CHAPTER 93

Polypoid Diseases of the Gastrointestinal Tract

Joseph L. Lelli, Jr.

Polyps are any masses that project into the lumen of the gastrointestinal tract. Some masses that appear to be polyps are subepithelial. True intestinal polyps, however, are of an epithelial origin. Polyps in children most commonly occur as an isolated lesion referred to as a *juvenile polyp*. However, more rarely, polyps in children can occur as a genetically related disease with features including multiple polyps (polyposis) in the gastrointestinal tract, heritability within a family, and an increased lifetime risk of developing a related cancer in the gastrointestinal tract or in other organ systems. Children with these features are considered to have a "polyposis syndrome." Polyposis syndromes in children are classified into two groups, namely adenomatous polyposis syndromes or hamartomatous polyposis syndromes (Table 93-1).

Polyps are common during childhood, occurring in approximately 1% of preschool and school-aged children.[1] Because of their high incidence, polyps of the gastrointestinal tract represent the most frequent cause of rectal bleeding in toddlers and preschoolers aged 2 to 5 years of age. Juvenile polyps are most common (80%) and are followed by lymphoid polyps (15%).[2] Adenomatous polyps occur in less than 3% of all children with polyps.

Juvenile Polyps

Juvenile polyps were first described by Verse in 1908.[3] For many years, all polyps in children were considered adenomas[4] and were often treated with radical procedures. Horrilleno[5] first used the term *"juvenile polyp"* in 1957 to describe a histologically distinctive colorectal polyp that occurred predominately during childhood. In 1962 Morson[6] made an important contribution when he demonstrated that juvenile polyps were benign hamartomas, thereby distinguishing them from potentially malignant adenomas. Less radical treatment of these polyps, however, was slow to follow. The distinction between isolated juvenile polyps and juvenile polyposis was first made by McColl and colleagues in 1964,[7] and three distinct forms of juvenile polyposis were further defined by Sachatello in 1972.[8] Kaschula in 1971[9] followed by Enterline in 1976[10] reported cases of children with both juvenile and adenomatous polyps. Billingham[11] reported the presence of solitary adenomas in children with juvenile polyps in 1980. These early reports of the coexistence of juvenile and adenomatous polyps led to the identification of adenomatous and malignant changes in juvenile polyps.[12–14] However, only polyps associated with juvenile polyposis have malignant potential in children.[15–17] The distinction between the commonly occurring isolated juvenile polyps, which are benign, and the rare juvenile polyposis syndromes, which may be malignant, has become increasingly important.[15,16,18,19]

Jass[20] has proposed the following criteria for increased risk for cancer in children with polyps: (1) more than five juvenile polyps in the colon, (2) polyps throughout the gastrointestinal tract, and (3) any number of polyps associated with a family history of juvenile polyposis. Jass's criteria clarify the three distinct juvenile polyposis syndromes originally described by Sachatello in 1972.[8] On the basis of Jass's and Sachatello's studies, the following classification of juvenile polyps is most commonly used:

I. *Isolated Juvenile Polyps* (nonmalignant): fewer than five polyps confined to the colon without a family history of juvenile polyposis.
II. *Juvenile Polyposis Syndromes* (malignant potential):
    1. *Diffuse juvenile polyposis of infancy:* widespread polyposis of entire gastrointestinal (GI) tract in patients younger than 6 months of age.
    2. *Diffuse juvenile polyposis:* multiple polyps throughout the GI tract, but mostly in the stomach, distal colon, and rectum, usually occurring in patients 6 months to 5 years of age.
    3. *Juvenile polyposis coli:* multiple juvenile polyps confined to the distal colon and rectum in patients 5 to 15 years of age.

Juvenile polyposis syndromes, Cowden disease, and Peutz-Jeghers syndrome are all classified as hamartomatous polyposis syndromes (see Table 93-1).

TABLE 93-1
Classification of Polyposis Syndromes

Classification	
Adenomatous polyposis syndromes	1. Familial adenomatous polyposis (FAP) 2. Gardner syndrome 3. Turcot syndrome
Hamartomatous polyposis syndromes	1. Juvenile polyposis 2. Cowden disease 3. Peutz-Jeghers syndrome

ISOLATED JUVENILE POLYPS

Pathology

Juvenile polyps, which are also known as *retention, inflammatory* or *cystic polyps,* are the most common type of polyp found in the GI tract and account for 80% of polyps in children. Such polyps are generally considered hamartomas[6] or a malformation in which normal colonic tissue has become arranged in a haphazard manner.[20]

Grossly, the typical polyp has a glistening, smooth, spherical, reddish head and ranges from 2 mm to several centimeters in diameter (Fig. 93-1). Polyps will often have an ulcerated surface, which accounts for the rectal bleeding. A cross section shows cystic spaces filled with mucus (Fig. 93-2). Juvenile polyps are typically attached by a long, narrow stalk covered by colonic mucosa. This stalk predisposes the polyp to torsion, which results in venous congestion, surface ulceration, bleeding, and auto amputation.

Microscopically, the surface of the polyp has a single layer of colonic epithelium. This epithelial layer is often ulcerated or replaced with granulation tissue. When inflammation occurs, the epithelium may show a reactive hyperplasia that can mimic dysplasia or adenomatous changes.[21] The main body of the polyp consists of dilated or cystic epithelial tubules that are lined by normal colonic epithelium. These tubules and cystic lakes are embedded in a lamina propria and an abundant, loose, vascular, and fibrous stroma (Fig. 93-3). The stroma is usually heavily infiltrated with neutrophils, eosinophils, lymphocytes, and monocytes. Mitotic figures are rarely seen. Only two descriptions of malignant changes in a solitary juvenile polyp are present in the literature,[22,23] and according to Jass,[20] only one of these may be a true malignant condition. In a longitudinal study of patients with solitary polyps, no increased risk for developing colorectal cancer could be found.[24]

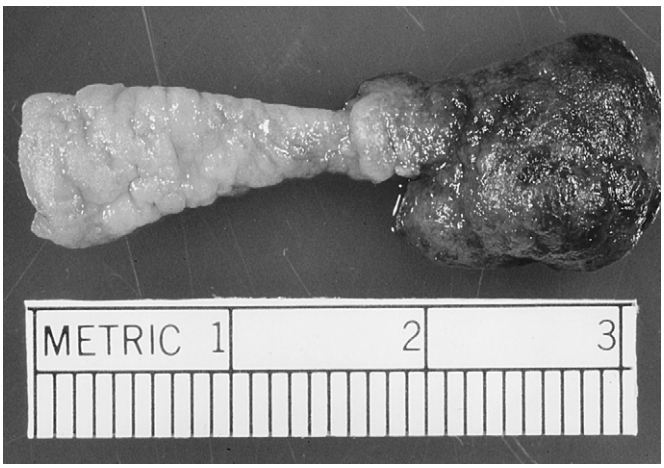

FIGURE 93-1 Typical juvenile polyp with its stalk attached.

