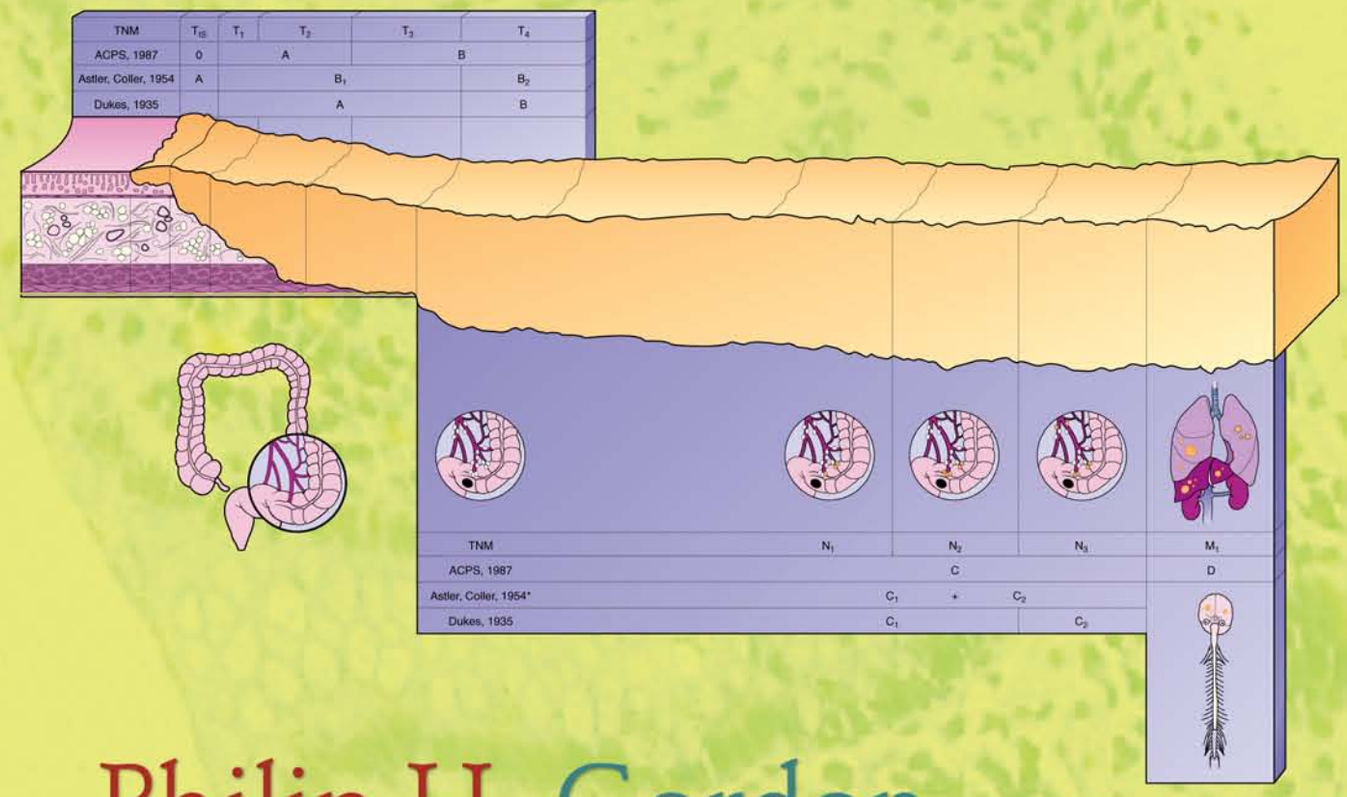
Neoplasms of the Colon, Rectum, and Anus

Second Edition



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Santhat Nivatvongs

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Colon, Rectum, and Anus
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I am once again deeply indebted to my wife
Rosalie
for her constant patience and understanding through the burden of this third edition. Her constant life-long support has made all my professional accomplishments possible.

To my wonderful children
Laurel *and* **Elliot**
of whom I am extremely proud.
My love and gratitude to all.
—PHG

To my two angels
Marisa *and* **Nitara**.
Thinking of them makes me smile;
talking to them recharges my energy.
—SN

Preface

Colorectal carcinoma remains the second leading cause of death from malignancy. In the eight years that have elapsed since our last edition, the proliferation of information published in the surgical literature makes it necessary to update and elaborate on these developments. Highlights in the revision include new data regarding the incidence, prevalence, and trends in colorectal carcinoma. There is an update on the genetics of colorectal carcinoma in general and in particular HNPCC. Extensive discussion of the indications for and interpretation of genetic testing and the invaluable role of genetic counseling are described in detail. We believe this is a disease that, with appropriate screening, can for the most part be prevented and therefore suggestions for screening are made. The value and role of virtual colonoscopy is discussed. There is an update on the propriety of adjuvant therapy with its limitations and complications and possible fine tuning of indications for adjuvant therapy. There is also updated information on the treatment of recurrent metastatic carcinoma providing prognostic indicators for recurrence following therapy. A section on intra-luminal stenting for obstruction has been added and new information on the staging of rectal carcinoma. There is revised description of sphincter saving operations (pouch, coloplasty, coloanal anastomosis) and a discussion of total mesorectal excision with results of the use of this technique. There are updated results on the treatment of carcinoma of the rectum with a discussion of the propriety of the use of local excision of rectal carcinoma. The section on palliative management of patients with rectal carcinoma has been expanded and there is a discussion on the role of preoperative neoadjuvant treatment for rectal carcinoma. A new section on the management of presacral bleeding has been included.

The laparoscopy chapter has been totally revised and expanded. The indications for laparoscopic colectomy have been revisited and expanded as newer technology has become available and increased experience has been gained. The new instrumentation of equipment that is available has been outlined including subjects such as handports and robotic surgery. Techniques of laparoscopic colectomy have been added. The results of laparoscopic colectomy, conversion rates, detailed morbidity, and mortality by disease process have been updated. Difficult situations such as obesity, inflammatory masses, and fistulas have been described. Quality of life and cost issues have been included. A major expansion of the complications, including incidence and prevention of complications with laparoscopic colectomy have been described.

The book is replete with color illustrations and photographs adjacent to the text material rather than grouped at the beginning, middle, or end of the book. New illustrations have been added and others redrawn to conform to better understanding and improvement in operative technique. Each chapter is heavily referenced for those interested in further documentation.

We hope we have accomplished our goal of summarizing the enormous body of knowledge published in the literature and share our personal experience and preferences with our readers. We strove for a book that strikes a balance of being authoritative and detailed without being so inclusive that somewhat irrelevant material and minutia are included. We sincerely hope our efforts will provide the practicing surgeon and surgeon in training, the appropriate information to permit them to provide a rational and up to date course of action to the ultimate benefit of each of their patients.

Information in this text has been reprinted from the third edition of our comprehensive textbook *Principles and Practice of Surgery for the Colon, Rectum, and Anus*. We trust that non-colorectal specialists such as oncologic and general surgeons, radiologists, and others who diagnose and treat this kind of malignancy will find this book useful.

Philip H. Gordon
Santhat Nivatvongs

Contents

1 Benign Neoplasms of the Colon and Rectum

Santhat Nivatvongs

POLYPS OF COLON AND RECTUM

The word "polyp" is a nonspecific clinical term that describes any projection from the surface of the intestinal mucosa regardless of its histologic nature. Polyps can be conveniently classified according to their histologic appearance:

1. Neoplastic tubular adenoma, villous adenoma, and tubulovillous, adenoma and serrated adenoma
2. Hamartomatous—juvenile polyps, Peutz-Jeghers syndrome (PJS), Cronkhite-Canada syndrome, Cowden's disease
3. Inflammatory—inflammatory polyp or pseudopolyp, benign lymphoid polyp
4. Hyperplastic

NEOPLASTIC POLYPS

Adenomas

A neoplastic polyp is an epithelial growth composed of abnormal glands of the large bowel. A neoplastic polyp has been termed an adenoma and is classified according to the amount of villous component. Those with 0% to 25% villous tissue are classified as tubular adenomais, 25% to 75% as tubulovillous adenomas, and 75% to 100% as villous adenomas (1). Tubular adenomas (Fig. 1) account for 75% of all neoplastic polyps; villous adenomas (Fig. 2), 10%; and tubulovillous adenomas (Fig. 3), 15%. The villous growth pattern is most prominent in sessile large adenomas, particularly those located distally in the rectum. There remains considerable uncertainty as to the nature of villous growth, whether it is merely a manifestation of continued growth of tubular adenomas, or whether it is a distinct phenotype that may reflect an acquired genetic change. In favor of the former is the rarity of small villous adenomas and large purely tubular adenomas (1).

