Hereditary Colon Cancer—Part I

Much of our knowledge of tumor suppressor genes and heritable cancers has come from the study of heritable forms of colorectal cancer (CRC), which is the focus of this monograph (Fig 1). The most common form of heritable CRC is Lynch syndrome, which may account for as many as 5% to 10% of all cases of CRC (Fig 2). The next most common is familial adenomatous polyposis (FAP), which is responsible for approximately 1% of CRC cases. Finally, there are the hamartomatous polyposis syndromes (juvenile polyposis, Cowden syndrome, and Peutz-Jeghers syndrome), which together account for approximately 1% of CRC cases. FAP was originally recognized as an autosomal dominant syndrome manifested by hundreds of colorectal adenomatous polyps, leading to colorectal carcinoma in virtually 100% of untreated, affected patients.\(^4,5\) The cumulative lifetime incidence rate of FAP has been calculated to be 1 in 10,000 people, which is less than 1% of that seen for colorectal cancer.\(^4,6\)

Historical Perspective

One of the first recognized accounts of gastrointestinal (GI) polyposis was published by Menzelio\(^7\) in 1721, and this was most likely inflammatory in etiology. Multiple colonic adenomatous polyps were reported in 1859 by Chargelaiqne.\(^8\) This was followed by both Lebert in 1861 and Richet in 1873 publishing case reports of different patients probably being affected by FAP.\(^9\) Clearly in 1881, Sklifasowski\(^10\) documented a case of FAP in a 51-year old man initially presenting with bloody diarrhea, leading to the discovery of rectal polyps. The inherited predisposition of FAP was shown by Cripps\(^11\) in reporting a brother and a sister both having FAP in 1882. This familial inheritance was supported by Smith’s report\(^12\) in 1887 of 3 cases of multiple polyps in the lower bowel all from the same family. Similarly, Bickersteth\(^13\) in 1890 published a case of FAP in 2 successive generations, affecting a mother and her son. The association of colorectal carcinomas and FAP was first recognized by Smith in 1887 and the progression of adenomas to adenocarcinoma was histologically documented by Handford in 1890.\(^12,14\) Lockhart-Mum-
Mery clarified the familial predisposition of FAP as autosomal dominant in 1925.

**Natural History of FAP**

Clinically, FAP is a disease defined as greater than 100 adenomatous colorectal polyps. Polyp development is age-dependent, usually first
becoming evident around puberty. Therefore, any number of adenomatous polyps found in a teenager would be suspicious for FAP, especially if there is a family history. The natural history for FAP is characterized by the development of greater than 100 adenomatous colorectal polyps by the end of the second or third decade (Fig 3). These patients will virtually all develop colorectal cancer, if their life is not prematurely ended from other causes, or they have not undergone a prophylactic colectomy. In 1 of the most complete reviews of a national polyposis registry, Bulow found the median age for development of colorectal adenomatous polyps to be 16 years (range, 5-38 years). The first symptoms from the lower GI tract developed by the age of 29 years (range, 2-73 years), and the development of colorectal carcinoma occurred at a median age of 36 years (range, 17-67 years). The earliest signs and symptoms of lower GI involvement in patients with FAP is blood per rectum, vague abdominal pain, tenesmus, diarrhea, and/or obstruction.

A milder form of FAP known as attenuated adenomatous polyposis coli (AAPC) has been defined as fewer than 100 adenomatous colorectal polyps. Characteristically in AAPC, not only are the number of polyps fewer than 100, but morphologically they tend to be flat rather than

FIG 3. A colon carpeted with adenomatous polyps from a patient with familial adenomatous polyposis (reproduced with permission from Nivatvongs S. Principles and Practice of Surgery for the Colon, Rectum, and Anus. Second ed. Quality Medical Publishing; 1999). (Color version of figure is available online.)
polypoid. This has led to some confusion and another term used in the literature, the hereditary flat adenoma syndrome. The polyps are predominantly right sided with rectal sparing and are also associated with upper GI lesions, autosomal dominant inheritance, and APC gene mutations.\textsuperscript{20-23} Colorectal cancer is usually diagnosed later in life in AAPC compared with FAP. Lynch and colleagues\textsuperscript{22} reported an average age of diagnosis at 52.5 years, and Brensinger and colleagues\textsuperscript{24} noted a mean age of diagnosis of colorectal cancer at the age of 50 years.

**Turcot’s Syndrome**

Turcot’s syndrome is the association of colonic adenomatous polyposis and brain tumors. This association was originally reported in 1949 by Crail.\textsuperscript{25} Later the syndrome was named after Turcot and colleagues,\textsuperscript{26} who described a brother and sister who presented at ages 15 and 13 years with symptomatic colonic adenomatous polyposis and developed central nervous tumors. The brother developed acute myelitis secondary to a medulloblastoma located in the medulla spinalis 3 years after presentation and eventually died. The sister died at age 21 due to a large left frontal lobe glioblastoma.\textsuperscript{26} Paraf and colleagues\textsuperscript{27} reviewed the literature regarding Turcot’s syndrome and found 2 distinct groups. The first group (group I) contained patients with gliomas of the central nervous system (CNS) associated with colorectal adenomatous polyps.\textsuperscript{27} These patients predominantly had germline mutations in mismatch repair genes. The second group (group II) was predominantly medulloblastoma associated with colonic adenomatous polyposis and these patients showed a predominance of germline mutations in the APC gene.\textsuperscript{27} More than 95\% of CNS tumors in group I patients were associated with gliomas, compared with less than 40\% of the CNS tumors in group II. These gliomas were diagnosed at a mean age of 26 years, whereas in the general population the diagnosis is usually between 45 and 60 years.\textsuperscript{28} Paraf and colleagues\textsuperscript{27} felt that the gliomas found in FAP families (group II) are most likely a sporadic event, or a random association. Hamilton and colleagues\textsuperscript{29} evaluated 14 families with Turcot’s syndrome, finding 10 families with germline mutations in the APC gene. Eleven of 14 (79\%) patients in these 10 families had medulloblastomas. Hence, the relative risk of developing a cerebellar medulloblastoma in patients with FAP is 92 times that of the general population.

**Gardner’s Syndrome**

The first description of extracolonic lesions associated with colonic polyposis was by Devic and Bussy\textsuperscript{30} in 1912. They described a woman
with multiple colonic polyps, mandibular osteomas, sebaceous cysts, and lipomas. In 1935, Cabot reported a case in which the polyps not only involved the colon, but the small bowel as well. They also noted epidermoid inclusion cysts, osteomas, and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Fitzgerald reported a case of colonic polyposis associated with osteomas, desmoid tumors, and numerous rudimentary and permanent teeth embedded in the alveolar processes. This association of FAP with extracolonic lesions was clearly defined in a series of articles characterizing a Utah family with FAP by Gardner. Gardner described the syndrome, later named after him, coined by Smith as: multiple colonic adenomatous polyps, osteomas of the skull and mandible, and multiple epidermal cysts. Later, Gardner expanded on the associations to include supernumerary and impacted teeth, dentigerous cysts, fibromatosis, and osteomatosi. As more families with FAP were described in the literature, additional extracolonic manifestations, such as CHRPE, were found and proposed to be part of Gardner’s syndrome. However, the finding that both FAP and Gardner’s syndrome patients had mutations led to Gardner’s syndrome being classified as a phenotypic variant (subtype) of FAP.

**Duodenal Polyps/Carcinoma**

The recognition of upper GI cancer (specifically periampullary cancer) as being a significant cause of mortality in patients with FAP is a testament to the value of prophylactic colectomy for reducing the risk of colorectal cancer. The earliest report of periampullary cancer in a patient with FAP was provided by Cabot in 1935. However, the association of gastroduodenal polyps in patients with FAP was noted in 1895 by Hauser.

As techniques and technology have developed in upper endoscopy, combined with longer follow-up, higher prevalence rates for duodenal adenomatous polyps in FAP patients have been found, ranging from 88% to 92%. The cumulative lifetime risk for the development of duodenal adenomatous polyps has been estimated at 90% to 98%, despite the reliance on forward-viewing endoscopes. The diagnostic advantage of a side-viewing endoscope was noted in a series by Spigelman and colleagues, in which an additional 47 of 102 (46%) patients had duodenal adenomas that were not seen with a forward-viewing endoscope. By using a side-viewing endoscope Groves and colleagues prospectively followed the upper GI tract in 114 patients with FAP, and found 111 of 114 (97%) patients had duodenal adenomas. Despite the absence of duodenal polyps, adenomatous changes can still be histolog-
ically present on biopsies of grossly normal appearing duodenal muco-
sa.\textsuperscript{44} This was noted in 8.7\% and 22\% of FAP patients in series reported
by Spigelman and colleagues\textsuperscript{38} and Ranzi and colleagues,\textsuperscript{45} respectively.
Church and colleagues\textsuperscript{39} found that 65 of 129 (50\%) patients with FAP
had adenomatous changes in a normal appearing ampulla of Vater. A
typical endoscopic view of adenomatous changes in the periampullary
region of a patient with FAP is shown in Fig 4.

With the identification of duodenal polyposis in patients with FAP,
Sellner\textsuperscript{46} showed that similar arguments for the adenoma-carcinoma
sequence made by Morson and colleagues were also valid for small
intestinal tumors: the mean and median age of diagnosis of the small
bowel adenomas is younger compared with the adenoma-with-carcinoma
and carcinoma; the spatial distribution of the adenomas, adenoma-with-
carcinoma, and carcinoma is similar; and the frequency of adenoma-with-
carcinoma found is similar to the frequency of carcinomas in the small
bowel. With the lifetime prevalence of duodenal adenomas associated
with FAP nearing 100\% and evidence for the small bowel dysplasia-
carcinoma sequence, it is important to know the risk of duodenal
carcinoma in patients with FAP. Multiple authors have examined national
institutional polyposis registries, finding the prevalence of duodenal
carcinoma or cumulative risk of developing duodenal carcinoma to range
from 1\% to 6\% with the mean/median age of diagnosis ranging from 47

\textbf{FIG 4.} Endoscopic view of periampullary adenomatous changes seen in a patient with familial
adenomatous polyposis (reproduced with permission from Iida M, Yao T, Itoh H, Watanabe H, Matsui
The relatively recent adoption of prophylactic colectomy and subsequent improved survival of FAP patients has resulted in duodenal carcinomas becoming more prevalent in these patients. However, the prevalence estimates are immature, as seen in Danish Polyposis Registry data in which only 4 of 98 (4%) patients with FAP and prophylactic colectomy have died. Belchetz and colleagues found colorectal cancer was the cause of death in 83% to 100% of FAP cases per decade from the 1930s to the 1960s. By the 1990s, colorectal cancer was the cause of death in 5 of 11 cases (45%) and duodenal cancer was the cause in 2 of 11 cases (18%). A retrospective review from the Cleveland Clinic Foundation Registry evaluated the cause of death in 132 patients with FAP from 1915 to 1987. In 16.7% of patients the etiology was not determined, periampullary carcinoma was the etiology in 8.2% (at a mean age of 49.1 years; range, 29-66 years), and colorectal cancer still was the predominant cause of death in 58.2% (at a mean age of 41.7 years; range, 25-75 years). Subset analysis of 36 patients having had a prophylactic colectomy revealed that 22.2% died from periampullary cancer (at a mean age of 49.4 years). In a slightly alternative approach to quantify the risk of duodenal cancer, Offerhaus and colleagues calculated the relative risk of developing duodenal and ampullary carcinoma in patients with FAP from the Johns Hopkins Registry compared with the Surveillance, Epidemiology, and End Results (SEER) data for the general population at 331 and 124, respectively. More recently, Bulow and colleagues performed a large prospective upper GI surveillance study of 368 FAP patients from 5 nations in which 4 patients developed duodenal carcinoma over the surveillance period. The cumulative incidence rate of duodenal cancer was calculated to be 4.5% at 57 years. Spigelman and colleagues proposed a duodenal classification to try to predict high risk groups for progression of duodenal adenomatous polyps to carcinoma, allowing evaluation and treatment resources to be focused appropriately (Table 1).