FIGURE 93-2 Gross cross section of juvenile polyp with typical cystic "lakes" filled with mucus.

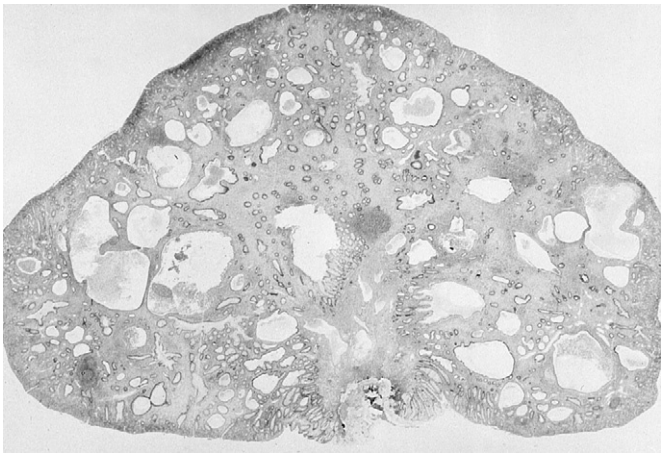

FIGURE 93-3 Photomicrograph of typical juvenile polyp. The surface shows a smooth, flattened, colonic epithelium. Large tubular and cystic lakes are present, embedded in an abundant, loose stoma.

Etiology

The etiology of juvenile polyps is unknown, but several authors have suggested hereditary,[25] genetic,[26] hamartomatous malformation,[6] and inflammation.[27] Recent data suggest that juvenile polyps result from a structural rearrangement of the mucosa secondary to an inflammatory process.[28] The initial event is probably ulceration and subsequent inflammation of the mucosa, leading to obstruction of regional, small colonic glands of the mucosa. The obstructed glands proliferate, branch, and dilate, forming a cystic structure. The cystic structure pushes up the mucosa, leading to further ulceration, inflammation, and formation of granulation tissue. As the

cycle continues, an increasingly larger and larger mass pushes into the lumen. The fecal stream and peristalsis push the mass down the lumen, causing the stalk to elongate and resulting in the typical pedunculated appearance of the juvenile polyp.

Incidence

Although the incidence of juvenile polyps is unknown, they are believed to occur in approximately 1% of all preschool children.[1] Most juvenile polyps appear in the first decade of life, with the peak incidence between 3 and 5 years of age.[1] The polyps are solitary in 50% of cases, with the remainder having 2 to 10 polyps. The location of these polyps has changed over the past 10 years. Historically, 70% of the polyps were found in the rectum. Today, only 40% are found in the rectum or sigmoid colon, whereas 60% are found evenly distributed throughout the proximal colon.[1] Juvenile polyps are rarely seen after adolescence.

Clinical Presentation

The most common presenting symptom of a juvenile polyp is bleeding (93%) that results from ulceration of the polyp surface. Blood loss is usually minimal and appears as bright red streaks of blood over the surface of the stool. Abdominal pain (10%), which is believed to be caused by traction on the polyp from peristaltic activity, and prolapse of the polyp (4%) are other less common presenting symptoms. Prolapse of the rectum and encopresis have also been reported.[1] Many juvenile polyps will autoamputate, resulting in spontaneous cessation of rectal bleeding.[29]

The differential diagnosis of juvenile polyps encompasses all of the causes of rectal bleeding in toddlers through children who are 6 years of age. Anal fissures and rectal prolapse cause rectal bleeding but are easily distinguished from polyps on physical examination. Bleeding from Meckel diverticulum or duplication of the intestine usually causes more substantial blood loss than that from a polyp, and the blood usually commingles with the stool rather than coating it. Bleeding from an intussusception is accompanied by abdominal pain that is substantially worse than that seen with polyps. Inflammatory bowel disease is usually accompanied by diarrhea, which is not seen with polyps. Blood dyscrasias, such as Henoch-Schönlein purpura, should also be considered in the differential diagnosis.

Treatment

The diagnosis and treatment of juvenile polyps requires a combination of history, digital rectal examination, and colonoscopy. The shift of juvenile polyps to the more proximal colon[29] and the concern for the presence of juvenile polyposis (>5 polyps), with its increased risk of malignancy, mandates that the entire colon be surveyed. Children with suspected polyps should have a digital rectal examination initially. Polyps in the rectum can be easily removed during anoscopy. Following removal of a rectal juvenile polyp, pancolonoscopy, in a well-prepared bowel, should be performed to determine if additional, more proximal polyps are present.[30] Children with juvenile polyposis and adenomatous changes are more likely to have right-sided polyps[31]; therefore all polyps should be removed and undergo histologic evaluation. Complications following endoscopic removal of polyps are rare.

Polyposis Syndromes

Gastrointestinal polyps are the result of a defect in the balance between cellular growth promotion and cellular growth inhibition. The defect results from either an activated oncogene that has upregulated a growth-promoting protein or the loss of function of a growth-inhibiting protein, usually by the inactivation of a tumor suppressor gene. In the polyposis syndromes there has been inactivation of a tumor suppressor gene.[32,33] A resulting gastrointestinal cancer occurs when there are additional genetic defects. Polyposis syndromes can be classified into adenomatous polyposis syndromes and hamartomatous polyposis syndromes.