Dysplasia describes the histologic abnormality of an adenoma according to the degree of atypical cells, categorized as low-grade (mild), moderate, and high (severe). Thus high-grade dysplasia designates a condition one step away from an invasive carcinoma. The frequency of high-grade dysplasia correlates with the size of the adenoma (Fig. 4). The term carcinoma-in-situ, or "intramucosal carcinoma" should be avoided, since it implies a biological potential for distant spread, which is unwarranted and could result in overtreatment (1).

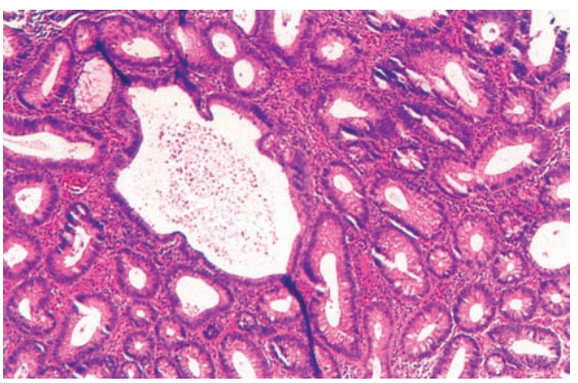

FIGURE 1 ■ Tubular adenoma.

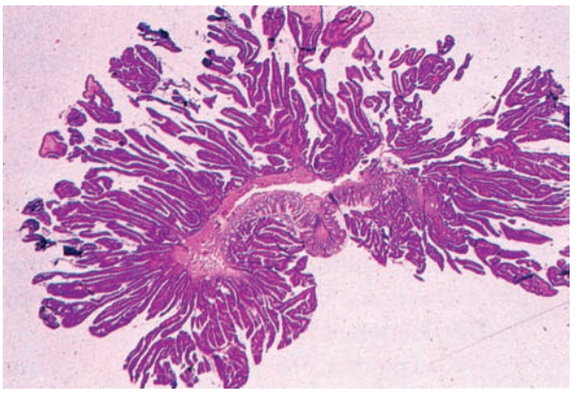

FIGURE 2 ■ Villous adenoma.

Neoplastic polyps are common. Since data on the clinical recording of adenomas may be biased due to selection of patients and diagnostic methods, most accurate epidemiologic data on adenomas are obtained from autopsy studies. In autopsy series adenomas are present in 34% to 52% of males and 29% to 45% of females over 50 years of age. Most adenomas (87–89%) are less than 1 cm in size (2,3). The number, but not the size, of adenomas, increases with age (2). Carcinomas are found in 0% to 4% (2–5). The National Polyp Study, a multicenter randomized clinical trial in the United States, included 3371 adenomas in 1867 patients detected by colonoscopy (6). This study gives valuable information regarding the natural history and characteristics of polyps: 66.5% of polyps were adenomas, 11.2% were hyperplastic, and 22.3% were classified as "other" (normal mucosa, inflammatory and juvenile polyps, lymphoid hamartomas, submucosal lipomas, carcinoids, and leiomyomas). The majority of the adenomas (69%) were in the left colon (Table 1). The sizes of the adenomas were $\leq$0.5 cm, 38% 0.6 to 1 cm, 37% and 1 cm, 25%.

It is important to note that the size, the extent of villous component, and the increasing age are independent risk factors for high-grade dysplasia. The increased frequency of high-grade dysplasia in adenomas located distal to the splenic flexure is attributable mainly to increased size and villous component rather than to location per se. Multiplicity of adenomas affects the risk of high-grade dysplasia but is dependent on size and villous component and thus is not

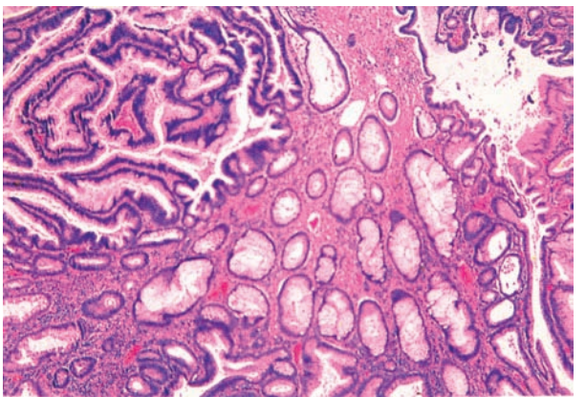

FIGURE 3 ■ Tubulovillous adenoma; mixture of tubular and villous glands.

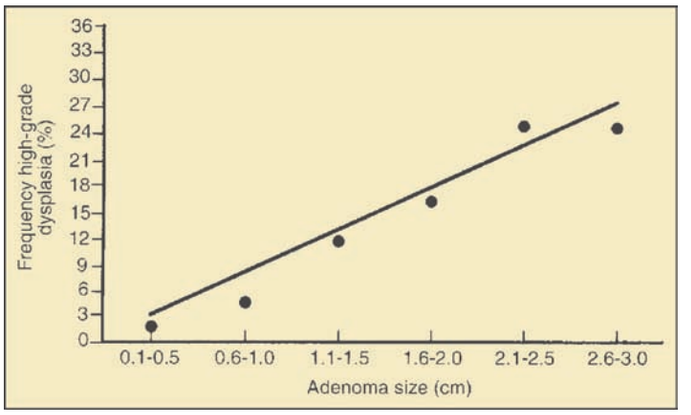

FIGURE 4 ■ Relationship between adenoma size and frequency of dysplasia. *Source*: From Ref. 6.

an independent factor (6). Invasive carcinomas are uncommon in adenomas < 1 cm, and the incidence increases with and increased size of the adenomas (Table 2) (7,8).

Adenoma-Carcinoma Sequence

The Observation

The concept that carcinomas of the colon and rectum derived from benign adenoma was observed by Dukes (9) of St. Mark's Hospital, London, in 1926. Jackman and Mayo (10) coined the term adenoma-carcinoma sequence in 1951. After decades of debates and challenges by those who believed that carcinoma of the colon and rectum derived de novo (11,12), the adenoma-carcinoma sequence has finally become widely accepted and currently is the rationale of the approach to the secondary prevention of colorectal carcinoma by colonoscopic polypectomy (1,13–16). Circumstantial evidence supporting the adenoma-carcinoma sequence abounds and explains the high concurrence rate of carcinoma and adenoma and the frequent findings of contiguous benign adenoma in the resected carcinoma (17). Numerous studies (most of which are retrospective), based on tumor registry reports, hospital records, pathology reports, surgical specimens, and colonoscopy show a coexistence of adenomas and adenocarcinomas of the colon and rectum ranging from 13% to 62% (18). The cumulative incidence curve of adenomas based on data from the Norwegian Cancer Registry precedes the corresponding incidence

TABLE 1 ■ **Distribution of Colorectal Adenomas Diagnosed by Colonoscopy**

Site	(%)
Cecum	8
Ascending colon	9
Hepatic flexure	4
Transverse colon	10
Splenic flexure descending colon	4
Descending colon	14
Sigmoid colon	43
Rectum	8
Total	100

Source: From Ref. 6.

TABLE 2 ■ **Relationship Between Size of Adenoma and Carcinoma**

Size (cm)	Adenoma (No.)	Invasive Carcinoma (%)
< 0.5	5027	0
0.6–1.5	3519	2
1.6–2.5	1052	19
2.6–3.5	510	43
> 3.5	1080	76

Source: From Ref. 7.

curve of carcinomas by about five years (Fig. 5). It should be kept in mind that adenomas are first diagnosed and reported to the cancer registry simultaneously with the diagnosis of colorectal carcinoma, indicating a longer time span between the two types of lesions than the curve indicates. It is manifested also in the natural history of both familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC) syndrome. The latter was originally thought to offer support to the de novo school of thought but several studies have since demonstrated coexisting and contiguous adenomas associated with HNPCC carcinoma with a frequency similar to that observed with sporadic carcinomas (1). Due to the high prevalence of adenomas and the relatively far less frequent incidence of carcinomas, only a small proportion of adenomas give rise to carcinomas (20).