Recently, various investigators have prospectively examined upper endoscopy screening to stratify the risk for developing duodenal carcinoma using the Spigelman classification system. Groves and colleagues prospectively screened 114 patients with FAP from the St. Mark’s Polyposis Registry starting in 1988 with a side-viewing endoscope with complete data on 99 patients by 1998 to 1999. Patients were graded using the Spigelman classification, and 6 of 99 (6%) developed duodenal carcinoma. Separated by their initial duodenal polyp classification, duodenal carcinoma developed in 4 of 11 (36.4%) patients with Spigelman stage IV polyposis, 1 of 41 (2.4%) patients with Spigelman stage III polyposis, 1 of 44 (2.3%) patients with Spigelman stage II
polyposis, and no duodenal carcinoma was diagnosed in Spigelman stage I or 0 polyposis. Bjork and colleagues retrospectively reviewed 180 patients screened with upper endoscopy from 1982 to 1999 from the Swedish Polyposis Registry. Fourteen patients were identified with Spigelman stage IV duodenal adenomatosis. Five of 14 (36%) patients developed periampullary adenocarcinoma, 3 (60%) of whom had previously been diagnosed with stage IV adenomatosis. The time course for the development of periampullary adenocarcinoma from stage IV adenomatosis was 3.6 years (range, 0.5-9 years). The median age at the diagnosis of cancer was 50 years (range, 44-57 years). The last screening endoscopy was a median of 16 months (range, 4-31 months) before detection of cancer. Endoscopy performed for symptoms was performed 2.5 months (range, 1-10 months) before operation, and only 1 of 5 (20%) detected the cancer preoperatively. In 2004 Saurin and colleagues reported a higher cumulative risk of 50% at 70 years for the development of Spigelman stage IV duodenal polyposis after prospectively following 35 patients with FAP undergoing upper endoscopic (forward and side viewing) surveillance. It is evident that FAP patients with stage IV adenomatosis are at an increased risk (4.5%-36.4%) of developing periampullary adenocarcinoma. Unfortunately, investigators have not been able to correlate the site of germline mutation of the APC gene and developing duodenal cancer, which may help stratify high risk groups for duodenal carcinoma.

Endoscopy has been suboptimal in detecting periampullary adenocarcinoma, and both endoscopy and local excision have been inadequate in interrupting the progression from stage IV duodenal polyposis to duodenal/periampullary carcinoma. Bjork and colleagues report that only 2 of 7 (29%) patients with FAP and symptomatic duodenal carcinoma were diagnosed preoperatively despite endoscopic examination close to surgery. Cahen and colleagues retrospectively reviewed 23 patients be-

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**TABLE 1. Spigelman classification of duodenal polyps**

<table>
<thead>
<tr>
<th>Points†</th>
<th>Polyp number</th>
<th>Polyp size (mm)</th>
<th>Histological type</th>
<th>Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-4</td>
<td>1-4</td>
<td>Tubular</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>5-20</td>
<td>5-10</td>
<td>Tubulovillous</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>&gt;20</td>
<td>&gt;10</td>
<td>Villous</td>
<td>Severe</td>
</tr>
</tbody>
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†Stage 0, 0 points; stage I, 1-4 points; stage II, 5-6 points; stage III, 7-8 points; stage IV, 9-12 points.
between 1984 and 1994 diagnosed histologically with an ampullary adenoma. Twelve patients had local resection and 11 underwent pancreaticoduodenectomy. Seven of 23 (30%) patients were diagnosed with infiltrating adenocarcinoma postoperatively, not identified by endoscopic biopsy. Local resection was incomplete in 6 of 12 (50%) patients, 3 for adenomas and 3 for adenocarcinoma. This is supported by the experience of Galandiuk and colleagues, who examined 34 duodenal villous and tubulovillous adenomas in 32 patients (22% with polyposis syndromes). After resection in 22 (69%) patients, 47% were found to have malignancy. A 28% recurrence rate was noted after segmental resection, local excision, or endoscopic excision, but 0% for those undergoing pancreaticoduodenectomy (n = 5). Penna and colleagues reviewed 12 patients with FAP from 1978 to 1988 who underwent duodenotomy and duodenal polypectomy. At a mean postexcision time of 13.3 months (range, 5-36 months) after duodenotomy all 12 patients had endoscopic recurrence of their duodenal polyps. In a later review, Penna and colleagues retrospectively identified 16 patients with FAP and stage IV duodenal polyposis who had undergone surgical treatment. Six patients underwent duodenotomy and polyp resection with all having recurrence of duodenal polyposis 6 to 36 months following the surgical polypectomy. After a mean of 53 months (range, 36-72 months) all but 1 patient had stage III or IV duodenal polyposis. Ten patients were treated with pancreaticoduodenectomy, 3 for a preoperatively diagnosed duodenal carcinoma. Of the 6 patients without preoperative diagnosis of duodenal carcinoma who underwent pancreaticoduodenectomy, 2 (33.3%) were found to have invasive carcinoma. Of these 6 patients no gastric or jejunal polyps were found grossly or at random biopsy 6 to 95 months postoperatively. Alarcon and colleagues retrospectively reviewed prospectively collected data on patients with FAP having undergone surgical or endoscopic treatment for duodenal adenomas at the Cleveland Clinic Foundation. All 5 patients treated for an advanced adenoma failed local surgical excision, with 1 developing adenocarcinoma. Three patients undergoing pancreatic sparing duodenectomy at a mean follow-up of 45.7 months (range, 40-50 months) had no recurrence of advanced polyps (2 patients had a small tubular adenoma in the duodenal bulb). With similar experiences both Bulow and colleagues and Groves and colleagues recommend that FAP patients with stage IV duodenal polyposis should be given the opportunity to discuss prophylactic pancreaticoduodenectomy.

With aggressive endoscopic surveillance and treatment, Bleau and colleagues described a different experience in which they evaluated 37 patients with FAP and periampullary adenomas undergoing follow-up for
a mean of 4.8 years (range, 1-13.8 years). Eighteen of these 37 patients had surveillance biopsies alone and 6 of 18 (33%) had eventual enlargement of the adenomas, 11 were unchanged (61%), and 1 demonstrated improvement. The remaining 19 of 37 patients were treated with thermal ablation; 10 of 19 (53%) had resolution, 7 of 19 (37%) had marked improvement, 1 of 19 (5.3%) was unchanged on biopsy, and 1 of 19 (5.3%) patients had recurrence after 2 years of negative biopsies. Eleven of these 19 patients undergoing thermal ablation had aggressive treatment including yearly push enteroscopy, duodenoscopy, and ampullary biopsies. Positive biopsies for adenomas resulted in an endoscopic retrograde cholangiopancreatography (ERCP) being performed with a prophylactic sphincterotomy, and thermal ablation of the adenomas with re-examination every 2 to 6 months. Only 1 of 11 of this selective group had progression to high grade dysplasia.

Therefore, if surgical intervention is declined or not physiologically feasible, FAP patients with stage IV duodenal polyposis, or patients with dysplasia or large adenomas, should be followed every 3 months with screening upper endoscopy, random biopsies, and endoscopic ultrasound (EUS). Bleau and Gostouts’ experience suggests that adding thermal ablation may reduce the adenoma numbers and size. Screening endoscopy with random biopsies is recommended to start at age 30 years. For Spigelman stages 0 and I, the interval of upper endoscopy and random biopsies should be every 5 years. Patients with stage II duodenal polyposis are recommended to undergo endoscopy every 3 years with biopsy, whereas for stage III disease patients the interval should be every 1 to 2 years with the addition of EUS.

The role of endoscopy to treat stage IV duodenal polyposis may be limited, but has not been rigorously evaluated in less advanced stages, I through III. Endoscopic interventions have included snare polypectomy and, more recently, endoscopic mucosal resection. Either technique may incur a greater risk at the ampulla of Vater (eg, pancreatitis, which can be fatal). Additional techniques include thermal ablation either via electrocautery, ND:YAG laser, or argon beam. Photodynamic therapy has been used, but there has been a tradeoff between limited superficial polyp destruction and unacceptable photosensitivity depending on the chemical sensitizer used.

Recent trials of cyclo-oxygenase inhibitors have shown a role in therapy. Nugent and colleagues enrolled 24 patients with FAP at least 5 years after colectomy and Spigelman stage III or IV duodenal polyposis. Twelve patients were randomized to 12 months of sulindac (200 mg twice per day) therapy that was blinded to the evaluating physicians. After a
6-month period there was only a trend toward polyp regression \((P = 0.12)\) assessed by taped endoscopy. These data were later reviewed by Debinski and colleagues\(^64\) who found that in polyps smaller than 2 mm regression occurred in 9 of 11 (82\%) patients receiving sulindac therapy, whereas regression was noted in 4 of 12 (33\%) patients in the placebo group \((P = 0.02)\). New polyps were observed in 2 (18\%) patients in the sulindac arm, whereas 5 (42\%) patients in the placebo group had new polyps. There was no difference for polyps larger than 3 mm. In a similar study, Richard and colleagues\(^65\) followed 8 patients with FAP who underwent removal of a 1 cm or larger periampullary polyp. All patients had retained small duodenal polyps. Sulindac therapy consisted of 150 mg twice per day for a mean follow-up of 17.5 months (range, 10-24 months). Three patients had the sulindac therapy discontinued due to side effects (eg, abdominal cramps and upper GI bleeding). No regression of small periampullary polyps was described. One patient developed an invasive periampullary carcinoma while receiving sulindac and 3 patients developed large recurrent periampullary polyps.\(^65\) A recent randomized, double-blind, placebo-controlled trial published in 2002 by Phillips and colleagues\(^66\) evaluated celecoxib, a selective COX-2 inhibitor, and duodenal polyposis in patients with FAP over 6 months. Comparing 32 patients receiving 400 mg twice per day versus placebo, there was a significant reduction in duodenal polyps \((P = 0.033)\). In addition, patients \((n = 10)\) with significant disease (at least 5\% area covered by duodenal adenomas) receiving 400 mg twice per day of celecoxib compared to placebo \((n = 9)\) had a 31\% reduction in the involved duodenal area \((P = 0.049)\).\(^66\) Chemoprevention using celecoxib 800 mg per day has been recommended for Spigelman stage IV and possibly stage III duodenal polyps.\(^42\)

**Gastric and Distal Small Bowel Polyps**

The increased appreciation of gastric polyps in patients with FAP was similar to the situation where duodenal adenomas were increasingly studied as the lifespan of patients increased and the endoscopy technology advanced. The estimates of prevalence range from 28\% to 68\%.\(^39,44,67-72\) Typically the gastric polyp distribution is described as multiple throughout the fundus and body of the stomach (Fig 5) and histologically they are hyperplastic polyps. As the antrum and prepyloric areas are approached the number of polyps significantly decreases and the histology changes to predominantly adenomatous (Fig 6).\(^39,44,67,68,70\) These fundic gland hyperplastic polyps are defined by disordered architecture with cystic dilation of oxyntic glands and glandular budding.\(^39,68,73\)

