprung's disease, the standard definitive pull-through procedures have been performed with good results. A few patients with Hirschsprung's disease have aganglionosis that is limited to the distal several centimetres of the rectum. Such patients will often respond to a limited procedure aimed at reducing the abnormally high tone of the internal sphincter, and it may be possible to avoid performing a definitive bowel resection and pull-through. As with any surgical procedure, it is important to select the patients carefully. In general, anomyectomy should probably be reserved for patients with ultrashort-segment Hirschsprung's disease who have chronic constipation that has been managed medically with some success. In most of these children, no radiographic transition zone will be noted on the contrast enema. In addition, some paediatric surgeons recommend that the procedure be limited to children older than 2 years of age.

## TOTAL COLONIC AGANGLIONOSIS

A more severe form of Hirschsprung's disease is total colonic aganglionosis, which occurs in 5% to 8% of patients. In these children, the entire colon is aganglionic and the small intestine may be involved as well. In the most extreme cases, the entire intestine may be involved. Total colonic aganglionosis is associated with a family history of Hirschsprung's disease in 12% to 21% of cases. Signs and symptoms of the condition are more severe than those associated with other forms of Hirschsprung's disease. Total colonic aganglionosis is more commonly recognized in the neonatal period and in some patient series was more likely to present with severe enterocolitis. The mortality rate of total colonic Hirschsprung's disease was historically very high, presumably because of delayed diagnosis in infants with severe enterocolitis. Recently the expected survival for long-segment aganglionosis has improved dramatically with increased awareness of the condition and improvement in nutrition and surgical care, but the morbidity associated with the condition remains high. The diagnosis of total colonic aganglionosis remains a difficult problem. There is not an absolute relation between the severity of illness at presentation and the length of aganglionosis. In one recent report of 21 children with total colonic aganglionosis, 65% of the patients received the diagnosis in the first 2 weeks of life, but 19% of the children had a more indolent course and were older than 20 weeks of age at the time of diagnosis. Abdominal distension, delayed passage of meconium, and constipation were the most common presenting signs, and the physical findings associated with total colonic Hirschsprung's disease in the clinical series are tabulated in Table 12. In most cases, the diagnosis was made when the patients had evidence of acute bowel obstruction. Nearly two thirds of the children had histologic confirmation of the diagnosis from biopsy specimens obtained during abdominal exploration. The usefulness of the contrast enema is limited in making the diagnosis of total colonic aganglionosis because the transition zone is rarely visualized. However, in rare cases an occult colonic perforation may be discovered with a contrast enema performed to evaluate for the presence of neonatal intestinal obstruction (Fig. 14). As with other types of Hirschsprung's disease, children with total colonic aganglionosis can present in an acutely ill condition or they can have relatively minor signs and symptoms. To establish the diagnosis of total colonic aganglionosis, the clinician must have a high index of suspicion, and the condition should be considered in any neonate who has signs of intestinal obstruction. Once the diagnosis of Hirschsprung's disease is established, the level of aganglionosis must be determined by performing multiple intestinal biopsies, and the surgeon must then elect to perform a primary pull-through procedure to create a diverting enterostomy. Although there are reports of infants with total colonic aganglionosis who underwent successful primary correction, most paediatric surgeons prefer to place a diverting ileostomy and defer definitive correction until the child is larger. One potential difficulty with primary definitive surgical management is the necessity of determining the level of aganglionosis with frozen-section biopsy specimens. It is always possible that ganglion cells may be discovered in the resected colon specimen when the permanent section histologic slides are evaluated. The likelihood of this occurrence varies among medical centres, but one must be cautious about removing the entire colon from a newborn child on the basis of preliminary frozen-section pathologic evaluation. The most conservative treatment plan in children with total

colonic Hirschsprung's disease is to place an initial diverting ileostomy. If an ileostomy is created at the time of diagnosis, the surgeon should be aware of the obligate losses of sodium and bicarbonate ions that occur after operation. Infants, who may have an immature intestine and kidneys, are often unable to compensate for these increased losses. They may have decreased weight gain and metabolic acidosis if these ions are not adequately supplemented. Indeed, studies have documented that infants with ileostomies attempt to compensate for their intestinal losses of sodium by inducing the renin/aldosterone axis to decrease renal losses of the ions. It is generally recommended that infants with an ileostomy be provided with a minimum of 6 to 10mEq of sodium per kilogram per day and that frequent measures of serum sodium be used to guide treatment. Until several decades ago, the mortality rate for children with total colonic Hirschsprung's disease was nearly 65%, owing principally to the failure in recognizing the condition in infants presenting with signs of intestinal obstruction. With improved early recognition and better anaesthetic and nutritional management, survival has improved markedly. The first operation designed specifically for the management of total colonic aganglionosis was Lester Martin's modification of the Duhamel procedure. The aim of this procedure was to increase liquid and electrolyte absorption by performing a very long side-to-side anastomosis between the ganglionic pulled-through intestine and the portion of aganglionic colon extending to the splenic flexure. The initial results were encouraging and the development of this procedure helped to increase the recognition of total colonic aganglionosis and provide hope for successful management of the condition. Subsequent reports have demonstrated that any of the three standard corrective procedures for Hirschsprung's disease may be used to treat total colonic disease. Other modifications of these procedures have been described, such as that of Kimura and colleagues in which an extensive patch of right colon is onlaid into the intestine before the pull-through is performed to improve water absorption. Boley described a similar procedure with the right colon used to improve functional outcome. The number of operative procedures available gives testimony that there is currently no perfect treatment for patients with total colonic Hirschsprung's disease. As with the more common shorter segment Hirschsprung's disease, no prospective trials have compared the different operations. Although the mortality rate is acceptably low, none of the generally used procedures are without significant morbidity. For example, the Martin modification of the Duhamel procedure is associated with a high incidence of diarrhoea despite the inclusion of approximately one third of the colon in the fecal stream. In addition, there are often recurrent infectious complications such as rectal abscess or life-threatening enterocolitis. Such problems have been attributed to inefficient emptying of the rectal pouch and have at times required a permanent ileostomy for management. The Swenson procedure has been associated with excessive diarrhoea and enterocolitis. In one report of 16 children with total colonic aganglionosis who had either the Swenson or the Kimura procedure, there was a better outcome in children who had Kimura's modification. The Duhamel procedure, performed without the Martin modification, is associated with nearly a 25% incidence of enterocolitis but generally has had acceptable results. In one report of 10 patients with total colonic aganglionosis, the Soave endorectal pull-through has also been shown to have an acceptable mortality and morbidity rate. However, in another report of five children who had the Soave procedure with the ileum to anus anastomosis, there was a relatively high incidence of diarrhoea and abnormalities in sodium balance. It appears