Adenomatous Polyposis Syndromes

All of the adenomatous polyposis syndromes are distinguished by the development of a large number of adenomas in the colon. Additionally, these syndromes are associated with extracolonic manifestations such as duodenal polyps; benign soft tissue tumors such as osteomas of the mandible, long bones, and skull; and congenital hypertrophy of the retinal pigmented epithelium (CHRPE) (Table 93-2). Adenomatous polyposis syndromes include familial adenomatous polyposis (FAP), most common in children; Gardner syndrome; and Turcot syndrome.

Familial Adenomatous Polyposis

FAP is distinguished by the progressive development of hundreds to thousands of adenomatous polyps in the colon. By 15 years of age 50% of those that carry the FAP gene will have polyps. The lifetime risk for developing a colorectal cancer is 100%; however, the average age for developing an adenoma in FAP is 16 years and 39 years for developing a colorectal cancer.[34]

TABLE 93-2
Extracolonic Features in Familial Adenomatous Polyposis

Cancer (Lifetime Risk)	*Other Lesions*
Duodenal (1%-5%)	CHRPE
Pancreatic (2%)	Nasopharyngeal angiofibromas
Thyroid (2%)	Osteomas
Brain (medulloblastoma) (<1%)	Radiopaque jaw lesions
Hepatoblastoma (0.7% of children < 5 yr old)	Dental abnormalities
	Lipomas, fibromas, epidermoid cysts
	Desmoid tumors
	Gastric adenomas/fundic gland polyps
	Duodenal, jejunal, ileal adenomas

CHRPE, congenital hypertrophy of the retinal pigment epithelium.
Modified from Cruz-Correa M, Giardello FM: Diagnosis and management of hereditary colon cancer. Gasroenterol Clin North Am 2002;31:537-549.

HISTORY

The first case of adenomatous polyposis was recorded by Covisart in 1847,[35] but it was Chargelaigue,[36] who, 12 years later, gave the first definitive account of the disease in a 16-year-old girl and a 21-year-old man. The first pathologic description of these colonic polyps was reported by Virchow in 1867,[37] with Woodward in 1881[38] being the first to distinguish between neoplastic and inflammatory polyps. The first familial association of these polyps was described by Cripps in 1882[39] between a 9-year-old boy and his 17-year-old sister. However, the malignant potential of these polyps was not recognized until 1890 by Handford.[4]

The first recorded operations for polyposis are credited to Lilienthal[21] in North America and subsequently to Lockhart-Mummery at St. Mark's Hospital in London, as reported by Thompson and Watne.[40,41] Lockhart-Mummery, in 1925,[42] concluded that (1) multiple adenomatous polyps develop in succeeding generations, (2) afflicted individuals develop cancer at an early age, and (3) the adenomas are an antecedent to cancer. In 1927 Cockayne[43] described the mode of inheritance as Mendelian dominant, which was later confirmed by Dukes in 1930[44] and Lockhart-Mummery in 1939.[45] Since then, FAP has become a model for understanding the adenoma-carcinoma sequence.[46]

The detection of a deletion in chromosome 5q[47] in a patient with Gardner syndrome has led to characterization of the gene responsible for FAP, the *APC* gene.[48–57] The 5q deletion or alteration in the *APC* gene results in a gene product with a truncated protein, which subsequently causes the *APC* gene to act as a tumor suppressor gene.[32,33] Mouse models for FAP have been developed,[58] and these will facilitate research in gene therapy.

PATHOLOGY

FAP is defined as the presence of at least 100 visible adenomatous polyps in the large intestine.[59] However, patients with fewer polyps have been diagnosed as having FAP, and one patient who had early onset of colorectal cancer and had a 5q gene deletion had only one endoscopically detectable polyp.[60]

Colorectal polyps are the hallmark of FAP. Although 100 polyps is the usual threshold for diagnosing this disorder, patients coming to colectomy in their teenage years typically have thousands of polyps (Fig. 93-4). Two types of FAP seem to exist: the sparse type, which is characterized by hundreds of polyps, and the profuse type, which is characterized by thousands of polyps. Utsunomiya and colleagues[61] have shown that the history of the two types is different—patients with the profuse type tend to develop adenocarcinoma at an earlier age.

In FAP the polyps are typically scattered throughout the colon, which allows diagnosis by sigmoidoscopy. The polyps vary in size from 1 to 2 mm in diameter, and when present, pedunculated polyps can be 1 cm in diameter or larger (Fig. 93-5). During duodenoscopy, biopsy of normal-appearing duodenal mucosa may reveal microscopic adenomas too small to be seen macroscopically. These microadenomas may consist of only three or four dysplastic crypts that usually have a tubular adenomatous structure.[62]

Adenomatous polyps result from a neoplastic transformation of at least one epithelial cell that is in the proliferative portion of a crypt.[63] The transformed clone then populates the upper part of the crypt, which divides by budding.[63] Crypt fusion is then responsible for further growth of the adenoma. This neoplastic transformation, called *dysplasia,* implies atypical morphologic characteristics, with nuclear enlargement and stratification. Adenomas seem to pass through gradations of dysplasia until invasive adenocarcinoma develops.[64] Extension of neoplastic cells into the basement membrane of the colonic epithelium represents carcinoma in situ. As the neoplastic cells extend beyond the basement membrane, the tumor becomes microscopically invasive. Because the colonic mucosa does not contain lymphatics, metastasis does not usually occur until the tumor invades through the muscularis mucosa into the submucosa.