Spigelman and colleagues\(^38\) prospectively evaluated 102 patients with
FAP for upper intestinal polyps with upper endoscopy (the majority with a side-viewing endoscope). The gastric fundus polyps were on average smaller (mean diameter, 4.7 mm) and more numerous (1-30), whereas the antral polyps were less numerous (range, 1-15) and slightly larger (mean diameter, 6.4 mm). The duodenal polyps ranged in numbers from 1 to 50 and the size was on average larger with a mean diameter of 9.4 mm.\textsuperscript{38} They also noted the distribution of adenomas in the stomach was limited to the antrum. The duodenal adenomas were predominately periampullary. They suggested that the adenoma formation was related to being exposed to bile, and were consistent with experimental and epidemiological evidence that have linked bile to intestinal cancer growth.\textsuperscript{38} Two years later, Spigelman and colleagues\textsuperscript{74} related the development of gastric adenomas in patients with FAP to duodenal gastric reflux. They identified

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5}
\caption{Endoscopic views of gastric fundus polyps from patient with familial adenomatous polyposis (reproduced with permission from Schulmann K, Reiser M, Schmiegel W. Colonic cancer and polyps. Best Pract Res Clin Gastroenterol 2002;16:91-114). (Color version of figure is available online.)}
\end{figure}
FIG 6. (A) Gross photo of duodenal adenocarcinoma in patient with familial adenomatous polyposis (FAP); (B) Distribution of gastric fundic gland polyps (white) and duodenal or gastric adenomas (black) in 102 FAP patients, with each dot representing 1 patient (reproduced with permission from Jarvinen H, Nyberg M, Peltokallio P. Upper gastrointestinal tract polyps in familial adenomatosis coli. Gut 1983;24:333-9).
7 and 9 patients with FAP with and without gastric adenomas, respectively. All patients underwent scintigraphic duodenogastric reflux evaluation. One patient with adenomas was excluded due to a vasovagal response during the scintigraphy. The patients with adenomas had a greater degree of duodenogastric reflux, rated as a median of 6 (range, 4-6) on a 1-to-6 scale, whereas the patients without gastric adenomas had a median severity of 3 (range, 0-3; \( P = 0.017 \)). Prolonged reflux was noted in all 6 patients with gastric adenomas, whereas only 4 of 9 (44.4%) patients without gastric adenomas had prolonged reflux.

In 1962, Murphy and colleagues\(^7\) were the first to describe gastric carcinoma arising from an antral adenomatous polyp in a patient with FAP. Since this initial observation there have been limited reported cases of gastric cancer in FAP patients. Jagelman and colleagues\(^4\) published an extensive review in 1988 of 10 registries including 1255 patients with FAP. Invasive adenocarcinoma of the stomach was described in 7 (0.6%) cases. In 1988, Goodman and colleagues\(^7\) reported 2 cases of gastric adenocarcinoma associated with fundic gland polyps. The locations of these gastric cancers included 1 in the antrum and the second in the upper body of the stomach.\(^7\) Nugent and colleagues\(^5\) reviewed 222 patients with FAP who underwent a total colectomy from 1948 to 1990 at St. Mark’s Hospital. Thirty-two extracolonic cancers were reported in 31 patients, and only 1 of these 222 (0.45%) patients had developed stomach cancer.\(^5\) Offerhaus and colleagues\(^5\) examined the Johns Hopkins Registry and compared the rate of gastric cancer in patients with FAP to the general population. They found no significant increased risk. However, in 1993 Iwama and colleagues\(^7\) reported 27 of 1050 Japanese FAP patients (2.6%) with gastric carcinoma, with a standardized mortality ratio (observed/expected) for gastric cancer of 3.43 compared with the normal population. Therefore, the higher prevalence of gastric cancer in FAP patients is not explained by the higher prevalence of gastric cancer in Japan’s general population. Overall, the incidence of gastric carcinoma in FAP patients is such that routine screening or prophylactic surgery is not required.

Our knowledge of the association between jejunal and ileal polyps, cancer, and FAP is less extensive. Not only are there few symptoms secondary to small bowel lesions, but the means for evaluating the small bowel distal to the ligament of Treitz are limited. However, in 1977 Ohsate and colleagues\(^7\) published a series of 7 consecutive patients with FAP undergoing colectomies who had intraoperative enteroscopy performed, and 6 of 7 (85.7%) patients had small intestinal adenomas. Four of 7 (57.1%) had proximal jejunal adenomas, and 1 (14.3%) had an ileal
adenoma. Ross and Mara\textsuperscript{79} reported 2 cases of small bowel carcinoma in FAP patients. One carcinoma was located in the jejunum and the other was in the ileum. With such a low number of jejunal and ileal carcinomas in patients with FAP, it appears that routine screening is unwarranted, although with new technology such as capsule endoscopy, there may be a role for routine screening.

**Desmoid Tumors**

McFarlane\textsuperscript{80} published the original description of a desmoid tumor in 1832. In 1923, Nichols\textsuperscript{81} noted the association between desmoid tumors and FAP. Gardner\textsuperscript{34} described extracolonic findings in patients with FAP in 1951 that included multiple colorectal polyps, fibromas, osteomas, sebaceous cysts, odontomas, supernumerary teeth, and desmoid tumors.

Desmoids are classified as extra-abdominal, abdominal wall, and intra-abdominal. They are locally invasive without metastatic potential and therefore are usually referred to as benign.\textsuperscript{82-85} However, they may be the cause of significant morbidity and mortality. Desmoid tumors are fibrous masses that can arise from fibroblasts throughout the body.\textsuperscript{86} Grossly, the tumors are rubbery and dense.\textsuperscript{87} The cut surface may be white to pinkish in color with interlacing white fibrinous bundles\textsuperscript{88} (Fig 7). Their margins are ill-defined and are usually found invading local structures with an associated minimal reactive inflammation. Histologically, there is an abundance of collagen with a moderate amount of spindle cells (well-differentiated fibroblasts). Although mitotic figures are rare, frequent myofibroblasts are present, suggestive of an abnormal healing response to tissue injury.\textsuperscript{89}

Desmoid tumors are often found incidentally, but it is not uncommon for them to cause obstruction symptoms involving the small bowel or ureters.\textsuperscript{90-92} Jones and colleagues\textsuperscript{93} reported that 16 of 26 (62\%) patients in the Cleveland Clinic Familial Polyposis Registry presenting with symptoms had pain associated with the desmoid mass. Clark and Phillips\textsuperscript{86} reported that one third of patients with desmoids had pain. Occlusion of mesenteric blood vessels can lead to mesenteric ischemia, and fistulas and sepsis may also be caused by desmoids.\textsuperscript{94-96} Compression of the larger veins can predispose to deep venous thrombosis.\textsuperscript{97} Not only can peripheral nerve compression cause pain, but motor and sensory deficits may also be present. More unusual presentations can include GI bleeding.\textsuperscript{98}

Radiographically, computed tomography (CT) reveals a mass of soft tissue density with an infiltrative appearance and occasional streaks or areas of fat. Before the development of a well-defined mass, they may be
seen as a subtle tissue infiltration of mesenteric fat very similar to postoperative changes. Progression leads to a “whorl-like” appearance of the soft tissue, containing localized areas of mesenteric fat, sometimes referred to as mesenteric fibrosis (Fig 8). Eventually, a defined mass develops characteristic of a desmoid tumor.99

The prevalence of desmoid tumors in FAP has been estimated from 4% to 38%91-93,100-106 (Table 2). Gurbuz and colleagues103 reviewed the Johns Hopkins Polyposis Registry and calculated the absolute risk of developing a desmoid tumor in patients with FAP to be 2.56 per 1000 person-years, with a relative risk of 852 compared to the general population. Heiskanen and Jarvinen106 estimated the cumulative probability of developing a desmoid tumor in FAP by the age of 60 years to be 21%.

Desmoid tumors can be highly morbid and are the cause of death in 10% to 23% of FAP patients.54,93,103 When limiting the evaluation to the subset of patients with FAP having a prophylactic colectomy or protocolectomy, 11 of 36 (30.6%) died from desmoid tumor complications.54
From life-table analysis, Gurbuz and colleagues\textsuperscript{103} calculated the 20-year survival rate from desmoids to be 79%.

The etiology of desmoid tumors is unknown. Retrospective reviews suggest that precipitating factors include trauma, hormonal influences (gender, pregnancy, and oral contraceptives), and a genetic predisposition with specific \textit{APC} mutations.\textsuperscript{86,91-93,101-106} A high proportion (68\% to 89\%) of desmoid tumors develop after colonic resection in FAP (Table 2). Lynch and Fitzgibbons\textsuperscript{107} highlighted the role that surgical trauma plays in the etiology of desmoid tumors with the report of a 25-year old man with FAP who underwent laparoscopic confirmation of total desmoid involution in response to chemotherapy. Nineteen months following a “second look” laparoscopic procedure, the patient became symptomatic with a small bowel obstruction due to a recurrent desmoid tumor, and the desmoid tumor was noted to involve all 3 trocar sites.

Hormonal factors (including pregnancy due to the heightened estrogenic state) appear to predispose to desmoid tumors. From the series listed in Table 2 (except for Kadmon and colleagues\textsuperscript{105}), 59\% to 66\% of
the female patients with FAP were pregnant before the development of a desmoid tumor.\textsuperscript{92,102,103,106} Observational studies and case reports have suggested that oral contraceptives appear to predispose to desmoid development and there has been desmoid regression after menopause.\textsuperscript{93,94,108-111} Desmoid tumors have been shown to express estrogen receptor in 33\% to 75\% of patients\textsuperscript{112,113} and antiestrogen binding sites have been reported in up to 79\% of desmoid tumors.\textsuperscript{113}

The natural history of desmoid tumors is of continued growth, frequently leading to local morbidity and mortality from obstruction or invasive symptoms. However, there are documented cases of spontaneous regression. Tsukada and colleagues\textsuperscript{114} evaluated the treatment regimens in patients with FAP and desmoid tumors and found that 2 of 12 (17\%) in the control arm receiving no therapy had remission (1 complete and 1 partial). Penna and colleagues\textsuperscript{91} reported complete regression of desmoids in 2 of 10 (20\%) FAP patients having no therapy.

