approximately 15% of sporadic cases. Mutations in at least seven other genes encoding proteins involved in enteric neurodevelopment, including the RET ligand glial-derived neurotrophic factor, endothelin, and the endothelin receptor, have also been described. However, these account for fewer than 30% of patients, suggesting that many other defects remain to be discovered. Because penetrance is incomplete, modifying genes or environmental factors must also be important. In addition, it is clear that sex-linked factors exist, since the disease is more common in males, but, when present in females, tends to involve longer aganglionic segments.

MORPHOLOGY

Diagnosis of Hirschsprung disease requires documenting the absence of ganglion cells within the affected segment. In addition to their characteristic morphology in hematoxylin and eosin–stained sections, ganglion cells can be identified using immunohistochemical stains for acetylcholinesterase.

The rectum is always affected, but the length of the additional involved segments varies widely, from the rectum and sigmoid colon in most cases to the entire colon in severe cases. The aganglionic region may have a grossly normal or contracted appearance. In contrast, the normally innervated proximal colon may undergo progressive dilation (Fig. 17-3) and, in time become massively distended **(megacolon)**, reaching diameters of as much as 20 cm. This may stretch and thin the colonic wall to the point of rupture, which occurs most frequently near the cecum. Mucosal inflammation or shallow ulcers may also be present in normally innervated segments, making gross identification of the extent of aganglionosis difficult. Hence, intraoperative frozen-section analysis is commonly used to confirm the presence of ganglion cells at the anastomotic margin.

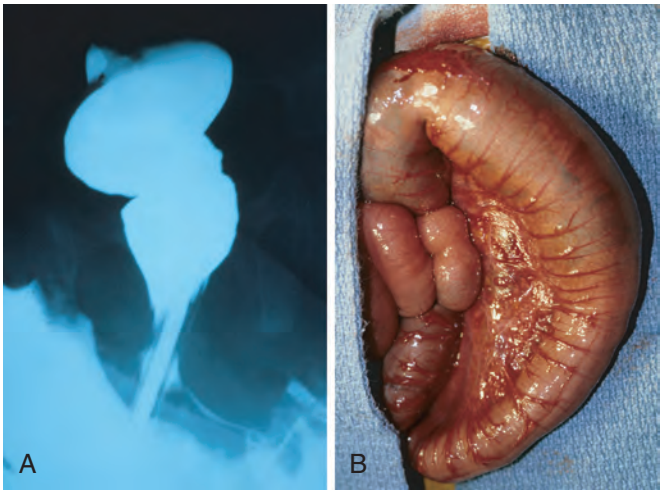

Figure 17-3 Hirschsprung disease. **A,** Preoperative barium enema study showing constricted rectum (bottom of the image) and dilated sigmoid colon. **B,** Corresponding intraoperative photograph showing constricted rectum and dilation of the sigmoid colon. (Courtesy Dr. Aliya Husain, The University of Chicago, Chicago, Ill.)

Clinical Features. Hirschsprung disease typically presents with a failure to pass meconium in the immediate postnatal period. Obstruction or constipation follows, often with visible, ineffective peristalsis, and may progress to abdominal distention and bilious vomiting. When only a few centimeters of rectum are involved occasional passage of stool may occur and obscure the diagnosis. The major threats to life are enterocolitis, fluid and electrolyte disturbances, perforation, and peritonitis. The primary mode of treatment is surgical resection of the aganglionic segment followed by anastomosis of the normal proximal colon to the rectum. Even after successful surgery, it may take years to attain normal bowel function and continence.

In contrast to the congenital megacolon of Hirschsprung disease, acquired megacolon may occur at any age as a result of Chagas disease, obstruction by a neoplasm or inflammatory stricture, toxic megacolon complicating ulcerative colitis, visceral myopathy, or in association with functional psychosomatic disorders. Of these, only Chagas disease (discussed later) is associated with loss of ganglion cells.

KEY CONCEPTS

Congenital malformations of the GI tract

- The GI tract is a common site of developmental abnormalities. In these cases, defects of other organs that develop in the same embryonic period should be sought.
- **Atresia, and fistulae,** are structural developmental anomalies that disrupt normal gastrointestinal transit and typically present early in life. **Imperforate anus** is the most common form of congenital intestinal atresia, while the esophagus is the most common site of fistulization.
- **Stenosis** may be developmental or acquired. Both forms are characterized by a thickened wall and partial or complete luminal obstruction. Acquired forms are often due to inflammatory scarring.
- **Diaphragmatic hernia** is characterized by incomplete diaphragm development and herniation of abdominal organs into the thorax. This often results in pulmonary hypoplasia. **Omphalocele** and **gastroschisis** refer to ventral herniation of abdominal organs.
- **Ectopia** refers to the presence of normally formed tissues in an abnormal site. This is common in the gastrointestinal tract, with **ectopic gastric mucosa** in the upper third of the esophagus being the most common form.
- The **Meckel diverticulum** is a true diverticulum, defined by the presence of all three layers of the bowel wall, that reflects failed involution of the vitelline duct. It is common and is a frequent site of gastric ectopia, which may result in occult bleeding.
- **Congenital hypertrophic pyloric stenosis** is a form of obstruction that presents between the third and sixth weeks of life. There is an ill-defined genetic component to this disease, which is most common in males.
- **Hirschsprung disease** is caused by the absence of neural crest derived ganglion cells within the colon. It causes functional obstruction of the affected bowel and proximal dilation. The defect always begins at the rectum, but extends proximally for variable lengths.