Although the adenoma-carcinoma sequence concept has been favored by most authors as the main pathogenesis of colorectal carcinoma, the "de novo" origin of carcinoma developing from normal mucosa has received some attention in recent years as an alternative pathway (19). In support of this de novo theory, authors (21–23) reported early colorectal carcinomas without evidence of adjacent adenomatous cells. In the series reported by Stolte and Beckte (22) of 155 such lesions, 59% of the lessions were Polyponl and 34% were flat. However, proponents for the adenoma-carcinoma sequence may argue that these types of lessions are so aggressive that the infiltration destroys the adenomatous remuants. Muto et al. (24)

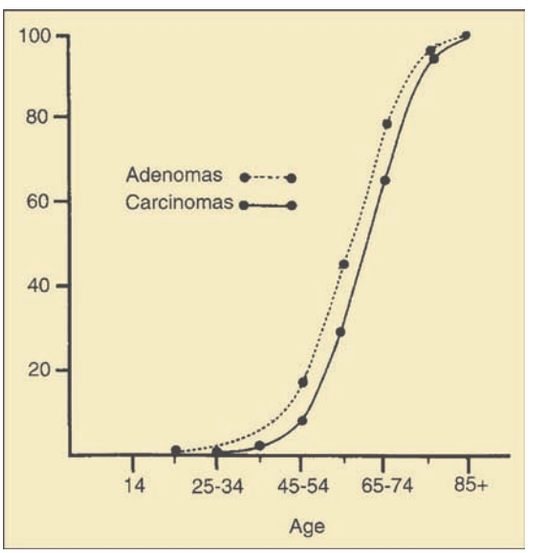

FIGURE 5 ■ Cumulative incidence of colorectal adenomas and carcinomas recorded in the Norwegian Cancer Registry 1983 to 1985. *Source*: From Ref. 19.

thought that all genetic alterations may take place rapidly, one after another, without a chance for morphologic changes to be expressed as seen in the adenoma-carcinoma sequence. They said, "until a specific responsible gene for de novo carcinoma is detected, de novo carcinoma arising directly from normal mucosa is only an imaginary entity. Until then, the term 'de novo' carcinoma is better avoided and instead de novo-type carcinoma should be used."

Molecular Genetics

Molecular genetic discoveries provide substantial support for the adenoma-carcinoma sequence concept (25). An adenoma represents an epithelial proliferation derived from a single cell (crypt). Its de-velopment occurs as a series of genetic mutations. The progression of colorectal epithelium from normal to adenoma to carcinoma can be simplified as in Figure 6.

The initial step in colorectal carcinogenesis is the mutation in the adenomatous polyposis coli (*APC*) gene on chromosome 5q. The *APC* gene is inactivated, causing the affected cells to proliferate. These cells are thus primed for subsequent growth-enhancing mutation, which is more likely because of the increased rate of cell division.

Hypomethylation of DNA has been identified as the next factor involved in colorectal carcinogenesis. Loss of methylation of CpG dinucleotides occurs in cells that are already hyperproliferative because of the inactivation of the *APC* gene. These changes produce a growth of the affected cells resulting in adenoma formation. Hypomethylation of DNA may be directly linked to the K-*ras* (Kirsten rate sarcoma virus) activation that enhances the dysplasia so that the neoplasia can progress.

Because K-*ras* is an oncogene, thus mutation of one allele is enough to produce an effect. K-*ras* mutations can occur in the absence of *APC* gene mutations but, in this case, are usually limited to aberrant crypt foci (ACF) that do not progress to malignancy. In cells that have already suffered *APC* mutation (both alleles need two "hits"), K-*ras* mutation will drive progression. Small adenomas tend to advance to intermediate adenomas.

The transition from intermediate to advanced (or late) adenoma is associated with a distinct genetic alteration on the long arm of chromosome 18. This alteration is correlated with the mutation of a gene that maps to 18q21, named deleted in colon cancer (*DCC*). Specific *DCC* mutation has been detected in a number of colorectal carcinomas and carcinomas that have lost the capacity to differentiate into mucus-producing cells that have uniformly lost *DCC* expression.

The progress from advanced adenoma to carcinoma is frequently accompanied by loss of heterozygosity (i.e., mutation of one of two alleles) on chromosome 17p and mutation of the *p53* gene that maps to 17p. These cumulative losses in tumor suppressor gene function accompanied by activation of dominant oncogenes drive the clonal expression of cells from the benign to the malignant site (25).

A fuller account of molecular genetics of colon and rectal adenocarcinoma is provided in Chapter 23.

Diagnosis of Large Bowel Adenomas

Clinically, there are two morphologic types of polyps, pedunculated and sessile. The pedunculated polyp has a stem lined with normal mucosa, called a stalk or a pedicle, and has the appearance of a mushroom (Fig. 7). A sessile polyp grows flat on the mucosa (Fig. 8). A pedunculated polyp rarely is >4 cm in diameter, whereas a sessile polyp can encompass the entire circumference of the large bowel.

Adenomas of the large bowel are usually asymptomatic and are frequently discovered during routine radiologic studies or endoscopic examinations. Bleeding per rectum is the most common finding if the polyp is situated in the rectum or sigmoid colon. A large pedunculated polyp in the lower part of the rectum may prolapse through the anus. A large villous adenoma may manifest as watery diarrhea; in rare instances it causes fluid and electrolyte imbalance. Intermittent abdominal pain from recurrent intussusception or spasm may occur with a large colonic polyp but is unusual. Mild anemia may follow chronic bleeding from an ulcerative polyp. With a small polyp, up to 8 mm, biopsy and electrocoagulation can be performed, preferably using a "hot" biopsy forceps for histopathologic examination. A large polyp should be completely snared or excised and sent for histopathologic

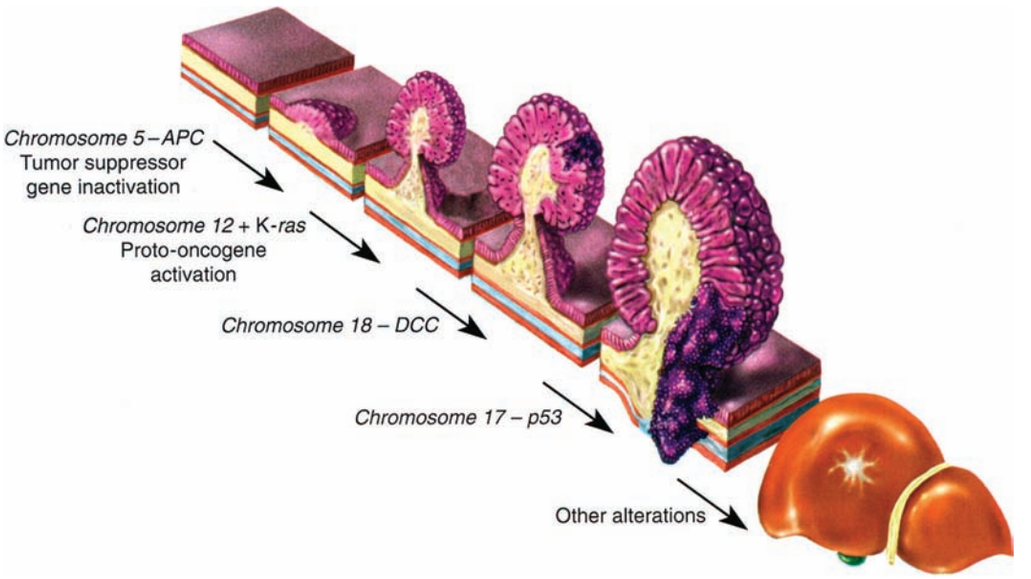

FIGURE 6 ■ A genetic model for the adenoma-carcinoma sequence. Tumorigenesis proceeds through a series of genetic alterations that accumulate. The histopathologic stages of colorectal tumor development are shown with increasing size and dysplasia until an invasive carcinoma is formed. *Abbreviations*: DCC, deleted in colon cancer; APC, adenomatous polyposis coli. *Source*: Modified from Ref. 26.

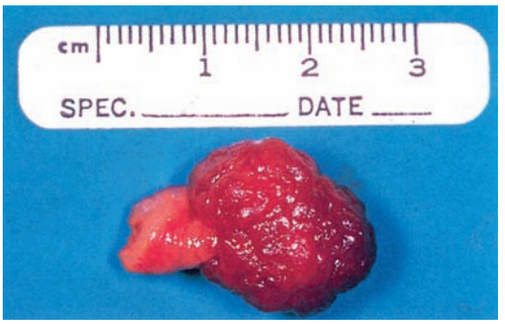

FIGURE 7 ■ Pedunculated polyp.

examination. A biopsy of a large polyp does not represent the entire lesion and presents difficulty in the interpretation of an invasive carcinoma. Occasionally, biopsy may cause displacement of the gland into the submucosa and can be misinterpreted as an invasive carcinoma (27). This pseudoadenomatous invasion can also be caused by trauma from hard feces, repeated twisting of the stalk with subsequent ulceration of the surface (28).

Management of Benign Adenomas

Colonoscopy has revolutionized the management of large bowel polyps. Most polyps throughout the entire colon and rectum can be excised through the colonoscope with minimal morbidity. At the present time, colonic resection or colotomy and polypectomy are reserved for cases in which colonoscopic polypectomy cannot be performed, such as lesions that are too large or too flat, or when the colonoscope cannot be passed to the site of the polyp.