Despite the spontaneous regression noted for some desmoid tumors, the majority do not regress. Three main modalities of therapy have been used: surgical resection, pharmacological treatment, and radiation therapy. Areas targeted by pharmacological intervention have included hormonal modulation (antiestrogens and megestrol), nonsteroidal anti-inflammatory

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**TABLE 2. Literature review of desmoid tumors in familial adenomatous polyposis registries**

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients with desmoids (% of FAP patients)</th>
<th>Male: female</th>
<th>Age of diagnosis mean/median (yr)</th>
<th>Years after surgery mean/median</th>
<th>Prior surgery (%)</th>
<th>Family history (%)</th>
<th>Pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al\textsuperscript{93}</td>
<td>29 (8.9)</td>
<td>7:22</td>
<td>29.8</td>
<td>2</td>
<td>86</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lotfi et al\textsuperscript{102}</td>
<td>24 (13)</td>
<td>7:17</td>
<td></td>
<td></td>
<td>83</td>
<td>12.5</td>
<td>65</td>
</tr>
<tr>
<td>Penna, 1993</td>
<td>29 (12)</td>
<td>16:13</td>
<td>32</td>
<td>5.8</td>
<td>69</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gurbuz et al\textsuperscript{103}</td>
<td>83 (10)</td>
<td>36:47</td>
<td>31</td>
<td>9</td>
<td>68</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>Rodriguez-Bigas et al\textsuperscript{104}</td>
<td>24 (38)</td>
<td>15:9</td>
<td>28.5</td>
<td>3.1</td>
<td>83</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kadmon et al\textsuperscript{105}</td>
<td>29 (17)</td>
<td>10:19</td>
<td>34.5</td>
<td>NA</td>
<td>76</td>
<td>10.3</td>
<td>10</td>
</tr>
<tr>
<td>Heiskanen and Jarvinen\textsuperscript{106}</td>
<td>29 (14)</td>
<td>12:17</td>
<td>28</td>
<td>NA</td>
<td>69</td>
<td>13.7</td>
<td>59</td>
</tr>
<tr>
<td>Soravia et al\textsuperscript{92}</td>
<td>97 (12.4)</td>
<td>38:59</td>
<td>F:29.1 M:32.1</td>
<td>4.6</td>
<td>80</td>
<td>42.2</td>
<td>60</td>
</tr>
<tr>
<td>Klemmer et al\textsuperscript{101}</td>
<td>30 (6)</td>
<td>10:20</td>
<td>F:27.1 M:33.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bulow\textsuperscript{6}</td>
<td>9 (4)</td>
<td>1:8</td>
<td>37</td>
<td>NA</td>
<td>89</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
agents (NSAIDs, including indomethacin, sulindac, and colchicine), cAMP modulators (theophylline, chlorthiazide, testolactone, and ascorbic acid), cytotoxic chemotherapy (doxorubicin, dacarbazine, actinomycin D, vinblastine, and methotrexate), and other miscellaneous agents (interferon gamma, interleukin 2, warfarin, and imatinib mesylate). Recommen-
dations for treatment using these modalities have often have relied on anecdotal reports and small, poorly controlled studies.

The specific mechanism of action by which NSAIDs affect desmoid tumors has not been determined. They do inhibit cyclo-oxygenase enzyme resulting in the reduction of prostaglandin synthesis. There has been some evidence to suggest that by reducing the prostaglandin level, the immunosuppressive effect is limited, allowing improved immune surveillance and reduction of desmoid growth. Prostaglandins have also been demonstrated to induce cAMP synthesis and inhibit the production of ornithine decarboxylase, an enzyme associated with tumor proliferation.\textsuperscript{114,116,117} Recommendations for treatment using these modalities have often have relied on anecdotal reports and small, poorly controlled studies.

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Some of the studies supporting the use of NSAID therapy in desmoid tumors associated with FAP are listed in Table 3.\textsuperscript{86} NSAID therapy is not innocuous, however; Tsukada and colleagues\textsuperscript{114} reported side effects in 4 of 14 (29%) patients treated with sulindac including GI bleeding (2 patients), gastric ulcer (1 patient), and nausea and vomiting (1 patient). Tsudada and colleagues\textsuperscript{114} also noted a delayed response to sulindac. Of 8 patients who had tumor regression while receiving sulindac, 3 were

\begin{table}
\begin{center}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Reference & No. of patients & Drug & Complete regression & Partial regression & Static & Progression \\
\hline
Klein\textsuperscript{†} & 2 & Indomethacin & 0 & 0 & 0 & 2 \\
Tsukada et al\textsuperscript{114} & 14 & Sulindac (300-450 mg/day) & 1 & 7 & 4 & 2 \\
Tsukada et al\textsuperscript{114} & 4 & Indomethacin (75-150 mg/day) & 1 & 0 & 1 & 2 \\
Waddell and Kirsch\textsuperscript{121} & 4 & Sulindac (300-400 mg/day) & 0 & 2 & 1 & 1 \\
Jones et al\textsuperscript{93} & 3 & Indomethacin & 0 & 0 & 0 & 3 \\
Jones et al\textsuperscript{93} & 6 & Sulindac (150-400 mg)** & 0 & 4 & 2 & 0 \\
\hline
\end{tabular}
\end{center}
\caption{Nonsteroidal anti-inflammatory drug use in treatment of intra-abdominal desmoids associated with FAP*}
\begin{flushright}
**Two patients also received tamoxifen (20 mg day).
\end{flushright}
\end{table}
Hormonal agents (such as tamoxifen and toremifene) are thought to act through 2 different mechanisms: estrogen receptor dependent and independent. By blocking estrogen binding on target tissues, the activation of certain genes (including ornithine decarboxylase) that influence growth and proliferation are restricted. The second method is independent of the estrogen receptors, by promoting the secretion of transforming growth factor-β in fibroblasts, which in turn inhibits growth of abnormal fibroblasts present in desmoid tumors. Several series evaluating hormonal modulation in desmoid tumors are summarized in Table 4. The response rate (complete and partial regression) varies between 25% and 100% for these limited series and, like the NSAIDs, are a viable first line therapeutic alternative to interventions such as surgical and cytotoxic chemotherapy.

Progestogens have had some success. Tsukada and colleagues treated 2 patients with progesterone and both had tumor regression and a decrease in pain. Bauernhofer and colleagues reported regression and

### TABLE 4. Treatment with antiestrogens of intra-abdominal desmoids in patients with familial adenomatous polyposis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Prior therapy</th>
<th>No. of patients</th>
<th>Drug</th>
<th>Complete regression</th>
<th>Partial regression</th>
<th>Static</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brooks†</td>
<td>9F, 3M</td>
<td>Toremifene (200-600 mg)</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Tsukada et al¹¹⁴</td>
<td>3F</td>
<td>Tamoxifen (10-40 mg/day)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tonelli et al**</td>
<td>Tamoxifen, sulindac, or nothing</td>
<td>Raloxifene (120 mg day)</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Soravia et al⁹²</td>
<td>4</td>
<td>Toremifene</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male.

pain resolution from an intra-abdominal desmoid tumor in a 26-year old woman with FAP for 17 months while being treated with goserelin acetate and tamoxifen therapy. There has been some limited success such as reported by Waddell and colleagues\textsuperscript{121} using testolactone, considered a cAMP modulator. They reported that 3 of 4 (75\%) patients with FAP had complete or major regression of their intra-abdominal desmoid tumor after testolactone therapy.

Cytotoxic chemotherapy has been reported in a very small number of patients with FAP complicated by desmoid tumors. This usually is limited to patients after a trial of NSAID therapy, typically sulindac combined with an antiestrogen such as tamoxifen or toremifene. Table 5 summarizes a few more recent and larger series of cytotoxic chemotherapy used for controlling desmoid tumors.\textsuperscript{122-125} Overall, there is efficacy for the regimens using doxorubicin and dacarbazine. However, their use is usually limited to patients with symptomatic desmoids who have failed a trial of NSAID and hormonal modulation due to their well known side effects.

Imatinib mesylate, a selective tyrosine kinase inhibitor, has been a relatively new treatment for chronic myelogenous leukemia and GI stromal tumors. Mace and colleagues\textsuperscript{126} treated 2 patients with recurrent desmoid tumors, but not associated with FAP, with Imatinib 400 mg twice per day. There was a 50\% reduction in size defined radiographically in 1 patient and the second patient had a stabilization in desmoid size and a concomitant improvement in symptoms. This very preliminary result, combined with our lack of information about the long-term toxicity and response rates should prompt further clinical trials.

Recommendation of surgical therapy for desmoid tumors has been limited to symptomatic intestinal or ureteral obstruction, due to the high mortality and morbidity rates and limited effectiveness of the surgical approach.\textsuperscript{93} Berk and colleagues\textsuperscript{127} found that among 13 surgically treated patients with FAP and intra-abdominal desmoid tumors, 7 (54\%) died of desmoid-related complications. The recurrence rate after surgical excision was 85\%. Similarly, Lofti and colleagues\textsuperscript{102} completed a retrospective review of 24 patients with mesenteric desmoid tumors and FAP, 21 of whom underwent surgical intervention. Eight were considered resectable, and 5 were able to have complete removal of the lesion. Three of the 5 (60\%) resected lesions recurred, and 1 patient developed short bowel syndrome. Recurrent lesions developed in 2 to 4 years, with the recurrences being unresectable. Only 1 patient remained free of recurrence and symptoms after surgical treatment. Interestingly, 2 of the resectable lesions that were not biopsied or resected did not clinically
of the 13 patients with unresectable lesions, 6 had debulking interventions, with 5 (83%) having late complications due to further growth of the tumor. Five of 6 (83%) patients who only had biopsies performed of the unresectable lesion had no complications or clinical growth. Soravia and colleagues\textsuperscript{92} reported surgical management of 47 patients with FAP and intra-abdominal desmoid tumors, and 39 (83%) patients experienced recurrences. Rodriguez-Bigas and colleagues\textsuperscript{104} reported that 7 of 9 (78%) patients with FAP who underwent curative resection of a desmoid tumor experienced a recurrence. Zissiadis and colleagues\textsuperscript{128} reported 3 cases of patients with FAP and resected abdominal desmoid tumors; all 3 patients experienced a recurrence and 1 (33%) patient died due to direct complications of the desmoid tumor. In 1979, Harvey and colleagues\textsuperscript{129} recommended against initial wide local excision of mesenteric desmoids associated with FAP, based on their experience with 3 patients who underwent wide local excision as an initial treatment and who died from ensuing complications. Heiskanen and Jarvinen\textsuperscript{106} reviewed 17 patients in the Finnish Polyposis Registry with mesenteric desmoid tumors. Sixteen patients underwent surgical excision, with 2 of 9 (22%) having recurrence after excision of

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Failed prior treatment</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch et al\textsuperscript{124}</td>
<td>2</td>
<td>Sulindac, tamoxifen (2), partial resection, radiotherapy, vincristine, cyclophosphamide, azathioprine, and prednisolone</td>
<td>Doxorubicin and dacarbazine (5-7 cycles), then carboplatin and dacarbazine</td>
</tr>
<tr>
<td>Patel et al\textsuperscript{123}</td>
<td>4</td>
<td>Partial resection (3), complete resection (1)</td>
<td>Doxorubicin/dacarbazine (8-10 cycles)/cyclophosphamide (1 patient), then ifosfamide (1 patient)</td>
</tr>
<tr>
<td>Poritz et al\textsuperscript{125}</td>
<td>8</td>
<td>Tamoxifen (8), toremifine (2), clinoril (8), surgery (2)</td>
<td>Doxorubicin (8), dacarbazine (8), etoposide (1), carboplatin (6)</td>
</tr>
<tr>
<td>Tsukada et al\textsuperscript{122}</td>
<td>8</td>
<td></td>
<td>Doxorubicin, cyclophosphamide, vincristine, DTIC, actinomycin D, 5-FU, 10-diazaaminopterin</td>
</tr>
</tbody>
</table>

DTIC, dacarbazine; 5-FU, 5 flourouracil

the desmoid tumor. An additional 2 (22%) patients had significant complications. One of the 7 (14%) patients not undergoing excisional therapy eventually required surgical intervention for a small bowel obstruction. In the remaining 6 (86%) patients not undergoing resection, the desmoid tumor remained stable.\textsuperscript{106} Very rarely has small bowel transplantation been employed to allow complete surgical removal of a desmoid tumor.\textsuperscript{130} Not only do these studies support surgical trauma as a precipitating factor for desmoid tumors, but they suggest that surgical intervention should be avoided in asymptomatic patients and should only be used as a last alternative.