to be advantageous to leave some colon in the fecal stream to improve water and electrolyte absorption. This is accomplished in Duhamel's operations, the Martin procedure, the Kimura, and Boley procedures, and other reported techniques. This rationale is further supported by the experimental demonstration that such an included aganglionic colon segment does in fact contribute to the overall salvage of electrolytes. Taken together, these findings support the treatment of patients with total colonic Hirschsprung's disease with either the standard Duhamel procedure or the Soave operation with a colon patch. Another option is to perform one of the standard pull-through procedures in conjunction with a right colon mucous fistula. This allows the future use of the colon (as a patch) if the patient is impaired by excessive diarrhoea.

## **TOTAL INTESTINAL AGANGLIONOSIS**

The most severe form of Hirschsprung's disease is total intestinal aganglionosis, in which the aganglionosis extends through the entire small intestine or very nearly to the ligament on Treitz. This condition was uniformly fatal until the widespread availability of total parenteral nutrition, and the mortality rate remains high even today. There was essentially no successful treatment until the description by Zeigler and colleagues of the extended myectomymyotomy procedure. The operation is based on the concept that a length of aganglionic intestine that has had a strip of its seromuscular coat removed may serve as a passive conduit for enteral nutrients propelled from normally innervated proximal bowel. The length of intestine is kept short to allow for the passage of intestinal contents; a distance of only 40 cm between the transition zone and a jejunostomy is recommended. As a result, the children treated with this procedure have severe short-bowel syndrome in the postoperative period, and the aganglionic intestine must be given time to adapt until nutrient absorption increases. In a recent report of 16 children with total intestinal aganglionosis treated with extended myectomymyotomy, the survival was 62.5% and two patients were able to meet their nutritional needs solely with enteral feedings. Thus this procedure may be a definitive treatment for children with total intestinal Hirschsprung's disease or the procedure can serve as a bridge to intestinal transplantation.

## HIRSCHSPRUNG'S DISEASE IN THE ADULT

In rare cases, congenital aganglionosis may elude detection until the patient is well into adulthood. The diagnosis has been made as late as 73 years of age. The delay in diagnosis is usually related to the patient not seeking medical care or to physician error. Older patients with Hirschsprung's disease typically have a history of life-long constipation that begins in infancy or early childhood. The patients are usually dependent on enemas or cathartic agents and may go weeks between bowel movements. IN some cases, there may be the recent onset of diarrhoea or incontinence of stool related to fecal impaction with resulting overflow. Patients may report chronic abdominal pain, and on examination there is typically abdominal distension with palpable fecal masses. Generally, the constipation gradually worsens until the disease is recognized. In rare cases, patients may have enterocolitis or septic shock. Presumably, the symptoms are relatively indolent and long-standing because there is com pensatory hypertrophy of the normally innervated proximal colon, which can overcome the functional obstruction of the aganglionic distal bowel. Ultimately, there is decompensation of the markedly dilated bowel, resulting in acutely worse constipation or obstruction. The diagnosis is usually suggested by the findings on barium enema, which will demonstrate the typical dilated proximal colon and distal transition zone. Anorectal manometry reveals the absence of the anorectal inhibitory reflex in approximately 90% of cases. A full-thickness rectal biopsy should be performed to establish the diagnosis. Because of the thickness of the rectal mucosa in adults, the suction rectal biopsy usually results in insufficient tissue to make the diagnosis. As in other patients with aganglionosis, there is controversy regarding the optimal treatment for adults with Hirschsprung's disease. Some surgeons recommend creating a diverting colostomy when the diagnosis is made to allow the dilated ganglionic bowel to return to normal size and to improve the patient's nutritional status before the definitive pull-through procedure is performed. Other surgeons perform the corrective operation primarily. IT appears to be reasonable to individualize the decision regarding a diverting colostomy. For example, if severe enterocolitis is present when the diagnosis is made, then a preliminary colostomy is probably indicated. Moreover, a decompressing colostomy represents the most conservative management if there is substantial bowel dilation and may reduce the risk of anastomotic complications associated with the use of massively dilated bowel for the definitive procedure. In most reports of adult patients treated for Hirschsprung's disease, the Duhamel procedure has been used for definitive correction. The Soave and Swenson procedures have also been used, but there have been no prospective trials in which the different procedures have been compared. In one literature review of adults treated for Hirschsprung's disease, the Duhamel procedure was associated with fewer serious complications and a subjectively better functional outcome than either of the other operations. IT should be emphasized that as with all types of aganglionosis, the best method for treating adult patients is controversial, and the surgeon should individualize the decision based on personal experience.