Most pedunculated polyps can be snared in one piece since the pedicles are rarely >2 cm in diameter. Sessile polyps <2 cm usually can be snared in one piece. Large sessile polyps should be snared piecemeal and in more than one session as appropriate. Excised polyps must be prepared properly and sectioned so that all the layers can be examined microscopically and the evidence of invasive carcinoma detected.

Adenomas in the rectum present a unique situation. These lesions can be palpated with finger, suction, or endoscope. If there is no induration, the chance that a lesion is benign is 90% (29,30). There are a number of ways to remove a large adenoma in the rectum, including proctoscope or a colonoscope, per anal excision, trans anal endoscopic microsurgery and posterior proctotomy (see Chapter 19).

Patients with a neoplastic polyp have a higher risk of developing another polyp; so follow-up colonoscopy is advised. After the colon and rectum are cleared of polyps, follow-up colonoscopy every three to five years is adequate. A large sessile polyp, particularly villous type, is prone to recur, and a follow-up check of the polypectomy site should be done every 3 to 6 months the first year, every 6 to 12 months the second year, and every year thereafter to the fifth year. Then colonoscopic examination every three to five years is appropriate.

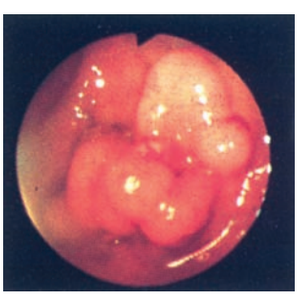

FIGURE 8 ■ Sessile polyp.

The Flat Polyp

In 1985, Muto et al. (31) called attention to a separate type of polyp called a "flat" adenoma. This type of polyp is unique in that it is usually small and flat, often with a central depression, and is difficult to detect with colonoscopy or even with the resected colon and rectal specimens. Ninety percent of flat adenomas are <1 cm and more than half are less than 5 mm (32). The significance of flat adenomas is the high incidence of carcinomas, which occur in 6% of patients, even when the lesions are as small as 2 to 4 mm, and rapidly rise to 36% when the lesions are 9 to 10 mm. Approximately 10% of the adenomas in the Muto series were flat adenomas. They were most frequently located in the left colon and the rectum. Lynch et al. (33) found similar flat adenomas in patients who were members of the same kindred under study for HNPCC. Most of the lesions were in the right colon. The flat adenomas, originally thought to occur mostly among Japanese, have also been found in studies from Australia, Canada, and the United Kingdom (32).

In a prospective study of 1000 executive patients attending for colonoscopy, flat or depressed lesions were examined by Rembacken et al. (34). Patients were not preselected and the indications were similar to other units in the United Kingdom. A flat adenoma was defined as mucosal elevations with a flat or slightly rounded surface and a height of less than half the diameter of the lesion. In practice, most flat adenomas were less than 2 mm in height and only very broad lesions were 5 mm high. During the examination, they used 0.2% indigo carmine dye, 3 to 6 mL, sprayed directly onto suspicious areas. Magnifying colonoscopy was also used.

The authors identified 321 adenomas, 119 (37%) were flat and 4 (1%) appeared depressed. Fifty-four percent of the flat or depressed lesions were situated between splenic flexure and rectum.

Seventy of the flat lesions (59%) were <10 mm in size (mean, 5 mm) and 4% had early carcinoma (invasive into submucosa); 49 flat lesions (41%) were >10 mm (mean, 21 mm), and 29% had early carcinoma. The mean size of the depressed lesions was 9 mm and three of four (75%) had early carcinoma, indicating their aggressiveness compared to other types of lesions.

Rembacken et al. (34) suggested, "Western colonoscopists refuse training in the recognition of flat, elevated and depressed lesion in order to detect colorectal neoplasms in their early stages." The readers should note that in this study, all of the patients had indications for colonoscopic examinations and not as a screening examination for low risk asymptomatic patients. In response to an editorial comment (35), Rembacken et al. wrote (34), "The use of indigo carmine dye is paramount to the detection of flat and depressed lesions and only takes a few seconds. Without the dye, it is difficult to evaluate non-polypoid

lesions because they generally appear to be erythematous patches, easily mistaken for scope trauma. The magnifying colonoscope does not help in the initial recognition of lesions but allows the endoscopists to assess the crypt pattern and predict the histology.''

Recent molecular analysis of such flat adenomas suggests that they are etiologically distinct from other polypoid adenomas (36). The mutation rate and the K-*ras* gene are both significantly reduced (16% in flat adenomas compared to 50% in ordinary colorectal adenomas) and do not occur in the same codons. The management of flat adenomas is the same as for sessile adenomas.

Why Remove a Polyp?

It has generally been accepted that most colorectal carcinomas are derived from benign adenomas through the adenoma-carcinoma sequence. It takes about five years from a clean colon to the development of an adenoma and about 10 years from a clean colon to the development of invasive carcinoma (13). Thus, removal of an adenoma is prophylactic against the development of colorectal carcinoma. Gilbertsen (37), in a retrospective study, showed that removal of rectal polyps in patients under surveillance with yearly rigid proctosigmoidoscopy results in a lower than expected incidence of rectal carcinoma. This result was confirmed by Selby et al. (38) in a case-control study using rigid proctosigmoidoscopy; screening examination produced a 70% reduction in the risk of death from rectal and distal sigmoid carcinoma. The National Polyp Study also showed that colonoscopic polypectomy results in a lower than expected incidence of colorectal carcinoma (39).

Most adenomatous polyps found on routine examination with rigid proctosigmoidoscopy, or through flexible sigmoidoscopy are small and have a minimal risk of harboring a carcinoma. Because we do not know, whether these small adenomas will continue to grow with eventual degeneration into an invasive carcinoma, their removal is logical provided it can be performed with minimal or no risk of complications. This approach also gives the opportunity to clear the colon and rectum and thus extends the follow-up time to several years. Another point of concern is whether the patient has a synchronous polyp or polyps more proximally and, if so, whether it is important to have it (or them) removed. The incidence of synchronous polyps beyond the reach of the rigid proctoscope or flexible sigmoidoscope is approximately 50% (6). However, most of these polyps are small and have little clinical significance.

It is debatable whether a total colonoscopy should be performed in every person in whom a small polyp is found in the rectum or sigmoid colon. A small hyperplastic polyp frequently found in the rectum or sigmoid has no malignant potential, nor has it been shown to predict an adenoma in the proximal colon (40–42); therefore no further evaluation or follow-up is indicated. Church (43) studied diminutive (1–5 mm) and small (6–10 mm) adenomas of the colon and rectim and found that although the risk of invasive carcinoma was low (0.1 % and 0.2%, respectively) the risk of severe dysplasia was significant (4.4% and 15.6%, respectively). He advised a cold excision or a hot snare as appropriate (Table 3).

A retrospective study using death from carcinoma as the end point, Atkin et al. (44) showed that the risk of development of carcinoma in the proximal colon is significant if the adenoma found in the rectum or sigmoid colon is >1 cm, if the polyp has a villous component, and if there are multiple adenomas. The authors also found that if a tabular adenoma found in the rectum or sigmoid colon is ≤ 1 cm. This risk of carcinoma remote to these sites is insignificant.

TABLE 3 ■ Risk of Diminutive and Small Adenomas

Size (mm)	No.	Severe Dysplasia (%)	Invasive Carcinoma (%)
1–5 (diminutive)	2066	4.4	0.1
6–10 (small)	418	15.6	0.2

No effect of age, site, or family history.
Source: From Ref. 43.

Natural History of Untreated Large Bowel Adenomas

A retrospective review of patients from the pre-colonoscopic era by Stryker et al. (45) analyzed 226 patients who had colonic polyps $\geq$10 mm in diameter and in whom periodic radiographic examination of the colon was elected over excision. Twenty-one invasive carcinomas were identified at the site of the index polyp at a mean follow-up of 108 months (range, 24–225 months). The risk of having a polyp $\geq$1 cm in size develop into an invasive carcinoma at 5, 10, and 20 years was 2.5%, 8%, and 24%, respectively.