The incidence of desmoid tumor development following ileal pouch-anal anastomosis (IPAA) has been reported at 5.6% to 6.2%,\textsuperscript{131-133} which is not significantly different than following ileorectal anastomosis (IRA), at 11%.\textsuperscript{131} However, when there is a family history of desmoid tumors in a patient with FAP, a proctocolectomy with IPAA should be considered as the initial operation of choice.

Radiotherapy is primarily used as an adjuvant for surgical intervention for abdominal wall or extra-abdominal desmoid tumors. The recurrence rate can be reduced from 40% to 70% to approximately 20% to 40% with

\begin{table}[h]
\centering
\begin{tabular}{lccc}
\hline
\textbf{Adverse effects} & \textbf{Regression} & \\
 & \textbf{Complete} & \textbf{Partial} & \textbf{None} \\
\hline
Cardiotoxicity (1 patient) & 2 & 0 & 0 \\
Probable cardiotoxicity (1 patient, who died) & 2 & 2 & 0 \\
Fatigue, neuropathy, abdominal pain, tumor necrosis, nausea, vomiting, mucositis, febrile neutropenia, palpitations, thrombocytopenia, diarrhea, headaches, anemia, pelvic abscess & 2 & 5 & 1 \\
Nausea, vomiting, diarrhea, septicemia, hepatitis, bone marrow depression, renal failure, encephalopathy & 2 & 1 & 0 \\
\hline
\end{tabular}
\end{table}
radiotherapy. Rarely is radiotherapy used for mesenteric desmoid tumors due to long term enteric complications. An interesting case report by Soule and Scanlon reported a desmoid not associated with FAP treated with multiple surgical excisions combined with radiation. Approximately 10 years after the first excision there was histologic confirmation of undifferentiated fibrosarcoma.

**Congenital Hypertrophy of the Retinal Pigment Epithelium**

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a flat, pigmented lesion with sharply defined borders, which is usually oval in shape (Fig 9). CHRPE lesions can be pigmented, depigmented, or heterogeneous, and of variable size. Histologically, these lesions are more characteristic of hamartomas than congenital hypertrophy. The morphology of these lesions in FAP is oval and heterogeneous. Kasner and colleagues described 3 types of CHRPE lesions: a single layer of hypertrophic cells, a localized proliferation of retinal pigment epithelium...
cells interposed between the retinal pigment epithelium basement membrane and the inner collagenous layer of Bruch’s membrane, and a multiple layer mound of hyperplastic cells.

Cabot\textsuperscript{31} first reported abnormal findings on retinal examination of patients with FAP in 1935. Blair and Trempe\textsuperscript{36} described the association of CHRPE in 3 FAP patients and the potential to identify affected patients by screening for CHRPE. These lesions are usually an incidental finding on ocular examination and are asymptomatic. However, there have been cases reported with involvement of the macula, resulting in visual and color defects.\textsuperscript{139,140} Solitary lesions can occasionally be mistaken for choroid melanoma, chorioretinal scar from toxoplasma, or secondary hyperplasia.\textsuperscript{139,141,142} Several publications have calculated the sensitivity and specificity of CHRPE to predict the association of FAP. These have varied in their positive criteria, from using greater than 4 CHRPE lesions, large or small CHRPE lesions, or just large lesions as positive criteria. The sensitivity ranged from 0.78 to 1.0 and the specificity differed from 0.581 to 0.925.\textsuperscript{137,143-152} CHRPE lesions are considered congenital and have been diagnosed as early as after a 28-week gestation.\textsuperscript{153} The majority of reports since 1984 estimated that approximately two thirds of families affected by FAP manifest CHRPE. This was consistent with Tiret and colleagues,\textsuperscript{154} who reported that 17 of 26 (65\%) FAP families had CHRPE. They noted that either all family members demonstrated findings consistent with CHRPE or none of the family members were found to have fundic changes consistent with CHRPE. Similarly, Olschwang and colleagues\textsuperscript{155} defined patients having the extracolonic manifestation of CHRPE when there were more than 3 small lesions or more than 1 large lesion on fundic examination. With these criteria 31 of the 33 FAP families either had all or none of the family members affected by CHRPE. The remaining 2 families each had 1 family member meeting the defined criteria for CHRPE. The proportion of families demonstrating CHRPE was 73\%.

**Thyroid Carcinoma**

Crail\textsuperscript{25} was the first to report thyroid cancer in a patient with FAP in 1949. In 1968, Camiel and colleagues\textsuperscript{156} established the association of thyroid cancer as an extracolonic manifestation of FAP, reporting 2 sisters with FAP and papillary thyroid carcinoma. The prevalence of thyroid carcinoma in patients with FAP has been estimated to be 0.7\% to 2\%.\textsuperscript{77,157-160} This likely underestimates the prevalence of thyroid carcinoma associated with FAP, since the diagnosis is made more frequently with ultrasound and on autopsy studies than with physical examina-
Hizawa and colleagues reviewed the records of 49 Japanese patients with FAP and found 1 of 43 (2.3%) patients diagnosed with thyroid neoplasms by physical examination, 2 of 8 (25%) by ultrasonography, and 4 of 9 (44%) by postmortem examination. The association of FAP increases a woman’s risk of thyroid cancer 25 to 160 times.

Cetta and colleagues reviewed 112 patients with FAP and thyroid carcinomas, finding the average age at diagnosis was 27.6 years, the female:male ratio was 17 to 1, and the histology was papillary in more than 95% of cases. Similarly, Harach reported a review of 102 cases with a female:male predisposition of 7.5:1, and the age of diagnosis was usually less than 30 years. Harach noted that only 3 of 102 (3%) patients died of thyroid cancer, 5 (5%) had lymph node metastases, and 2 (2%) had distant metastases. Giardiello and colleagues calculated the relative risk of developing thyroid cancer from the Johns Hopkins Registry of patients with FAP to be 7.6% and Houlston and Stratton calculated the absolute risk of developing thyroid cancer in patients with a history of FAP to be 2%.

Bulow and Bulow reported only 1 death due to thyroid carcinoma in the Leeds Castle Polyposis Group database for a mortality rate of 0.03%, a 10-year survival rate of 84%, and an incidence of only 1.2%. Therefore, they do not recommend regular thyroid screening beyond physical examination in FAP patients due to its unlikely effect on mortality. However, Cetta and colleagues recommend screening for thyroid malignancies starting at age 15 years for patients or kindred who are found to have CHRPE and/or an APC mutation at the 5’ end of exon 15 due to the association between these and thyroid cancer.

Bone and Dental Manifestations

Osteomas were first described with FAP by Gardner in 1951, and after a series of publications by Gardner and colleagues this became 1 of the clinical manifestations defining Gardner’s syndrome. Not only are the triad of osteomatosis, soft tissue tumors, and colonic polyposis part of Gardner’s syndrome, but the dental abnormalities of impacted and supernumerary teeth were described by both Gardner and Fader and colleagues in 1962 (Fig 10). Dental abnormalities associated with FAP include compound odontomas and abnormal root formation with a prevalence from 17% to 76%. These are benign lesions, but may cause problems due to growth and mass effect.

There is a high incidence of facial skeleton involvement with osteomas in patients with FAP, especially the mandible. The prevalence ranges from 76% to 93% when specialized orthopantomography is used for
evaluation, compared with a prevalence of 4.3% to 15% in patients without FAP.\textsuperscript{68,170,174-177} Like the development of colonic polyps, there appears to be an age dependence for the development of osteomata.\textsuperscript{178}

### Skin Manifestations

Epidermoid cysts were part of the initial characterization of Gardner’s syndrome.\textsuperscript{34} These are benign, located in the subcutaneous tissue, and are usually found on the limbs, face, and scalp in patients with FAP, compared with a predominantly back distribution in patients not affected by FAP\textsuperscript{6,179,180} (Fig 11). The prevalence of epidermoid cysts in patients with FAP reported by Leppard and Bussey\textsuperscript{179} in 1975 was 53% (39 of 74 patients), diagnosed at a mean age of 13 years. In this series, they noted the number of cysts to range from 1 to 20, with an average of 4, but 13

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig10}
\caption{Radiographic views of supernumerary teeth, including areas of osteosclerosis (reproduced with permission from Jones EL, Cornell WP. Gardner’s syndrome: review of the literature and report on a family. Arch Surg 1966;92:287-300).}
\end{figure}
patients (33%) had solitary cysts. The physical findings of sebaceous cysts during childhood should prompt one to screen for other manifestations of FAP.\textsuperscript{179}

**Hepatobiliary Tumors**

Case reports have described patients with FAP and hepatoblastoma\textsuperscript{181-187} or hepatocellular carcinoma.\textsuperscript{188} Kingston and colleagues\textsuperscript{189} are credited for first describing a hepatoblastoma in a patient with FAP. Hughes and
Michels\textsuperscript{186} reviewed 470 children of parents with FAP and found 2 (0.42\%) diagnosed with hepatoblastoma. Giardiello and colleagues\textsuperscript{190} calculated the relative risk in the first 4 years of life for children (at risk or affected) of a parent with FAP to be 847. Giardiello and colleagues\textsuperscript{190} also noted in their series that \(\alpha\)-fetoprotein levels are elevated in patients with FAP and hepatoblastoma in approximately two thirds of cases. Therefore, one can consider annual \(\alpha\)-fetoprotein measurements in at-risk children from ages 0 to 6 years in addition to an annual examination and possible ultrasound.\textsuperscript{191} There have been at least 10 cases of hepatocellular carcinoma associated with FAP published in the literature.\textsuperscript{188,192-198}

Burney and Assor\textsuperscript{199} reported 1 of the earlier associations of carcinoma in situ of the gallbladder with FAP in 1976. Lees and Hermann\textsuperscript{201} reported the first association of bile duct adenocarcinoma and FAP in 1981. Since this initial report, there have been a few additional reports of bile duct tumors in patients with FAP.\textsuperscript{200,202-204}

**Adrenal Tumors**

The first case report of an adrenal tumor associated with FAP was made by Devic and Bussy\textsuperscript{30} in 1912. Marchesa and colleagues\textsuperscript{205} reported a series of 738 patients with FAP in which 15 (2\%) had adrenal tumors diagnosed. Of the 738 patients, 162 underwent abdominal CT scanning, for a prevalence of 7.4\%. This compares to 0.6\% to 3.4\% in the general population.\textsuperscript{205} At least 16 cases of nonfunctional adrenal tumors associated with FAP have been reported in the literature.\textsuperscript{205-208} Functional adenomas diagnosed in patients with FAP are less common and have included pheochromocytoma, aldosteroneoma, and adrenocortical carcinoma.\textsuperscript{205,206,209-212}

**Genetics of FAP**

**APC Gene**

The first clue to the chromosomal locus of the \(APC\) gene came in 1986 when Herrera and colleagues\textsuperscript{213} found an interstitial deletion on chromosome 5q in a man with Gardner’s syndrome. This allowed 2 groups to further localize the \(APC\) gene to the chromosomal region 5q21-22 by genetic linkage in 1987.\textsuperscript{214,215} Linkage is a method for establishing the chromosomal location of a gene by examining the coinheritance of a disease phenotype in multigenerational families with specific alleles of genetic markers from known chromosomal regions. Using a positional cloning strategy from chromosome 5q21-22, the \(APC\) gene was identified in 1991 by 2 groups.\textsuperscript{216,217} Joslyn and colleagues\textsuperscript{218} identified deletions in a mother and daughter with FAP, and in another FAP patient, which
narrowed the candidate interval for the \textit{APC} gene to a 100-kb span. This region was cloned into yeast artificial chromosomes (YACs) vectors, then hybridized to a cDNA library, which identified 3 transcripts mapping to the region of the deletions. One of these genes was found to be mutated in the germline of 4 FAP patients, which caused premature stop codons and truncated proteins.\textsuperscript{217} The coding region of \textit{APC} was found to be comprised of 21 exons, spanning 8535 bp, and encoding for a 2843-amino acid protein with a mass of 311.8 kd. Kinzler and colleagues\textsuperscript{216,219} identified the \textit{APC} gene simultaneously by using a positional cloning approach and subsequently found mutations in exons 8, 9, and 15 in FAP kindreds. One of these mutations segregated in 12 affected individuals of a large FAP family, confirming that this was indeed the \textit{APC} gene.\textsuperscript{220} Powell and colleagues\textsuperscript{221} extended these studies to sporadic colorectal tumors and found that 63\% (10 of 16) of adenomas and 60\% (15 of 25) of carcinomas had somatic mutations within the \textit{APC} gene, the majority of which were found between codons 1281 and 1554. Miyoshi and colleagues\textsuperscript{222} reported similar findings, with somatic mutations of \textit{APC} in 81\% (35 of 43) of sporadic colorectal carcinomas and 75\% (6 of 8) of adenomas. These studies established \textit{APC} as the gene predisposing to FAP and suggested that somatic mutations play an important role at an early stage in the adenoma to carcinoma sequence leading to sporadic colorectal carcinoma.