Small intestinal mucosa can also be involved with adenomatous polyps. Polyps of the small intestine are frequently found around the orifice of the common bile duct.[65] Polyps in this region are variable in size, are often microscopic, and involve only a few crypts. Adenocarcinoma of the duodenal papilla and periampullary regions occurs in 2.9% of patients with FAP[65] and has been found in the common bile duct of these patients.[66]

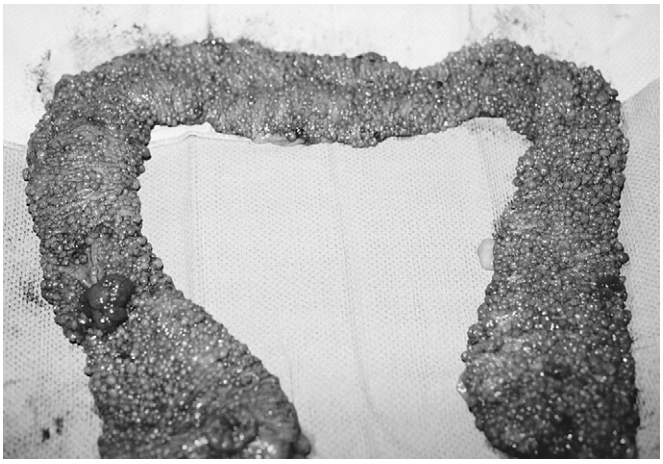

FIGURE 93-4 Gross specimen of the total colon in a patient with familial adenomatous polyposis demonstrating thousands of adenomatous polyps. Note the large adenoma in the ascending portion of the colon.

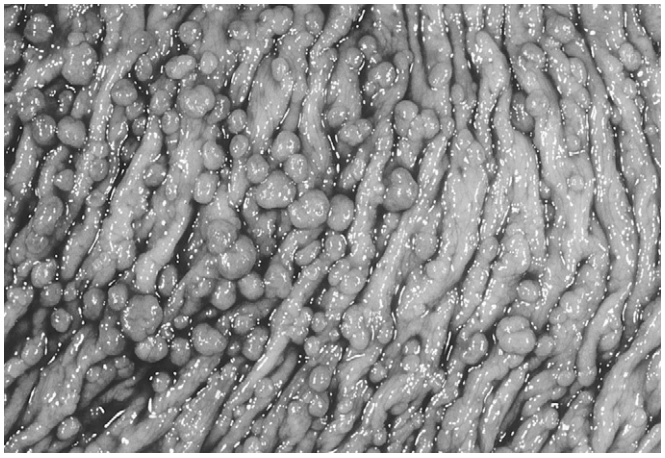

FIGURE 93-5 Close-up view of colonic mucosa demonstrating a "carpet" of small 1- to 2-mm adenomas in a patient with familial adenomatous polyposis.

Gastric polyps occur in patients with FAP, but they are usually benign polyps of the fundic gland.[67] These polyps result from cystic dilation of specialized gastric glands rather than from dysplasia. No evidence that neoplastic transformation occurs in polyps of the fundic gland exists.[68]

ETIOLOGY

The incidence of FAP ranges from 1 in 6000 to 1 in 12,000 births.[69–71] FAP is inherited as an autosomal dominant trait with a moderate incidence (10%) of new mutations.[72] The manifestations of FAP differ greatly, probably as a result of variation in the mutation of the *APC* gene. Although the occurrence of polyps is strongly related to genetics, the phenomenon of regression of rectal polyps after colectomy and ileorectal anastomosis was recognized in 1988[73,74] and points to the fact that the luminal environment also plays a role in the development of polyps.

FAP is caused by a mutation in the *APC* gene on the long arm of chromosome 5, where a variable deletion or alteration of the gene is associated with the disease. The *APC* gene codes for a protein product that acts as a tumor suppressor.[72] Because of this gene deletion, the probability of cancer (as diagnosed by biopsy during sigmoidoscopy) by 25 years of age is 90%.[4] In colorectal cancer cell lines that have an intact chromosome 5 introduced into the cells, the ability of the cells to induce tumor growth in mice is considerably reduced.[58,75] Similar results have been found for other tumor suppressor genes, namely the *TP53* gene on chromosome 17p and the deleted colorectal cancer gene *(DCC)* on chromosome 18q.[72] It has become apparent there is genetic heterogeneity in FAP. Certain germline mutations of the *APC* gene predispose to attenuated disease expression.[77,78] Further evidence indicates that additional modifier genes influence the severity of FAP.[79]

CLINICAL PRESENTATION

Although FAP has been recognized in infancy and early childhood, it is most frequently identified in early adolescence. Most patients are asymptomatic, but some present with increased frequency of defecation, rectal bleeding, anemia, and abdominal pain. Most (90%) are identified by routine surveillance because of a familial history of adenomatous polyposis.

Diagnosis is established by sigmoidoscopy and occasionally by air contrast barium enema. Sigmoidoscopy usually reveals a carpet of polyps that cover the entire surface of the colon. Biopsy of at least 10 polyps will confirm the diagnosis. In some patients with FAP, most of the polyps will be located in the proximal colon. If the diagnosis of FAP represents a new mutation (no other family members are known to have the disease), a careful examination of all family members is required.

Polyps are found in the stomach in up to 50% of patients with FAP, but only 6% of the polyps are adenomatous,[67] with the rest being fundic gland polyps (hamartomas). Polyps occur in the duodenum less often than in the stomach; however, duodenal polyps are much more likely to be adenomatous. Several series have demonstrated that up to 98% of FAP patients have visible duodenal polyps or at least a histologic abnormality with dysplasia, unicrypt adenomas, or hyperplasia in the duodenal mucosa.[65,67,80] Adenocarcinoma of the duodenal papilla or periampullary region eventually develops in 2.9% of patients with FAP.[65] For these reasons, upper endoscopy is necessary in all patients with this disorder.

TREATMENT

Malignant conditions of the colon will occur in all patients with FAP if left untreated. The average age for developing cancer is 39, with 7% developing cancer by age 20 and 15% by age 25.[81] Surgical removal of the entire colonic mucosa will prevent colorectal carcinoma. Most patients who present with symptomatic polyps already have a malignant condition.[81] Therefore colectomy is recommended at any age, if the child is symptomatic.

A wide range of surgical options exists. Total proctocolectomy with a permanent ileostomy prevents cancer but leaves a young patient with a permanent abdominal wall stoma. The physiologic and psychologic impact of a permanent ileostomy is substantial in adolescence. This operation can cause substantial sequelae because of the extensive pelvic dissection, namely, damage to the nervi erigentes with resultant bladder atony and in males, impotence. For these reasons, total proctocolectomy is not the treatment of choice for FAP in a pediatric patient.