Further study of this same group of patients by Otchy et al. (46) revealed that the cumulative probability of developing an invasive metachronous carcinoma at a site different from the index polyp was 2% at five years, 7% at 10 years, and 12% at 20 years. Over a median duration of polyp surveillance of 4.8 years (range, 1–27 years), 11 (5%) of the index polyps disappeared, 129 (57%) had no growth noted, and 86 demonstrated growth. Forty-two of the 86 polyps (49%) had at least a twofold increase in size. Seventy-one of the 86 polyps were removed, and 24 (34%) were carcinomatous. Fifteen of the 86 polyps that increased in size were not removed, and none of these patients developed a carcinoma. Forty-three of the 129 polyps that did not grow were eventually removed. Five of those polyps had carcinoma and one of these patients also developed a metachronous carcinoma at a later date. In addition, two of the 43 patients developed a colon carcinoma in areas distant from the site of the index polyp.

These data further support the recommendation for excision of all colonic polyps $\geq$10 mm in diameter and a periodic examination of the entire colon. Although this study has limitations inherent to any retrospective analysis, comparable prospective data are unlikely to be available in the future because of the widespread availability of colonoscopy and the compelling evidence to recommend the removal of neoplastic polyps.

What Happens to Smaller Adenomas?

Hofstad et al. (47) prospectively studied the growth of colorectal polyps. Colonoscopy was performed in 58 subjects. Polyps $\geq$10 mm were removed; polyps <5 mm, and 5 to 9 mm were left behind for a follow-up study. Colonoscopy

was followed-up by one investigator once a year. On the third year, polyps were removed by snare or hot biopsy. The measurement of the polyps was performed by a measuring probe plus photography. On the third year, 7 of 58 patients had only hyperplastic polyps. Twenty-nine individuals had one adenoma, 17 individuals had two to three adenomas, 5 individuals had four to five adenomas. Twenty-five percent of all the adenomas were unchanged in size whereas 40% displayed growth and 35% showed regression or shrinking in size. Adenomatous polyps < 5 mm showed a tendency to growth, while the adenomas 5 to 9 mm showed a tendency to reduction in size. The hyperplastic polyps showed a similar pattern. There was a tendency to increase growth in the adenomatous polyps in the younger age groups reaching significance from initial examination to the third year and from the first to the second year of re-examination. Moreover, in the patients with four to five adenomas at the initial examination, the polyps showed larger growth than the polyps in patients with only one or two to three adenomas. There were no differences in polyp growth between the sexes. A similar prospective study by Bersentes et al. (48) on adenomas of the upper rectum or sigmoid colon, size 3 to 9 mm, showed no regression or consistent linear growth rates with a 2 year follow-up.

In the study by Hofstad et al. (47), 86% of the individuals had at least one new polyp during the 3 years and 75% had at least one new adenoma. The newly discovered polyps were significantly smaller than the average size at initial examination. They were also more frequent in the proximal part of the colon (71%) than the polyps discovered at initial examination (38%). There were more new adenomas among those with more than four to five adenomas at initial examination, than those with one adenoma, reaching significance from initial examination to the first year of examination and from initial examination to third year. There were more new adenomas among patients ≥ 60 years of age than those < 60 years. No differences were found between the sexes.

Management of Adenomas with Invasive Carcinoma

The term ''invasive carcinoma'' is applied only when the malignant cells have invaded the polyp, either sessile or pedunculated, partially or totally, through the muscularis mucosa into the submucosa. Carcinoma superficial to the muscularis mucosa does not metastasize and should be classified as atypia (rather than carcinoma in situ or superficial carcinoma) (13). For this type of lesion, complete excision is all that is necessary. Follow-up of these polyps is the same as for benign polyps.

A polyp with invasive carcinoma or a malignant polyp is an early carcinoma. For the TNM classification, it is a $T_1N_xM_x$. Local excision for a malignant polyp can be curative if the lession can be adequately excised and if the lession has not spread to the regional lymph nodes or if there are no distant metastaces.

In 1985, Haggitt et al. (44) proposed a classification for polyps with adenocarcinoma according to the depth of invasion as follows (Fig. 9):

Level 0—Carcinoma in situ or intramucosal carcinoma. These are not invasive.

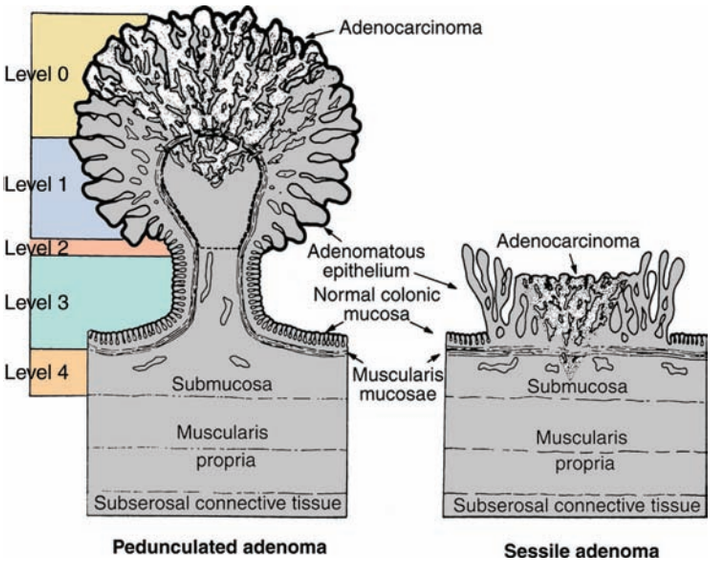

FIGURE 9 ■ Anatomic landmarks of pedunculated and sessile adenomas. *Source*: From Ref. 49.

Level 1—Carcinoma invading through the muscularis mucosae into the submucosa but limited to the head of the polyp (i.e., above the junction between the adenoma and its stalk).

Level 2—Carcinoma invading the level of the neck of the adenoma (junction between adenoma and its stalk).

Level 3—Carcinoma invading any part of the stalk.

Level 4—Carcinoma invading into the submucosa of the bowel wall below the stalk of the polyp but above the muscularis propria. By definition, therefore, all sessile polyps with invasive carcinoma are in level 4.

Pedunculated Polyp with Invasive Carcinoma

Using Haggitt classification, the risk of lymph node metastasis for pedunculated polyp Haggitt level 1, 2, and 3 is low (49–52). For these lesions, a complete snaring or a transanal excision is adequate. A close follow-up examination with endoscopy to detect a local recurrence should be performed every 3 to 6 months for the first year. This period can be extended to every 6 to 12 months in the second year and to every year for the next 2 years. Thereafter, endoscopy every 3 years is adequate. There have been reports in the literature that undifferentiated carcinoma and invasion of the malignancy into the lymphatic or vascular channels have a high risk of lymph node metastasis. In such situations, bowel resection should be performed even though the invasion is limited to the head of the polyp (53–57). A pedunculated polyp with level 4 invasion is treated the same way as a sessile lesion.

Sessile Polyp with Invasive Carcinoma

The Haggitt classification has been widely used for pedunculated polyps with invasive carcinoma in the United States but it is not adequate for sessile lesions. In 1993, Kudo (58) classified the submucosal invasion of the sessile lesions into three levels (Fig. 10):

Sm1—invasion into the upper third of the submucosa.
Sm2—invasion into the middle third of the submucosa.
Sm3—invasion into the lower third of the submucosa.

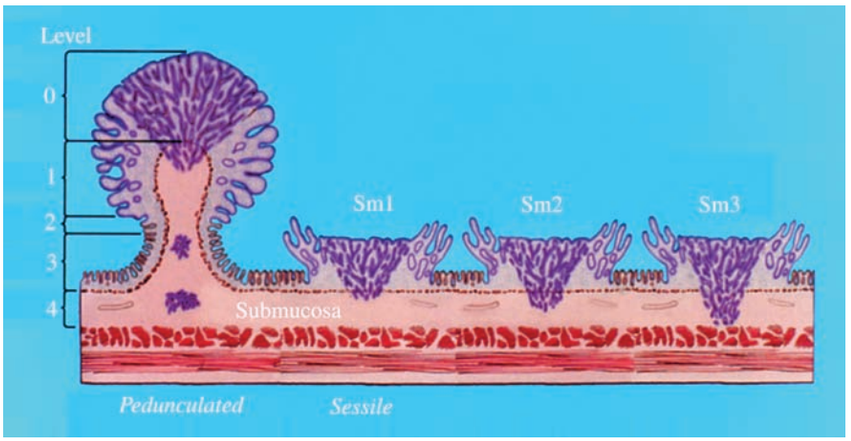

FIGURE 10 ■ Incorporation of Haggitt classification to Sm system. *Abbreviations*: Sm1 = Invasion into upper ⅓ of submucosa. Sm2 = Invasion into middle ⅓ of submucosa. Sm3 = Invasion into distal ⅓ of submucosa. Haggitt's pedunculated levels 1, 2, 3, are all in Sm1; pedunculated level 4 can be Sm1, Sm2, or Sm3. *Source*: With permission from the Mayo Foundation.