\textbf{APC Mutations in FAP Patients}

Once the \textit{APC} gene had been cloned, genetic testing of FAP patients could be performed. Because of the large size of \textit{APC}, complete examination of the coding sequence is daunting, and Groden and colleagues\textsuperscript{217} described using 23 PCR primer pairs for exon 15 alone (38 primer pairs for the whole gene). In 61 unrelated FAP patients in whom the entire gene was examined, they found mutations in 16, within exons 7, 8, 10, 11, and 15. Five mutations were found in codon 1309 and 4 at codon 1061 in exon 15.\textsuperscript{217,223} Nishisho and colleagues\textsuperscript{220} limited their study of 103 FAP patients to exons 8, 9, and the 5\textsuperscript{th} end of exon 15 and found 5 mutations. One FAP patient with Gardner’s syndrome and another with no extracolonic manifestations shared the same mutation in codon 302, suggesting that these differences in phenotype were not related to the site of mutation alone.\textsuperscript{220}

Miyoshi and colleagues\textsuperscript{224} studied 79 unrelated FAP patients, and found mutations in 53 (67\%). The types of mutations included 28 deletions, 2 insertions, 19 nonsense, and 4 missense mutations. Overall, 92\% were predicted to cause a truncated \textit{APC} protein. Most of these mutations
(68%) were in the 5’ portion of exon 15, and 10 were at codon 1309. The latter were seen in white, black, and Japanese FAP kindreds, suggesting that this was not a founder mutation. Forty percent of all mutations were found at 5 specific codons (302, 625, 1061, 1309, and 1546). Miyoshi and colleagues also found that 65% of somatic mutations in sporadic colorectal tumors (but only 23% of germline mutations in FAP patients) occurred between codons 1286 and 1513 in exon 15, which they designated the “mutation cluster region.” In these tumors, more than 60% had 2 APC gene mutations, consistent with a tumor suppressive role for this gene.

Van der Lujit and colleagues found 65 mutations in 105 unrelated FAP families (62%) and 2 with structural rearrangements of APC. Of the mutations, 57 (88%) created frameshifts or nonsense codons, 7 caused abnormal splicing, and 1 was an amino acid substitution. Most mutations were in exon 15 (58%), with 6 involving codon 1309 and 7 codon 1061. Beroud and Soussi assembled an APC mutation database in 1996 with more than 700 mutations, 332 in the germline of FAP patients and 402 from colorectal adenomas and carcinomas (http://perso.curie.fr/Thiery.Soussi/APC.html). Of the germline mutations, 220 (66%) were deletions, 21 (6%) were insertions, 85 (26%) were nonsense mutations, and 6 (2%) were missense mutations (Fig 12). Since the vast majority of APC gene mutations in FAP patients lead to a truncated APC protein, Powell and colleagues introduced a method for detecting these changes by transcribing RNA and translating into protein, which can be examined for changes in the size of the APC protein compared with the wild-type protein and can be detected by gel electrophoresis. Using this method, truncated APC gene products were found in 51 of 62 (82%) patients known to have FAP.

**APC and the Wnt Signaling Pathway**

APC affects Wnt signaling through its interactions with β-catenin (Fig 13). When the wnt receptor is activated at the cell surface, it causes cytoplasmic disheveled protein to bind to the protein axin and leads to its dephosphorylation. This allows for β-catenin to accumulate in the cytoplasm, rather than form complexes with axin and APC, where it would be phosphorylated and targeted for degradation. β-Catenin then travels to the nucleus, where it binds to transcription factors, such as T-cell factor 4, and increases the transcription of various genes. APC mutations may reduce β-catenin or axin binding, and thereby reduce phosphorylation and degradation of β-catenin. Mutations in β-catenin may also cause a reduction in its phosphorylation, leading to increased
transcription of its target genes. These genes include the oncogenes C-MYC and CYCLIND1\textsuperscript{228,229} and the matrix metalloproteinase matrilysin.\textsuperscript{230} APC may also play a role in cell adhesion through its regulation of $\beta$-catenin. The latter links E-cadherin to $\alpha$-catenin, which is bound to the actin cytoskeleton of the cell.\textsuperscript{231} This complex is present at the zonula adherens involved in epithelial cell adhesion.

**APC Gene Structure and Function**

There are several different domains in the APC protein, which allow it to perform several functions within the cell, including cell adhesion, playing a role in the cytoskeleton, and regulation of the cell cycle (Fig 14). Amino acids 6 to 57 at its N-terminal end are involved in the formation of APC homodimers,\textsuperscript{232} a potential mechanism for a dominant negative effect of a shorter, mutant APC protein inactivating the wild-type protein.\textsuperscript{233} Amino acids 453 to 767 are made up of 7 Arm repeats homologous to a portion of the *Drosophila* armadillo protein and $\beta$-catenin, and are likely important for association with other proteins, but not $\beta$-catenin.\textsuperscript{234} There are three 15-amino acid repeats located between codons 1020 and 1170, which are sites for $\beta$-catenin binding. There are seven 20-amino acid repeats dispersed between codons 1265 and 2035, which can also bind $\beta$-catenin, after phosphorylation of serine and


threonine residues by glycogen synthase kinase 3β (GSK3β).\textsuperscript{235} APC-bound β-catenin is also phosphorylated by GSK3β, and thereby subjected to proteolysis in a ubiquitin-dependent fashion.\textsuperscript{236} Nonphosphorylated β-catenin is not degraded and builds up in the cell. In the nucleus, it associates with transcription factors and regulates various genes, including the cell cycle genes \textit{C-MYC} and \textit{CYCLIND1}.\textsuperscript{228,229} The mutation cluster region, which is the site of many \textit{APC} mutations in colorectal tumors, encompasses the region of the 15-amino acid and first three 20-amino acid repeats involved in β-catenin binding and subsequent phosphorylation. The protein axin binds to \textit{APC} at 3 different sites between 20 amino acid repeats, thus forming an axin/\textit{APC}/β-catenin complex. Formation of this complex enhances phosphorylation of \textit{APC} and β-catenin by GSK3β, which enhances β-catenin degradation. \textit{APC} truncating mutations will eliminate most of the latter repeats, suggesting an important role in tumor formation.\textsuperscript{237}

The 3' end of \textit{APC} contains a region between amino acids 2219 and 2580 that binds microtubules,\textsuperscript{238} perhaps through association with the protein EB1.\textsuperscript{239} \textit{APC} protein has been demonstrated at the end of microtubules associated with the leading edge of epithelial cells, suggesting an important role in cell migration, such as in enterocytes in intestinal crypts.\textsuperscript{240} The terminal portion of \textit{APC} binds to DLG, the human counterpart of the \textit{Drosophila} disc large tumor suppressor gene. \textit{APC}/DLG complexes are found in the lateral cytoplasm of colon cells and at neuronal synapses,\textsuperscript{241} suggesting a role in cell adhesion or motility.

**Genotype-Phenotype Correlation**

One of the benefits of knowing the predisposing gene for a condition is to be able to determine the severity of its manifestations based on the specific genetic mutation present. Several studies have examined the influence of genotype on phenotype and several patterns have emerged. These relate predominantly to severe polyposis, attenuated polyposis, CHPRE, desmoid tumors, and extracolonic manifestations of FAP (Fig 15).

Severe polyposis is most commonly found when an FAP patient has a germline mutation between codons 1250 and 1464. Nagase and colleagues\textsuperscript{242} studied 22 unrelated Japanese FAP patients, and divided them into profuse (>5000 polyps or ≥10 polyps/cm\textsuperscript{2}; \(n = 5\)) and sparse (<5000, <10 polyps/cm\textsuperscript{2}; \(n = 17\)) types. Patients in the sparse group had mutations between codons 213 and 1249 and between 1465 and 1597. Patients with profuse polyps had mutations of codon 1250, 1309 (3
Gayther and colleagues found that mutations at codon 1309 or later in the APC gene predicted for a more severe FAP phenotype, as defined by an early age of onset (symptoms in teen years, cancer before age 30). Thirteen of 14 severe cases had mutations at codon 1309 (n = 9) or 3' (codons 1323, 1368, 1464, and 1537), whereas 5 cases classified as “average” had mutations in codons 764, 1061 (3 patients), and 1068. Nugent and colleagues found a higher number of polyps in 27 patients with a codon 1309 mutation (median 4000) than 61 patients with unknown mutations (median, 600; P = 0.0001). Caspari and colleagues compared FAP patients with codon 1309 mutations with those having mutations in other exons and found the former group to have an earlier mean age of diagnosis and death from colorectal cancer (30.8 and 32.6 years, respectively) than the latter (38.3, P = 0.016 and 40.5, P = 0.015, respectively). However, Giardiello and colleagues found more variability between and within FAP families (11 families, 74 affected patients) with codon 1309 mutations. The mean age of colorectal cancer diagnosis was 33 years, with a range of 19 to 61 years, and the extracolonic manifestations encountered in different families differed in

![Diagram of correlation of phenotype with mutations in different areas of APC](reproduced with permission from Fearnhead NS, Britton MP, Bodmer WF. The ABC of APC. Hum Mol Genet 2001;10:721-33).
type and their frequency. These findings suggested that the specific *APC*
mutation was not the only determinant of phenotype.\textsuperscript{246,247}

The attenuated form of adenomatous polyposis coli (AAPC) is a
phenotypic variant of FAP in which affected patients generally have less
than 100 adenomatous polyps and later age of onset of colon cancer.
Mutations in AAPC patients tend to be at either the 5′ end or 3′ end of
*APC*. Spirio and colleagues\textsuperscript{248} examined 7 AAPC families and found that
4 had mutations at codon 142 and 1 each in codons 77, 141, and 157.
Soravia and colleagues\textsuperscript{19} found 3 AAPC families with mutation at codon
184 and 1 each with mutations of codon 163, 330, 332, and 2047. No
desmoid tumors were found in these patients. Friedl and colleagues\textsuperscript{249}
described 2 families with AAPC and mutations in codon 1597. The
mutations seen in AAPC patients have been hypothesized to result in null
or weakly functional proteins, whereas other *APC* mutations may cause a
more severe phenotype through a dominant negative effect.\textsuperscript{248,249} Smith
and colleagues\textsuperscript{250} found that 5′ mutations led to unstable proteins that are
degraded within cells, whereas more 3′ mutations resulted in proteins
inhibiting the tumor-suppressor function by heterodimer formation.