Total abdominal colectomy with an ileorectal anastomosis and continued surveillance of the retained rectum has probably been the most common operation for FAP performed in the past. St. Mark's Hospital in London reported results with 215 patients undergoing this procedure.[40] Immediate postoperative complications included prolonged ileus (7%), anastomotic breakdown (2%), and bleeding (<1%), for a total complication rate of 10%. Frequency of defecation at late follow-up (6.5 years) was three stools per day, and less than 10% reported nighttime soiling. Continence was considered completely normal in 72%. Forty-four percent (44%) of the patients, however, required subsequent treatment for their rectal polyps. Depending on the density of the rectal polyps, the patients were evaluated every 3 to 6 months, with sigmoidoscopy and fulguration of any polyps greater than 5mm in diameter. Ten percent developed carcinoma in their rectal stump. The cumulative risk for rectal cancer was 10% at 50 years of age and 29% by 60 years of age.[81]

In more recent years, total colectomy with a rectal mucosectomy and an ileoanal pouch procedure has become the preferred operation for children with FAP. The J pouch is the preferred technique because of simplicity of construction and sparsity of complications.[82] Geiger and colleagues[83] reported a novel technique of a double-stapled, ileoanal, J pouch anastomosis with excellent outcomes. An inverse relationship exists between the size of the reservoir and the frequency of defecation.[84–87] Other factors that influence frequency of defecation include inflammation, sphincter function, and small intestinal motility. Larger reservoirs allow less frequent defecation but tend to be associated with more frequent bouts of inflammation of the reservoir ("pouchitis"), which probably results from stool stasis. In several recent series that studied 450 patients with reservoirs, the frequency of defecation ranged from 3.3 to 7.2 with an average of 5.8 stools per day.[88–93] Large series of patients with reservoirs, however, report an average rate of pouchitis of 23% and a pelvic sepsis rate of 8%.

FOLLOW-UP

In addition to colonic polyps, patients with FAP can develop a large assortment of benign extracolonic manifestations and occasionally other cancers (see Table 93–1). Endoscopy of the upper gastrointestinal tract and sigmoidoscopy should be performed annually in all patients. Removal of polyps in the duodenum can be done by endoscopic snaring or by open duodenotomy. Size larger than 1 cm in diameter, rapid growth, polyp induration, severe dysplasia, or villous change suggests the need for a more aggressive intervention. Recent data have shown that 42% of adenomas of the ampulla of Vater that are larger than 1 cm in diameter contain a foci of cancer compared with only 13% of those smaller than 1 cm.[94] The incidence of duodenal cancer, however, remains low at 1% to 5%. Sigmoidoscopy can be done easily in patients with an ileoanal pull-through. The anal canal and any short segment of rectal mucosa left behind must be carefully evaluated.

OTHER TREATMENTS

Drugs and several dietary supplements have been used to treat polyps. These include vitamin C,[95,96] sulindac,[96] dietary fiber,[97] and calcium.[98,99] In a randomized, double-blinded study of the use of sulindac, inhibition of both rectal and duodenal polyp growth was observed[100] and other studies have confirmed this finding.[71,101] In a randomized, double-blind, placebo-controlled study, however, standard doses of sulindac did not prevent the development of adenomas in subjects with FAP. Rectal cancer has been reported after prolonged sulindac treatment.

GARDNER SYNDROME

Between 1951 and 1955, Gardner and colleagues[102–105] established the association of colonic familial adenomatous polyposis and the extracolonic findings of multiple osteomas, fibromas, and epidermoid cysts. They also demonstrated that the syndrome was inherited in an autosomal dominant pattern.[102,104] The natural history and treatment of the colonic polyps is the same as for those patients with FAP. The osteomas are most frequently found in the skull and facial bones, and abnormal dentition with impaction and early tooth decay and supernumerary teeth are seen.[106] Sebaceous cysts are most commonly found on the legs, followed by the face, scalp, and arms. Lipomas and fibromas are also seen.

Periampullary cancer was thought to be more prevalent in Gardner syndrome than in those with FAP, but surveillance of the duodenum in patients with FAP has shown a high incidence of duodenal abnormalities in all patients. Because detailed surveillance of all patients with familial polyposis has revealed many subtle extracolonic manifestations, the distinction between Gardner syndrome and FAP is becoming less clear. FAP is probably an all-encompassing syndrome, in which patients manifest different signs as the condition evolves.[107]

Desmoid tumors of the abdominal wall and mesentery of the small intestine occur in approximately 20% of patients with Gardner syndrome. These tumors also occur in patients who only have the colonic manifestations of FAP and are the leading cause of death in those who have undergone a prophylactic colectomy. Desmoid tumors are a dense, fibroplastic proliferation that may remain localized or may become widespread throughout the mesentery or the abdominal wall. All stages of fibrous dysplasia including fibrosarcoma have been seen. Most desmoid tumors appear after surgery, usually within 6 to 30 months.[108] Desmoid tumors of the body wall may be observed initially because many of them remain static or even regress over several years.[108] For those that continue to grow or reach 10 cm in diameter, complete local excision is met with a recurrence rate of less than 10%, which is satisfactory. Most intraabdominal desmoid tumors do not become evident until they have reached a nonresectable size. Because of the difficulty in resecting intraabdominal desmoid tumors, several drugs have been tried with varied rates of success. Such drugs include steroids; antiestrogen agents (progesterone, tamoxifen, and toremifene); and nonsteroidal anti-inflammatory agents.[109–115]

TURCOT SYNDROME

Turcot, Despres, and St. Pierre[116] described two siblings who initially presented with colonic familial adenomatous polyposis and eventually died of intracranial brain tumors (glioblastoma and a medulloblastoma). Turcot believed that the brain tumors were extracolonic manifestations of FAP. Ependymomas and carcinoma of the thyroid (which are usually papillary in origin)[107] have also been described to occur in Turcot syndrome.

Hamartomatous Polyposis Syndromes

Hamartomatous polyposis syndromes are distinguished by an overgrowth of cells that are native to the area in which they normally occur. The overgrowth is in general not considered to have malignant potential. Several of the syndromes in this category, however, have an increased lifetime risk of developing either intestinal or extraintestinal cancers. The hamartomatous polyposis syndromes include juvenile polyposis syndrome, Cowden disease, and Peutz-Jegher syndrome.