The consensus workshop in Paris on November 30 to December 1, 2002, recommended Sm system for early carcinoma of the large bowel (59). The Sm system appears to be effective and practical. In the series by Nascimbeni et al. (60), the pathologist could evaluate the depth of invasion into Sm1, Sm2, and Sm3 in 97% of the cases. In fact, the Haggitt level for the pedunculated lesion can be incorporated into the Sm system (Fig. 10). The endoscopists must properly prepare the specimens and the pathologists must properly section them in order to examine the entire layers.

Among the increased risk factors for early colorectal carcinoma reported in the literature are: lymphovascular invasion, poor differentiation, gender, extensive budding, micro-acinar structure, flat or depressed lesions, and depth of invasion in submucosa (61). Recent studies with multivariate analysis showed the independent risk of lymph node metastasis in early carcinoma of rectum to be: lymphovascular invasion and invasion into the depth of the submucosa (Sm3) (60,62). When the rectum was divided into three levels, Nascimbeni et al. (60) showed that the lower third of rectum had a high risk of lymph node metastasis.

Some sessile lesions with invasive carcinoma < 2 cm in diameter in the colon, upper third and middle third of rectum can be adequately snared in one piece via colonoscopy. A microscopic free margin of at least 2 mm is considered adequate (53). A malignant lesion that is removed piecemeal requires further excision or resection. A sessile lesion that has high risk factors such as lymphovascular invasion and deep invasion into Sm3 level should have an oncologic resection. In case of a lower third rectal lesion, a full thickness transanal excision is required. Some authors advise postoperative radiation or chemoradiation (63–65); some series showed no advantage, or showed high recurrence rate (66,67). Benson et al. (67) reported a series of 21 patients with T1 adenocarcinoma of the lower third of the rectum (median 4 cm from anal verge) underwent radiation therapy without chemotherapy after a local transanal excision, the recurrence at five years was 39% and the disease-free survival at 5 years was 59%.

A sessile polyp with invasive carcinoma or an early carcinoma of the low rectum is unique in that in spite of favorable histopathologic parameters, a full thickness transanal excision has a high recurrence rate from 7% to 29% and a cancer-specific 5-year survival of 74% to 95% (Table 4) (66,68–70). In a retrospective study by Nascimbeni et al. (70) on the outcome comparing transanal local excision to oncologic resection for T1 carcinoma of low rectum revealed that for carcinoma of middle-third rectum or lower-third rectum, the 5-year and 10-year outcomes were significantly better for overall survival and cancer-free survival in the oncologic resection group. Local recurrence and distant metastasis were not significantly different. When it came to T1 carcinoma of the lower-third rectum, the authors showed the oncologic resection group had a trend of improved survival but was not statistically significant, possibly because of low statistical power from the small sample size.

Suitable cases of T1 carcinoma of rectum for a transanal excision are uncommon. Some authors recommended to do it even fewer (69). Transanal excision for a sessile polyp with invasive carcinoma, or a T1 carcinoma of the low rectum has a three to fivefold higher risk of carcinoma recurrence compared with patients treated by radical resection (71). Waiting to perform a radical resection after a local recurrence is a poor choice. In most series, the cancer-free survival for salvage resection in these patients is 50% to 56% (68,69). On the other hand, an immediate radical resection after local excision (within 1 month), gives a better prognosis, 94% cancer-free survival at 10 years and is comparable to primary resection in a case-controlled comparison (72).

In short, local excision for a sessile polyp with invasive carcinoma (T1) of the lower third of rectum has high local recurrence. It appears that the early lesion at this site is a locally disseminated disease. To improve the outcome, the recurrence rate has to be improved: options include doing more radical resection in young and good health patients;

TABLE 4 ■ **Selected Series of Local Recurrence and Survival After Transanal Excision for T1 Carcinoma of the Rectum**

Institution	No.	LR (%)	5-Yr Survival (%, CSS)	F-U (mo)
University of Minnesota (68)	69	18	95	52
Memorial Sloan-Kettering (66)	67	14	74	60
Cleveland Clinic (69)	52	29	75	55
Mayo Clinic (70)	70	7	89	60

Abbreviations: LR, local recurrence; CSS, cancer-specific survival; F-U, follow-up.

finding a better adjuvant therapy; or finding better ways in selection of patients, such as molecular markers in the future.

Serrated Adenoma

This is the term coined by Longacre and Fenoglio-Preiser in 1990 (73) to describe a new entity of mixed hyperplastic polyp/adenomatous polyp. In their study of 110 serrated adenomas, compared to 60 traditional adenomas and 40 hyperplastic polyps, they found that these lesions distributed throughout the colon and rectum, with a slight preponderance of large lesions (>1 cm) occurred in the cecum and appendix.

There are two types of mixed epithelial polyps: one in which adenomatous and hyperplastic glands are mixed (Fig. 11A), and one in which the adenoma has a serrated appearance on microscopic examination (Fig. 11B). Microscopic examination of the lesions shows goblet cell immaturity, prominent architectural distortion, cytologically atypical nuclei, rare upper zone mitoses, and absence of a thickened collagen table (73,74).

Grossly the lesion is flat and smooth; it may look like a plaque or thickened mucosa on colonoscopic examination (Fig. 12). This type of lesion can be easily missed on colonoscopy if the colon is overdistended stretching it flat or underdistended causing wrinkle on mucosa to mask it. Unlike the classic hyperplastic polyps that are small and

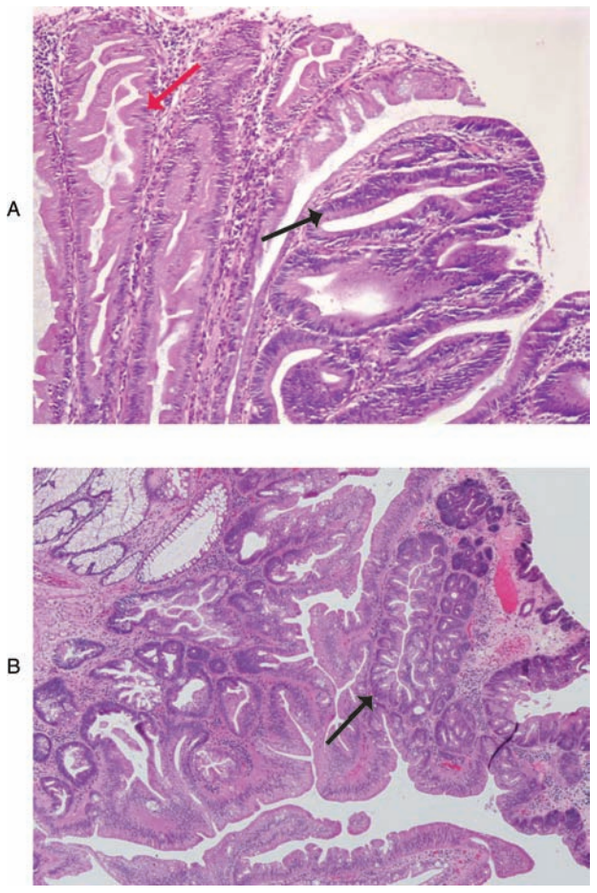

FIGURE 11 ■ (**A**) Mixed hyperplastic gland (*red arrow*) and adenomatous gland (*black arrow*). (**B**) Adenomatous gland with serrated appearance (*arrow*). *Source*: Courtesy of Thomas C. Smyrk, M.D., Mayo Clinic, Rochester, MN, U.S.A.

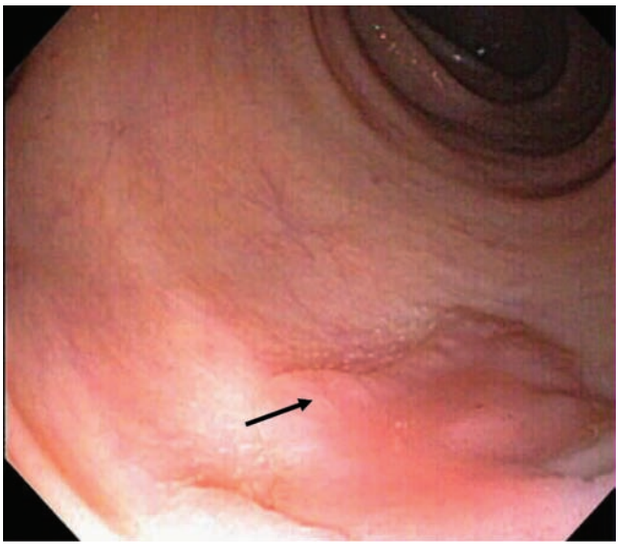

FIGURE 12 ■ Plaque-like serrated adenoma in transverse colon.

restricted to the rectum and rectosigmoid colon, serrated adenomas are larger and occur in both proximal and distal colon and rectum (75). Some of the individuals previously reported as having multiple hyperplastic polyps could instead have had multiple serrated adenomatous polyps (73).