The eye lesions defining the CHPRE phenotype are congenital, and as
such, are potentially the earliest sign that an individual at risk is a carrier
of a mutant *APC* gene. The sites of *APC* mutation are well-defined for this
extracolonic manifestation of FAP. Olschwang and colleagues\textsuperscript{155} found
that 7 families with a low incidence of CHPRE had mutations 5′ to codon
9, whereas 24 families with CHPRE had mutations 3′ to exon 9. Wallis
and colleagues\textsuperscript{251} examined 18 unrelated FAP patients positive for
CHPRE, and 8 who were negative, and found that the 8 CHPRE-negative
patients had mutations at or before codon 283 in exon 8, whereas those
positive for CHPRE had mutations from codon 457 (exon 10) to 1309
(exon 15). Based on these studies, Wallis and colleagues\textsuperscript{251} speculated
that exon 9 was a mutational boundary for the CHPRE phenotype.
Caspari and colleagues\textsuperscript{252} specifically evaluated members of 20 FAP
families with *APC* mutations between codons 1445 and 1578 and found
that none had CHPRE. This was supported by Davies and colleagues,\textsuperscript{253}
who found that 16 FAP families with mutations between *APC* codon 311
and 1444 all had CHPRE, whereas 4 families with mutations in codons 1444
to 1560 and 6 of 7 with mutations 5′ to exon 9 (codon 311) did not. These
studies suggest another mutational boundary for CHPRE in exon 15.

With respect to other extracolonic manifestations, Caspari and col-
leagues\textsuperscript{252} found that 33 of 36 members of 20 FAP families with codon
1445 to 1578 mutations developed desmoid tumors; the 3 patients without
desmoids in this group were all children. Wallis and colleagues\textsuperscript{254}
examined 105 unrelated FAP patients with APC mutations and found that 1 of 10 patients with mutations between codons 177 and 452 had desmoids, 3 of 25 with mutations between codons 457 and 1309 had desmoids, and 11 of 11 with mutations between codons 1395 and 1493 had desmoids. Giardiello and colleagues\textsuperscript{246} found desmoid tumors in members of 6 of 10 FAP families with the same codon 1309 mutation, but in 5 of these families only a small proportion of affected members had desmoids. Wallis and colleagues\textsuperscript{254} found a similar trend for osteomas and epidermoid cysts as seen for desmoid tumors. The trend for the incidence of duodenal adenomas, periampullary cancers, and gastric adenomas was not as clear for each of these APC mutation groupings.\textsuperscript{254} Davies and colleagues\textsuperscript{253} showed that FAP patients with APC mutations 3’ to codon 1444 had a significantly higher number of dental abnormalities than those without. It should be noted that most of these genotype-phenotype studies do not take into account how cases were diagnosed (genetic testing, symptoms, screening), the treatment that was received (prophylactic or therapeutic colectomy), and the age at diagnosis. Preisciuttini and colleagues\textsuperscript{255} found a significant ascertainment bias with an estimated age of onset of polyposis in children 15 years earlier than the affected parent. The number of polyps and severity of the phenotype may be impacted on by the age at diagnosis, and the frequency of extracolonic manifestations will depend on how carefully each has been screened for.

Approximately 6\% of Ashkenazim have missense mutations at codon 1307 (I1307K) of the APC gene but do not develop FAP.\textsuperscript{256} These individuals are at increased risk for developing colorectal adenomas and have a 1.5- to 1.7-fold increased risk for colorectal cancer.\textsuperscript{257} A condition resembling FAP, termed MYH polyposis, is inherited in an autosomal recessive manner and can be confused with FAP. Sampson\textsuperscript{258} examined 614 polyposis families from UK registries and found that 111 did not have APC mutations or apparent autosomal dominant transmission. Twenty-five had mutations of both copies of the MYH gene, a homolog of the bacterial mismatch repair gene, mutY. Sieber\textsuperscript{259} examined 107 FAP patients negative for APC mutations and found 8 with biallelic MYH mutations. They also found that 6 of 152 patients with 3 to 100 adenomas had biallelic, germline MYH mutations and suggested that patients with multiple adenomas or APC-mutation-negative FAP consistent with recessive inheritance should be tested for MYH mutations.

**Genetic Testing for APC Mutations**

There are several appropriate indications for referring patients for APC gene testing. If a patient is diagnosed with FAP (>100 colorectal...
adenomatous polyps, or many adenomatous polyps and a family history of FAP), then knowledge of the specific APC mutation in this individual will facilitate the testing of other family members at risk, and may yield clues about other expected phenotypic manifestations. A first degree relative of an FAP patient will be at 50% risk of also inheriting the mutant gene, unless the relative has a de novo mutation and is not the parent. Therefore, genetic testing is indicated to determine what type of surveillance will be necessary for these individuals at risk. In the situation of attenuated FAP, the clinical criteria for establishing the diagnosis are not as well defined (10-100 adenomatous polyps, or multiple adenomas in a relative of a patient with known FAP or attenuated FAP), but the same general strategy is recommended. More controversial is whether testing should be performed on individuals with multiple adenomatous polyps, without a family history of FAP, but with or without a family history of colon cancer. Giardiello suggested that in patients with at least 20 colorectal adenomas and no family history of FAP, there was a valid indication for genetic testing, and found that 25% (4 of 16) of such patients had APC mutations. On the other hand, of 44 patients with the indication of less than 20 colorectal adenomas, a history of colorectal cancer, family history of colorectal cancer, or family history of adenomas or cancers other than colorectal, only 1 patient was positive for the APC mutation. Therefore, the best indications for testing are: 1) being affected with FAP, 2) being at risk for FAP due to an affected first degree relative or relative with a known APC mutation, or 3) having 20 or more colorectal adenomas (which is suspicious for attenuated FAP).

There are several potential methods for testing whether individuals are carriers of a mutant APC gene. If there are a large number of affected individuals in a family, then one can perform genetic linkage testing using genetic markers from the region of APC. However, this does not yield information regarding the specific mutation and requires the participation of multiple family members. Since approximately 98% of germline APC mutations in FAP patients lead to premature stop codons, looking for a truncated APC protein is a useful method for detecting mutations. Powell and colleagues demonstrated in 1993 that 82% of 62 unrelated FAP patients had truncated APC proteins, and many clinical laboratories still use this technique. Other laboratories screen for the most common mutations or specific exons of the APC gene, but the most comprehensive method is direct sequencing of the entire gene, which will detect mutations in approximately 90% of FAP patients. According to the GeneTests website, there are 18 clinical laboratories offering APC gene testing (www.genetests.org). The price of full gene sequencing from
Myriad Genetics (Salt Lake City, UT) is $1685 and the price to test for a specific known mutation is $350. Some insurance companies may pay for APC gene testing, including Medicare, providing the above criteria are met.

Giardiello\textsuperscript{261} interviewed the physicians and genetic counselors of 177 patients who had APC gene testing in a commercial laboratory for the calendar year 1995. They found that 83% of these tests were ordered appropriately (with the criteria listed above). Sixty-nine percent of patients with a clinical diagnosis of FAP had an APC mutation detected, 49% of at risk patients from families with known mutations, 25% of patients with greater than 20 colorectal adenomas and no family history of FAP, and only 2% of patients with lesser indications for testing (<20 adenomas, family history of CRC or adenomas, other associated cancers). Only 19% of patients received genetic counseling before testing, and only 17% had informed consents obtained. Furthermore, in 32% of cases, the physicians did not realize that a result of “no mutation found” could be a false-negative result and they may have misinformed their patients. The authors determined that physicians need to be prepared to counsel their patients with the results of such testing or refer them to genetic counselors.\textsuperscript{261}

Colorectal Cancer Treatment Options

The well-defined colorectal cancer risk of nearly 100% by the fifth decade in patients with FAP has led to prophylactic colon resection becoming the standard of care.\textsuperscript{5,55,262-265} The surgical options include a colectomy with IRA, IPAA, or proctocolectomy with permanent ileostomy.

A sphincter-sparing procedure, such as an IRA or IPAA, is considered more advantageous than a proctocolectomy and permanent ileostomy due to the majority of patients’ desire to avoid a permanent ileostomy. However, a sphincter-sparing operation usually is not feasible when treating rectal carcinoma in patients with FAP involving the lower one third of the rectum. When colorectal cancer did not involve the lower one third of the rectum and a prophylactic resection was being performed, an IRA was generally performed. This was the standard approach until the IPAA was developed and started gaining popularity in the 1980s. The IRA is a 1-stage procedure, whereas the IPAA is usually a 2-stage procedure, involving a temporary diverting ileostomy to protect the newly constructed ileal pouch. Besides the additional morbidity of an ileostomy takedown, the operative morbidity is slightly higher with an IPAA procedure. Nyam and colleagues.\textsuperscript{133} reported a series of 187 patients from
the Mayo Clinic who underwent an IPAA for FAP, and found an overall complication rate of 24%. Intestinal obstruction was noted in 13% (n = 25), pelvic infection in 1.6% (n = 3), wound infection in 1.6% (n = 3), urinary tract infection/retention in 1.6% (n = 3), sexual dysfunction in 4.3% (n = 8), and other complications in 1.1% (n = 2). The bowel functionality of the pouch (IPAA) was quantified as a median of 4 stools per day, with a median of 1 stool at night; 41 (22%) of the patients had some spotting during some nights and 8 (4%) had nocturnal soiling. The daytime continence was 84%, with 12% having daytime spotting, and 4% had severe problems with incontinence. The bowel functionality of the pouch only adversely affected the quality of life in 2% of patients. Pouchitis was a rare problem, diagnosed in only 3.3% of patients. In another large series, Kartheuser and colleagues compared 171 FAP patients undergoing an IPAA to 22 FAP patients having an IRA with similar findings as Nyam and colleagues. One patient died following the IPAA procedure, and 46 (27%) experienced perioperative complications. Twenty-six (15.2%) patients had postoperative small bowel obstruction and 25 (14.6%) patients experienced non-small bowel obstruction complications. The non-small bowel obstructive symptoms included urinary tract infection, dehydration, pulmonary complications, thrombophlebitis, cardiac arrhythmia, renal colic, gastroenteritis, hepatitis, pelvic sepsis, fistula formation, and necrotizing enteritis. Late complications included anastomotic stricture in 7 (4%) patients. There was only 1 episode of transient impotence, no reported retrograde ejaculation experienced by the male patients, and no female sexual complications. Only 2 (1.2%) cases of pouchitis complicated the series. The bowel function between IPAA versus IRA reported by Kartheuser and colleagues showed the number of daytime stools were 4 versus 3, nocturnal stooling occurred in 26% versus 13%, normal daytime continence was 98% versus 100%, and normal nighttime continence was 96% versus 96%, respectively. Summarizing 2 additional series comparing IPAA versus IRA in patients with FAP, the stool frequency ranged from 4.5 to 5 versus 3 to 4, and normal continence was 60% to 87% versus 72% to 83%. The bowel function is clinically similar following IRA and IPAA procedures when performed in experienced hands. Despite the rectal resection with an IPAA, the impotence and retrograde ejaculation reported in the literature has only been 1% to 3%. More commonly seen is dyspareunia in females and leakage of stool during intercourse, which can be eliminated with emptying the pouch before intercourse. Fertility does not appear to be affected by IPAA if there was not a history of pelvic sepsis.
The advantage of IRA as a 1-stage procedure and the associated decreased morbidity must be balanced with the rectal cancer risk (Table 6). Bussey and colleagues\textsuperscript{262} reported a cumulative rectal cancer risk of 13% at 25 years in 174 FAP patients following an IRA, and DeCosse and colleagues\textsuperscript{270} found the same incidence in 294 patients at 25 years after IRA. Bulow and colleagues\textsuperscript{271} pooled the data from the Denmark, Finland, Holland, and Sweden national polyposis registries and found the cumulative incidence of metachronous rectal cancer to be 17% and 32% at 30 and 40 years of follow-up, respectively. Iwama and Mishima\textsuperscript{272} and Heiskanen and Jarvinen\textsuperscript{273} published a series of FAP patients from Japan and Finland who underwent IRA and found the cumulative risk for developing rectal cancer was 24.2% at 15 years and 25% at 20 years, respectively. Bess and colleagues\textsuperscript{274} reported a higher incidence of rectal cancer following IRA, which was 55% after 30 years. However, many patients from this series had an ileosigmoidostomy instead of an IRA, and 35 of 178 (20%) patients were excluded from analysis because they lacked rectal polyposis at the time of IRA. As a result, the rectal cancer occurrence may be falsely elevated.\textsuperscript{274} Iwama and Mishima\textsuperscript{272} noted that 2 of 62 (3%) patients with rectal stumps shorter than or equal to 7 cm developed rectal cancer after

<table>
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<th>Year</th>
<th>No. of patients</th>
<th>5 yr (%)</th>
<th>10 yr (%)</th>
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NCl, National Cancer Institute.