JUVENILE POLYPOSIS SYNDROME

Juvenile polyposis syndromes are uncommon. These syndromes can be separated into three distinct clinical entities: diffuse juvenile polyposis of infancy, diffuse juvenile polyposis, and juvenile polyposis coli.[8]

Diffuse Juvenile Polyposis of Infancy

Diffuse juvenile polyposis of infancy presents within the first few months of life,[15] usually without any family history.[20] Presenting signs include diarrhea, rectal bleeding, intussusception, protein-losing enteropathy, macrocephaly, clubbing of fingers and toes, and hypotonia.[117–121] The extent of diarrhea, rectal bleeding, and protein-losing enteropathy is directly related to the number of polyps present. The entire GI tract is frequently involved. Treatment for this syndrome is usually aggressive, starting with total parenteral nutrition and intestinal rest. The latter measure reduces the protein and blood loss and decreases the incidence of intussusception.[122] When the nutritional status of the patient has been stabilized, portions of the intestine with the most polyps are

removed. Despite appropriate treatment, this disease is almost universally fatal; only 2 of 12 patients are reported as surviving beyond 2 years of age.[7,17,117–121,123–126]

Diffuse Juvenile Polyposis

Children with diffuse juvenile polyposis are usually 6 months to 5 years of age and present with mild rectal bleeding and prolapse but may also have protein-losing enteropathy, intussusception, and malnutrition.[15] For this age group it is important to distinguish juvenile polyposis from familial adenomatous polyposis. Polyps associated with diffuse polyposis are found throughout the bowel, most often in the stomach, distal colon, and rectum.[15] Endoscopic polypectomies and segmental bowel resection are used in the treatment of this disease. These children usually do well, although the need for recurrent therapy is common.

Juvenile Polyposis Coli

Juvenile polyposis coli occurs in children between the ages of 5 and 15 years of age. This disorder is usually characterized by bleeding of bright red blood from the rectum, anemia, rectal prolapse, or all of these disorders. Polyps are usually limited to the distal colon and rectum.[15] Approximately 50% of the patients will have a family history, indicating an autosomal dominant pattern of inheritance.[17] Associated congenital defects including cleft palate, malrotation, polydactyly, and abnormalities of the heart and cranium have been described.[20]

Pathology Any child with five or more polyps, polyps throughout the GI tract, or even one polyp if the child has a family history of juvenile polyposis is considered to have a juvenile polyposis syndrome.[20] Most patients with such syndromes will have approximately 50 to 100 colorectal polyps. Patients with diffuse juvenile polyposis of infancy and diffuse juvenile polyposis will also have polyps in the stomach, small intestine, or both. The importance of identifying children with a polyposis syndrome lies in the need for long-term surveillance due to the high risk of carcinoma (17%) occurring at an early age (mean age at diagnosis of carcinoma is 35.5 years).[15]

The gross appearance of a polyp in juvenile polyposis is the same as one in isolated juvenile polyps. Approximately 20% of the polyps in juvenile polyposis, however, present grossly as a multilobular mass resembling a cluster of polyps attached to a stalk (Fig. 93-6).[18] Histologically, these polyps demonstrate more epithelium with a villous or papillary configuration. Epithelial dysplasia can occur in juvenile polyps* and in coexisting adenomas found in conjunction with juvenile polyps.[9,14,16,18,131–136] Severe dysplasia, which could be considered carcinoma in situ, has been found in patients with juvenile polyps associated with juvenile polyposis syndrome.[137] Lobular polyps have a higher propensity for more severe dysplasia (47%) than the nonlobular polyps (10%).[18] Several reports of infiltrating adenocarcinoma of the colon and rectum in association with juvenile polyposis exist.[8,12,129,131,138–140] According to the St. Mark's Polyposis Registry in London, the cumulative risk for cancer in patients with a juvenile polyposis syndrome by age 60 is 68%.[19,128]

*References 9, 12–14, 16, 18, 25, 127–132.

FIGURE 93-6 Gross specimen of colon in a patient with juvenile polyposis syndrome. Note small adenomas and multilobular clusters of polyps attached to stalks.

Treatment The autosomal dominant pattern of inheritance and the 68% cumulative risk for cancer by age 60 means that treatment must include long-term follow-up of patients with polyposis and their family members. Some advocate prophylactic colectomy and rectal mucosectomy with endorectal ileal pull-through as a primary treatment.[129] Others recommend regular screening (every 2 years) with colonoscopy and random biopsy[141] and subsequent colectomy if severe dysplasia, rapid polyp formation, or bleeding occurs.[16] One patient had a colectomy and ileosigmoidostomy at 4 years of age only to develop inoperable cancer of the sigmoid colon at 27 years of age.[18] First-degree relatives should be screened because of the familial nature of the disease. The approach to patients with juvenile polyposis should be similar to that taken for patients with familial adenomatous polyposis.

PEUTZ-JEGHER SYNDROME

History

The association of intestinal polyps with mucocutaneous pigmentation spots of the mouth, hands, and feet was first reported by Peutz in 1921.[142] In 1944[143] Jegher first reported two cases. In 1949[144] he and his colleagues added 8 more to 12 other cases he had collected from personal communications. Jegher and colleagues[144] subsequently defined the two main features of the syndrome: melanin spots on the buccal mucosa and lips, with variable melanin pigmentation on the face and digits, and polyposis of the intestinal tract. In 1954 Bruwer, Bargen and Kierland[145] were the first to use the term *Peutz-Jeghers syndrome*. In recent years, reports of intestinal and extraintestinal cancers have led to a reassessment of the management of these patients.[146]

Pathology

Peutz-Jeghers syndrome is characterized by melanotic spots, ranging in color from brown to black, occurring on the lips, around the mouth, and on the buccal mucosa. These spots can also be found on the hands, feet, nasal mucosa, and conjunctivae and in the rectum.[146] The pigmented spots are usually present at infancy and usually fade at puberty.