Clinical Importance of Serrated Adenoma

Based on the observation that 11% of serrated adenomas in the series of Longacre and Fenoglio-Preiser (73) contained foci of intramucosal carcinoma, it was surmised that an individual lesion would carry a significant malignant potential. Nevertheless, the rarity of serrated adenoma (0.6% of colorectal polyps) would minimize their contribution to the overall burden of colorectal malignancy (76). Torlakovic and Snover (74) reported six patients with serrated adenomatous polyposis. Each patient had at least 50 polyps, ranging from 0.3 to 4.5 cm in size, mostly sessile. Three patients had diffuse polyps, two patients had the polyps in the left colon, and one patient had them in the right colon. Four patients had carcinoma.

Why are serrated adenomas infrequently observed in endoscopic practice? The answer may lie partly in under diagnosis and partly in their rapid evolution to carcinoma. The latter suggestion is supported by the demonstration of DNA microsatellite instability in mixed polyps and serrated adenomas and by analogy with the aggressive adenomas in hereditary nonpolyposis colorectal cancer (HNPCC) (76).

Genetics

The known alterations include K-*ras* mutation, low and occasional high level microsatellite instability, 1pLOH, and methylation of HPP1/TPEF (a putative anti-adhesion molecule). Additional genetic alterations may be observed in neoplastic subclones occurring within or adjacent to hyperplastic polyps. These include loss of expression of MGMT or hMLH1 (77).

Sporadic MSI-L and MSI-H carcinomas may evolve through the serrated adenoma pathway (76). The serrated adenoma pathway is likely to show marked molecular heterogeneity, but patterns are beginning to emerge. The view

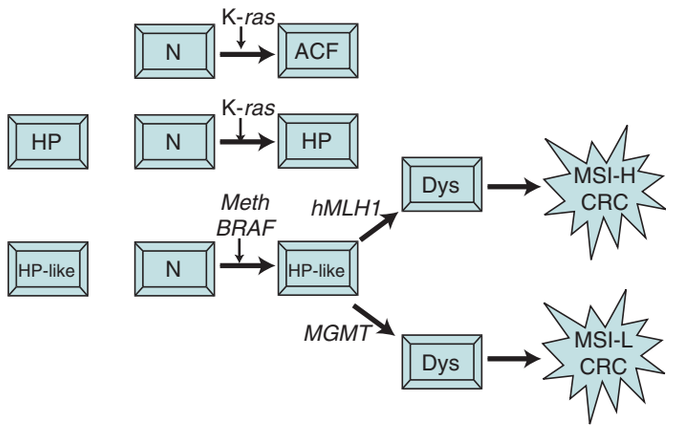

FIGURE 13 ■ Possible key steps in three pathways to aberrant crypt foci (ACF), hyperplastic polyp, and hyperplastic-like polyp or small serrated adenoma. (See details in text.) *Abbreviations*: N, Normal mucosa; HP, hyperplastic polyp; Meth, methylation; BRAF, a gene encoding a kinase that is regulated by K-ras; DYS, dysplasia; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; CRC, colorectal carcinoma. *Source*: From Ref. 77.

that all, or even most, colorectal carcinomas are initiated by mutation of APC gene and evolve through the classical adenoma-carcinoma sequence may no longer be tenable. This understanding will surely transform our approach to the early detection and prevention of colorectal carcinoma (76).

Figure 13 illustrated the possible key steps in three pathways to ACF, hyperplastic polyp, and hyperplastic-like polyp or small, serrated adenoma. The molecular steps that determine growth of ACF into hyperplastic polyp are not known. Colorectal carcinoma is envisioned to arise from hyperplastic-like polyps (or sessile serrated polyps) in which the earliest events might be BRAF mutation synergizing with a methylated and silenced pro-apoptotic gene. Subsequent methylation of hMLH1 or MGMT then predisposes to mutation, dysplastic change, and finally to malignancy that is frequently characterized by MSI-H or MSI-L status. K-*ras* mutation may substitute for BRAF in methylator pathways culminating in MSI-L and some MSS colorectal carcinomas (78).

Management

Serrated adenomas are neoplastic polyps. The treatment is the same as in adenomatous polyps.

■ HAMARTOMATOUS POLYPS

A hamartoma is a malformation or inborn error of tissue development characterized by an abnormal mixture of tissues endogenous to the part, with excess of one or more of these tissues. It may show itself at birth or by extensive growth in the postnatal period.

Juvenile Polyps and Juvenile Polyposis

Juvenile polyps characteristically occur in children, although they may present in adults at any age. This type of polyp is a hamartoma and is not pre-malignant. Macroscopically they are pink, smooth, round, and usually pedunculated. The cut section shows a cheeselike appearance from dilated cystic spaces. Microscopic pictures show dilated glands filled with mucus and an abnormality

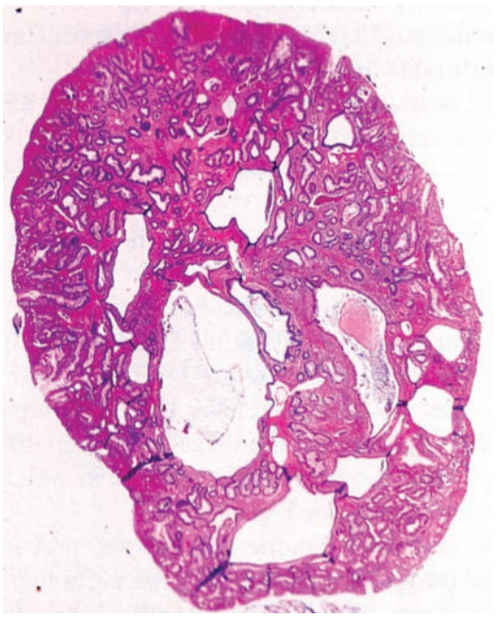

FIGURE 14 ■ Juvenile or retention polyp. Note the Swiss-cheese appearance from dilated glands.

of the lamina propria, which has a mesenchymal appearance (Fig. 14). The muscularis mucosa does not participate in the structure of the polyp. Bleeding from the rectum is a common finding. A moderate amount of bleeding can occur if the polyp is auto-amputated, a phenomenon not seen in other types of polyps. Intussusception of the colon occasionally occurs if the polyp is large. Treatment is by excision or snaring through a colonoscope or a transanal excision.

Juvenile polyposis is an entity characteristically and biologically distinct from solitary juvenile polyp or other polyposis. The condition was first observed by McCall et al. in 1964 (79). The term juvenile polyposis rather than juvenile polyposis coli is to be preferred as polyps are also found in the stomach and the small intestine (80). There are two types of juvenile polyposis: in infancy and in other variable age of onset (81).

Juvenile Polyposis of Infancy

Juvenile polyposis of infancy is a rare form. No family history is found. The infant presents with diarrhea, either bloody or mucinous, anemia, protein-losing enteropathy, intussusception; rectal prolapse develops between 8 and 10 months of age and leads to significant morbidity (81,82). The entire gastrointestinal (GI) tract is usually affected; the prognosis depends on the severity and extent of GI involvement. Death occurs before the age of 2 years in severe cases (80).

Surgery is indicated in cases of intussusception, or polypectomies in cases of rectal prolapse to reduce the leading point of the prolapse. Supportive care to replace fluid and electrolytes or total parenteral nutrition as indicated (82).

Juvenile Polyposis in Childhood and Adult

The majority of patients with juvenile polyposis manifest in their first or second decade but in 15% of patients, the diagnosis is delayed until they are adults. They usually present

with rectal bleeding and anemia. Family history of juvenile polyposis is found in 20% to 50% of patients. Various extracolonic abnormalities, described in 11% to 20% of cases, have included digital clubbing, pulmonary arteriovenous fistula, macrocephaly, alopecia, bony swellings, cleft lip, cleft palate, supernumerary teeth, porphyria, arteriovenous malformation affecting the skin, psoriasis, congenital heart disease, malrotation of the gut, abnormalities involving the vitello-intestinal duct, double renal pelvis and ureter, acute glomerulonephritis, undescended testes, and bifid uterus and vagina (80).

Patients with juvenile polyposis usually have 50 to 200 colorectal polyps and a proportion have polyps in the stomach and small intestine. Some patients seem to have relatively few polyps, but these tend to be the parent of the prospectus. It is conceivable that the juvenile polyps are produced only within the first few decades and are subsequently lost through autoamputation. Thus, juvenile polyposis may be diagnosed when a relatively old and asymptomatic parent is screened colonoscopically and the smallest number of polyps found on this basis is 5 (81).