IRA, whereas 27 of 161 (17%) with rectal stumps longer than 7 cm developed rectal carcinoma.

In the St. Mark’s Hospital series, the mean age for IRA patients was 26 years and the mean age of developing rectal cancer was 48.3 years. An earlier report by Moertel and colleagues found that the mean age of colectomy was 36 years and the age of metachronous rectal cancer diagnosis was also 48 years, suggesting that the risk for rectal recurrence is related to the chronological age rather than the age at the time of colectomy. This notion is supported by data from additional studies.

Patients may undergo completion proctectomy for rectal stump cancer or for uncontrolled rectal polyposis. The rate of completion proctectomies because of increasing rectal polyposis after an IRA ranges from 36.6% to 74%. The 5-year survival rate following metachronous rectal cancer in patients with FAP having undergone an IRA ranges from 60% to 78%. Patients undergoing an IPAA are not immune to development of pouch or perianastomotic polyps. Parc and colleagues had found the risk of developing ileal pouch polyposis to be 7% at 5 years, 35% at 10 years, and 75% at 15 years. However, no patients in this series developed ileal pouch carcinoma. Van Duijvendijk and colleagues reviewed 6 centers’ polyposis registries comparing a hand-sewn IPAA with mucosectomy (n = 62) to a double-stapled anastomosis (n = 35). The risk of developing adenomatous polyps at the anastomosis for the hand-sewn and stapled techniques at 7 years was 10% and 31%, respectively. Comparatively there have been few case reports of carcinoma following an IPAA, totaling just 8 cases. Therefore, an IRA is usually only recommended for patients with a lower chance of requiring a secondary proctectomy, such as patients with attenuated polyposis or those with rectal sparing of polyps. Bess and colleagues found that of 35 patients with rectal sparing undergoing IRA, none developed rectal cancer over a median follow-up of 15 years, whereas 46 of 143 patients not having rectal sparing at the time of IRA developed rectal cancer at a median follow-up of 19.1 years. The increased perioperative morbidity of IPAA may be avoided by performing IRA in these patients. However, they will require lifelong surveillance by endoscopy at least every 6 months, and if compliance is an issue these patients may be better served by IPAA. Proctocolectomy with a permanent ileostomy is usually reserved for patients who have rectal cancer diagnosed in the lower one third of the rectum and are not candidates for an anal sphincter sparing procedure.

Due to the risk for polyposis and metachronous cancer in the retained
rectum, it should be evaluated every 6 months with proctoscopy with removal of all polyps larger than 5 mm.\textsuperscript{191,288} The anal transitional zone and pouch following IPAA have a significantly lower risk for development of malignancy; therefore, surveillance endoscopy should be performed every 2 to 5 years depending on symptoms and previous findings.\textsuperscript{191,288}

There is evidence that NSAIDs can cause the regression of colon and rectal polyps. This can benefit patients with a retained rectum following an IRA and even the anal transitional zone following an IPAA for FAP. NSAID therapy works through COX-2-dependent and independent mechanisms. Prostaglandin levels are elevated in adenomatous polyps and carcinomas and have been hypothesized to play a role in colonic tumorigenesis.\textsuperscript{289} By using nonselective or selective COX-2 inhibitors and reducing these prostaglandin levels, the adenomatous polyp formation may be reduced.\textsuperscript{290} Additional evidence suggests a COX-2-independent pathway by growth inhibition mediated through induction of apoptosis.\textsuperscript{291,292} Giardiello and colleagues\textsuperscript{293} performed a randomized, prospective study and found that treatment with sulindac caused a reduction in the number and size of colorectal polyps in patients with FAP after 6 months of therapy. However, the number and size increased after termination of the sulindac.\textsuperscript{293} Winde and colleagues\textsuperscript{294} studied the rectal administration of sulindac in patients with FAP after an IRA and found that 87% had complete polyp regression after 48 weeks at 67 mg/d. There was a dedifferentiation from the high to low grade dysplasia in all but 2 patients, and a decrease in prostaglandin E2 levels.\textsuperscript{294} This is confounded by both Spagnesi and colleagues\textsuperscript{295} and Nugent and colleagues\textsuperscript{63} having reported a decrease in size and number of rectal polyps after IRA in FAP patients independent of NSAID administration. Clinically this reduction in polyps by sulindac may not correlate with elimination of the colorectal carcinoma risk. Lynch and colleagues\textsuperscript{296} reported a case of a patient with FAP who underwent a prophylactic IRA who developed multiple rectal adenomatous polyps. Three months after sulindac initiation, the rectal polyps had almost completely regressed. However, 15 months after starting sulindac and 37 years after the IRA the patient developed an ulcerated rectal adenocarcinoma.\textsuperscript{296} Similarly, Niv and Fraser\textsuperscript{297} reported a FAP patient treated by IRA who had received sulindac for 28 months (with the last 12 months without rectal polyps noted on endoscopy) but still developed a rectal adenocarcinoma. Spagnesi and colleagues\textsuperscript{295} measured crypt cell proliferation via thymidine labeling and found a “persistence of an abnormal mucosal proliferation after sulindac therapy, despite the reduction of polyp number, suggesting caution in assuming a
lower risk of rectal cancer in patients with FAP.” Nugent and colleagues measured rectal cell proliferation in patients with FAP having IRA. Their findings were contradictory to Spagnesi and colleagues in that there was a significant decrease in cell proliferation and polyp regression. More recently, Steinbach and colleagues showed in a double blind, placebo-controlled trial that treatment of FAP patients with celecoxib 400 mg twice per day for 6 months led to a 28% reduction in the mean number of polyps. At the current time there is no definitive evidence that NSAIDs reduce the risk for colorectal cancer in patients with FAP, including in the retained rectum or pouch following anal sphincter-sparing prophylactic surgery. Since there are well-known side effects of this therapy there is no clear recommendation for its routine use.

**Surveillance**

Patients who are at risk or in whom the diagnosis of FAP is suspected should first undergo a complete history, paying particular attention to family history, and physical examination. The family history is optimally obtained for 3 generations and confirmed with medical records. The physical examination should be complete, but with attention to areas affected by extracolonic manifestations of FAP: neurologic examination, fundoscopic examination (which is best performed by an ophthalmologist), dental examination, dermatologic assessment, thyroid examination, abdominal examination, and digital rectal examination.

When the family history is positive for FAP and a genetic mutation has been identified in the *APC* gene, then the at-risk patient is offered genetic counseling. If genetic testing is agreed to, a positive result indicates an affected individual has FAP and should undergo an annual flexible sigmoidoscopy beginning around the age of 10 to 12 years. This is approximately the same time that colonic adenomas first become evident on endoscopic examination, with a median age of onset at 16 years. Once colon or rectal adenomas are identified, the patient should be offered surgical intervention due to the knowledge that virtually 100% of FAP patients will develop colorectal carcinoma. Individuals of families with a known *APC* mutation who do not undergo genetic testing should also be screened annually starting at 10 to 12 years until the age of 25 years, followed by every 2 years until the age of 35 years, every 3 years until 50 years, and then per the guidelines for the general population. Patients for whom the familial history is positive for a specific *APC* mutation and the mutation was not identified by genetic testing can undergo colorectal cancer screening per the guidelines for the general population.
Screening in families without an identified APC mutation should be performed as described above for at-risk patients. Once polyps are diagnosed, surgical intervention is indicated.

Patients with a positive family history of AAPC with an identified APC mutation should undergo initial colonoscopy at age 15 years. If the baseline colonoscopy is consistent with FAP, then surgical intervention is indicated. If colonoscopy is consistent with AAPC, then endoscopic control may be performed, if feasible, followed by annual colonoscopy. If polypectomy is not feasible, then surgical intervention is recommended. Finally, if no polyps are seen during the baseline colonoscopy, then a repeat annual colonoscopy starting at the age of 20 years for patients with an APC mutation, or every 2 years starting at the age of 20 years for untested patients, is recommended. Individuals who test negative for the familial APC mutation causing AAPC should have a baseline colonoscopy at the age of 15 years. If the colonoscopy is negative, then routine colorectal cancer screening for the normal population applies. Patients with a positive family history of AAPC without an APC mutation identified should undergo baseline colonoscopy at age 15 years. If no colorectal adenomas are identified on this initial colonoscopy, then they may be followed with colonoscopy every 2 years starting at 20 years of age. However, if adenomas are initially identified at the baseline colonoscopy, then polypectomy may be performed followed by yearly colonoscopy. Again, if at any time the polyps cannot be controlled endoscopically, surgery is indicated. When there is no familial history of FAP, then the diagnosis will be made clinically. Either the patient is symptomatic from gastrointestinal polyps and requires colonoscopy, or there is suspicion based on identification of extracolonic manifestations such as CHRPE, childhood sebaceous cysts, osteomas, dental abnormalities, and so on. The diagnosis is established when more than 100 adenomatous colorectal polyps are identified and surgical intervention will be indicated. With a diagnosis of FAP, APC gene testing should be considered after genetic counseling to help in the management of at-risk individuals in the family.

Acknowledgments

This manuscript was supported by the Carver Charitable Trust, NIH Grant RO1-CA098193-01A1, NIH Grant 1U01 CA86389, the Jacqueline Seroussi Memorial Foundation, and revenue from Nebraska cigarette taxes awarded to Creighton University by the Nebraska Department of Health and Human Services. Its contents are solely the responsibility of
the authors and do not necessarily represent the official views of the State of Nebraska or the Nebraska Department of Health and Human Services.

REFERENCES

variant or attenuated form of adenomatous polyposis coli to the adenomatous polyposis coli (APC) locus. Am J Hum Genet 1992;51:92-100.


78. Ohsato K, Yao T, Watanabe H, Iida M, Itoh H. Small-intestinal involvement in


gene for familial polyposis coli maps to the long arm of chromosome 5. Science 1987;238:1411-3.


Niv Y, Fraser GM. Adenocarcinoma in the rectal segment in familial polyposis coli is not prevented by sulindac therapy. Gastroenterology 1994;107:854-7.