Although the polyps associated with Peutz-Jeghers syndrome can be found anywhere from the stomach to the rectum, they occur most commonly in the small intestine (55%). Approximately 30% of these polyps are found in the stomach and duodenum, and 15% are found in the colon and rectum.[147] Grossly, the polyps range from a few millimeters to several centimeters and present as smooth, firm, pedunculated lesions that are lobulated, in contrast to juvenile polyps, which are not lobulated. Peutz-Jeghers polyps are classified histologically as hamartomas of the muscularis mucosa[146] and demonstrate strands of smooth muscle fibers that divide the polyp into sectors (Fig. 93-7).[148–150] Adenomas can occur concurrently with Peutz-Jeghers polyps.

Etiology/Incidence

Peutz-Jeghers syndrome is rare and has an equal sex distribution; it has been described in all ethnic groups. Most cases of Peutz-Jeghers syndrome are inherited in an autosomal dominant pattern, but some develop de novo, most likely representing new, spontaneous mutations. Recently two groups of investigators have defined the genetic mutation associated with Peutz-Jeghers syndrome. In Peutz-Jeghers–affected individuals many (but not all) have a mutation of a novel serine/threonine kinase (LKB1 or STK11) with loss of kinase activity.[151,152] Routine genetic testing and gene therapy for this disease is under investigation but currently not available.[153]

Clinical Presentation

Because of the familial association of Peutz-Jeghers syndrome, the syndrome is often revealed in patients through screening programs. If there is no family history, patients usually present with crampy abdominal pain related to transient intussusception of a polyp. Abdominal radiographs will often demonstrate dilated or partially obstructed small intestine but rarely complete obstruction. Anemia resulting from occult blood loss and malignant conditions are other presenting signs. Thirty percent of patients present with signs and symptoms in the first 10 years of life, with 50% presenting by 20 years of age.[154,147]

Several reports of intestinal tumors in association with Peutz-Jeghers syndrome have been published.[155–160] Malignant changes in hamartomatous polyps of Peutz-Jeghers syndrome have been commonly reported.[101,159,161–167] Separate adenomatous and carcinomatous changes in hamartomas have also been reported, which suggests that the adenoma-carcinoma sequence occurs in the small intestine of patients with Peutz-Jeghers syndrome.[161] A review of 72 patients with the syndrome[159] showed that 22% developed cancer. Nine cases were gastrointestinal or pancreatic in origin, and seven were extraintestinal. Compared with an age-matched general population, patients with Peutz-Jeghers syndrome had a relative risk for death from gastrointestinal cancer alone that was 13 times greater, and the risk for death from all cancers was 9 times greater. The chance of dying from cancer by the age of 60 is approximately 50% in patients with Peutz-Jeghers syndrome.[146]

Extraintestinal tumors associated with Peutz-Jeghers syndrome include ovarian, cervical, and testicular neoplasms. Reported ovarian tumors include cystadenomas,[154,168,169] granulosa cell tumors,[135] and sex-cord tumors.[170–172] Adenocarcinoma of the cervix can occur and is usually associated with an ovarian tumor.[174] Sertoli cell tumors of the testicle have been found and cause gynecomastia in 50% of cases. These tumors are usually benign but have malignant potential[175–177]; thus an orchiectomy is recommended. Cancer of the breast, thyroid, bile duct, pancreatic, and gallbladder have all been described in association with Peutz-Jeghers syndrome.[146]

Treatment

Peutz-Jeghers syndrome should be suspected in any child who presents with colicky abdominal pain or occult anemia and melanotic pigmented spots. Recommendations for treatment have changed over the past decade because of the increasing concern of malignancy. The management protocol proposed by Phillips and Spigelman[146] includes the following annual evaluations: (1) symptoms related to polyps, (2) blood count to detect anemia caused by blood loss, (3) breast and pelvic examinations with cervical smears and pelvic ultrasonography in girls, (4) testicular examination with ultrasonography in boys, and (5) pancreatic ultrasonography. In addition, esophagogastroduodenoscopy and colonoscopy are recommended on a biennial basis, along with small intestine contrast studies. Recently magnetic resonance imaging (MRI) has shown promise as a surveillance modality for small intestinal screening.[178] Mammography is recommended at 25, 30, 35, and 38 years of age, biennially until 50 years of age, and then annually.

All polyps larger than 0.5 mm found at endoscopy should be removed. Laparotomy with intraoperative enteroscopy is recommended for removal of all small bowel polyps greater than 15 mm in diameter. The previous practice of radical intestinal resections should be avoided because of the recurrent nature of the polyps and the ensuing short-bowel syndrome that can occur. Any intestinal or extraintestinal tumors should be treated aggressively. Historical data indicate that the chance of patients with Peutz-Jeghers syndrome dying by the age of 60 is close to 60% compared with 25% in an age-matched general population.[146]

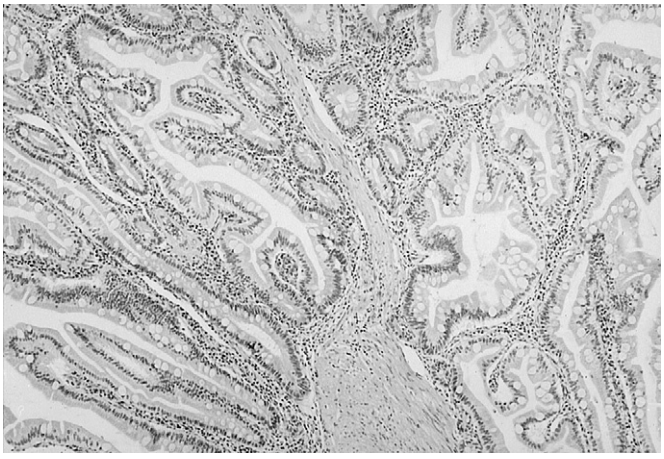

FIGURE 93-7 Photomicrograph of a Peutz-Jeghers polyp demonstrating a hamartomatous alteration of the muscularis mucosa. Smooth muscle fibers divide the polyp into sectors.

COWDEN DISEASE

Cowden disease is an autosomal dominant condition distinguished by multiple hamartomas that affects all three of the germ layers. Patients with Cowden disease are at an increased

risk of developing breast, thyroid, and endometrial neoplasias.[179,180] Eighty percent of patients present with dermatologic lesions including facial trichilemmomas, acral keratoses, papillomatous papules, or mucosal lesions. Other major but not necessarily pathognomonic criteria include breast carcinoma, thyroid carcinoma, macrocephaly, and endometrial carcinoma. Only 35% of patients who meet the criteria for Cowden disease will have gastrointestinal polyposis.[7] The polyps are typically juvenile polyps without any increased risk of developing a gastrointestinal cancer.

Nonepithelial Polyps

LYMPHOID POLYPS

History

The first case of lymphoid hyperplasia of the terminal ileum was described by Marina-Fiol and Rof-Carballo in 1941 as reported by Patel and Awen.[181] Fieber and Schaefer[182] reviewed eight cases previously described in the literature and added four of their own in 1966. Byrne and colleagues[183] reported only 44 cases in the world literature; however, lymphoid polyps were identified in 60% of children studied by Franken for remote abdominal complaints.[184] Thus the incidence of lymphoid polyps is probably higher than reported, but clearly most of them are asymptomatic, and, therefore, never identified.

Pathology

Lymphoid polyps vary in size from a few millimeters to 3 centimeters in diameter and are usually sessile in form. The polyps are caused by elevation of hyperplastic submucosal lymphoid aggregates. The overlying mucosa often becomes ulcerated, which gives the polyp the volcano-like appearance. Ulceration of the mucosa leads to occult blood loss. Hyperplasia of the submucosal lymphoid tissue is believed to be caused by nonspecific infections of childhood.[1,2,4,108]

Incidence

Lymphoid polyps tend to develop in young children within the first few years of life as a result of exposure to new bacteria and viruses.[122] The peak incidence is at 4 years of age and significantly diminishes by 5 years of age.

Clinical Presentation

Anemia resulting from blood loss and occasionally substantial rectal bleeding are the usual presenting signs of lymphoid polyps. Colonoscopy, air contrast barium enema, or both are the diagnostic methods of choice for diagnosing lymphoid polyps of the colon. An air-contrast barium enema will show small, uniform, umbilicated, polypoid filling defects that are distinct from juvenile or adenomatous polyps (Figs. 93-8 and 93-9).[183,184] Small elevations of otherwise-normal mucosa are seen on endoscopy, and biopsy will confirm the diagnosis. Histologic evaluation reveals lymphoid aggregates with large germinal follicles.[122]

Treatment

Lymphoid polyps are benign, are self-limiting, and tend to regress spontaneously.[42,185] Once a histologic diagnosis is made, expectant measures will usually be rewarded by regression of the lesions. Substantial uncontrolled bleeding and intussusception may require a more aggressive surgical approach.

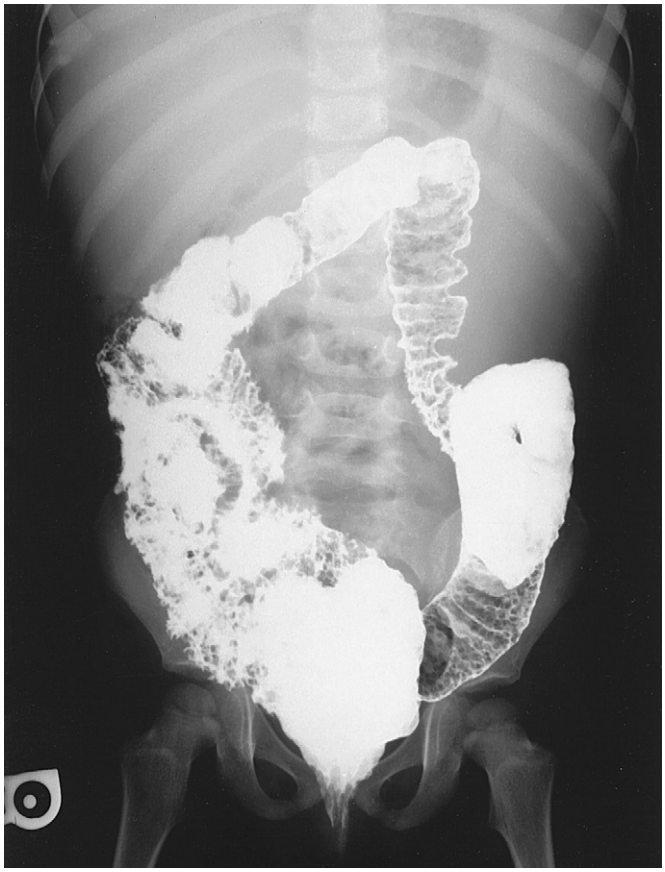

FIGURE 93-8 Barium enema showing multiple, small 1- to 2-mm mucosal nodules throughout the entire colon and terminal ileum. The central umbilication within these nodules seen on this postevacuation film is diagnostic of diffuse lymphoid hyperplasia.

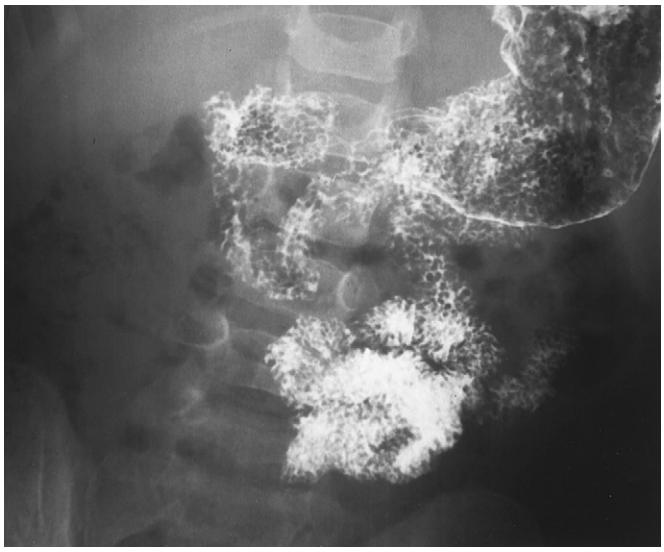

FIGURE 93-9 An upper gastrointestinal series showing diffuse lymphoid hyperplasia throughout the stomach and small intestine.

The complete reference list is available online at www.expertconsult.com.