Jass et al. (81) proposed a working definition of juvenile polyposis:

1. More than five juvenile polyps of the colorectum.
2. Juvenile polyps throughout the GI tract.
3. Any number of juvenile polyps with a family history of juvenile polyposis.

On the other hand, Giardiello et al. (83) suggested that the patients with as few as three juvenile polyps should undergo screening for colorectal neoplasm.

A Precancerous Condition

Although there is no evidence that isolated juvenile polyp could be malignant, it is now well established that juvenile polyposis is a precancerous condition (81,84–87). The risk of GI malignancy in affected members of juvenile polyposis kindred exceeds 50% in a series of kindred reported by Howe et al. (84).

In a classic paper on juvenile polyposis, Jass et al. (81) studied 87 patients with juvenile polyposis recorded in the St. Mark's Polyposis Registry, including 1032 polyps and 18 patients with colorectal carcinoma. They found that about 20% of juvenile polyps did not conform to the classical description. Grossly, they formed lobular mass (instead of spherical). These atypical juvenile polyps also revealed relatively less lamina propria and more epithelium than that found in the more typical variety and often adopted a villous or papillary configuration. Epithelial dysplasia occurred in both typical and atypical juvenile polyps but was very much more frequent in the latter. Nearly 50% of the atypical juvenile polyps showed some degree of dysplasia; these resembled adenomatous dysplasia. Eighteen patients in this series had colorectal adenocarcinoma with a mean age of 34 years (range 15–59 years). A high proportion of carcinomas were mucinous and/or poorly differentiated and this is in accord with case reports from other authors.

There is little direct information on the histogenesis of carcinoma in juvenile polyposis. Dysplasia has been shown to occur in two forms: (*i*) a focus of adenomatous change within a polyp, (*ii*) an adenoma showing no residual juvenile features (81).

On the mechanism of polyp-cancer sequence in juvenile polyposis, Kinzler and Vogelstein (85) postulated, ''an abnormal stroma can affect the development of adjacent epithelial cells is not a new concept. Ulcerative colitis is an autoimmune disease that leads to inflammation and cystic epithelium in the mucosa of the colon. Initially, the imbedded epithelium shows no neoplastic changes, but foci of epithelial neoplasia and progression to cancer eventually develops in many cases. The regeneration that occurs to replace damaged epithelium may increase the probability of somatic mutations in this abnormal microenvironment. The increased risk of cancer in juvenile polyposis syndrome and ulcerative colitis patients, therefore, seems primarily the result of an altered terrain for epithelial cell growth and can be thought of as a *landscaper defect*.''

Genetics

Juvenile polyposis is an autosomal dominant condition (84). The germ-line mutation is in the gene SMAD-4 (also known as DPC-4), located on chromosome 18q21.1 (88,89).

Management and Surveillance

There is no good information about prophylactic colectomy or proctocolectomy to prevent occurrence of carcinoma. The decision on performing the operation should be dictated by the number and the site of the polyps. Polyps of the colon and rectum that are too numerous for colonoscopy and polypectomies should have an abdominal colectomy with ileorectal anastomosis (IRA) or proctocolectomy with ileal pouch-anal anastomosis (IPAA) or an ileostomy (80,86,90,91).

In a series reported by Onsel et al. (90), 5 of 10 patients who underwent colectomy with IRA for juvenile polyposis required a subsequent proctectomy with a mean follow-up of 9 years (range 6–34 years). This and other studies suggest that proctocolectomy with ileoanal pouch procedure may be a better option as an initial operation (90,91).

The proband and relatives of the first degree should be screened, probably starting in the later teen years, by upper and lower GI endoscopy. If this initial screen is negative, a follow-up endoscopy should be performed every 3 years (92). For patients who have had a colectomy or an ileoanal pouch, surveillance should be performed periodically (90,91).

Howe et al. (93) recommended genetic testing as part of the workup. However, given the presumed genetic heterogeneity of this syndrome, failure to show a mutation in SMAD-4 does not support lengthening the surveillance interval to 10 years as they suggested (90).

Peutz-Jeghers Syndrome

PJS is a rare autosomal dominant disease characterized by GI hamartomatous polyposis and mucocutaneous pigmentation. It was originally described by Peutz in 1921 but was not clearly identified until attention was brought to it by Jeghers, McKusick, and Katz (94) in 1949. The syndrome comprises of melanin spots of buccal mucosa arid lips; the face and digits may be involved to a variable extent, but mouth pigmentation is the sine qua non of this portion

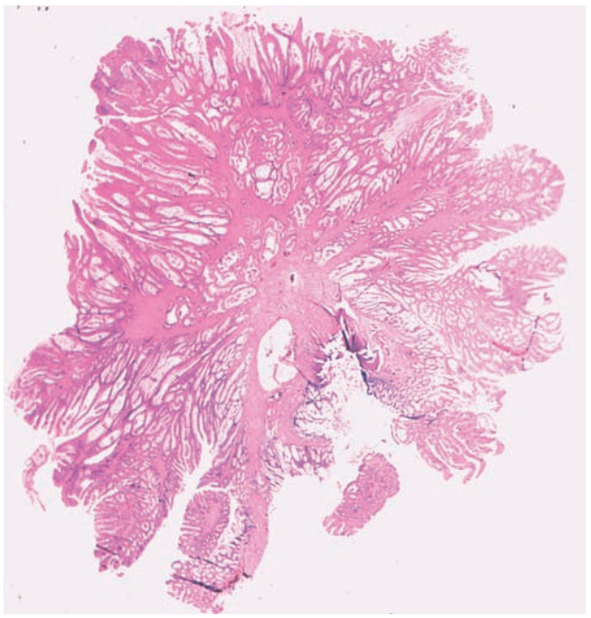

FIGURE 15 ■ Peutz-Jeghers polyp. Note Christmas-tree appearance from branching of muscularis mucosa.

of the syndrome. The presence of polyps in the small bowel is a constant finding of this syndrome, but the stomach, colon, and rectum also may be involved. The characteristic Peutz-Jeghers polyp has an abnormal muscularis mucosa branching into the lamina propria, giving the appearance of a Christmas tree (Fig. 15).

Diagnosis

Giardiello et al. (95) defined a definitive diagnosis of PJS by the presence of histologically confirmed hamartomatous polyps, plus at least two of the following:

1. Family history of the syndrome.
2. Labial melanin deposits.
3. Small bowel polyposis.

The diagnosis is ''probable'' if two of the three clinical criteria described above are present but without histopathological verification of hamartomatous polyps (95). Genetic testing may then be used to confirm the diagnosis (96).

For patients without a family history of PJS, definitive diagnosis depends upon the presence of two or more histologically verified Peutz-Jeghers type hamartomatous polyps (97). For patients with a first-degree relative with PJS, the presence of mucocutaneous hyperpigmentation is sufficient for presumptive diagnosis (96).

Genetics

To date, the only identifiable mutations causing PJS affect the serine/threonine-protein kinase 11 (STK11, also known as LKB1) gene, located on chromosome 19p13.3. Although PJS is inherited in an autosomal dominant manner, up to 25% of documented cases are not familial. These sporadic cases are felt to be due to de novo mutations in STK11 or low penetrance variance (96).

Genetic testing for STK11 mutations is available but they have variable sensitivity. In familial cases with a known genetic linkage to STK11, testing carries a sensitivity of 70%. In sporadic cases, genetic testing has sensitivity ranging from 30% to 67%. A significant proportion of familial and sporadic Peutz-Jeghers cases may result from mutations in genes other than STK11 (96).

High Risk of Cancers

It is a well-known fact that patients with PJS have high risk of developing cancer in many parts of the body. However, the risk varies depending on how the studies are undertaken. Giardiello et al. (98) conducted an individual patient metaanalysis to determine the relative risk (RR) of malignancy in patients with PJS compared with general population. The authors used strict criteria for the analysis. Searches of MEDLINE EMBASE, and referenced articles yielded 94 articles. Only six publications which consisted of 210 individuals qualified for the study. The results showed that the RR for all carcinomas was 15.2. A statistically significant increase of RR was noted for: esophagus (57.0), stomach (213.0), small intestine (520.0), colon (84.0), pancreas (132.0), lung (17.0), breast (15.2), uterus (16.0), ovary (27.0). There was no risk for testicular or cervical malignancy. The cumulative risk for all malignancy was 93% from age 15 to 64 years old.

Carcinoma in Peutz-Jeghers Polyps

Ordinarily, hamartomatous polyps should not degenerate into malignancy. However, there have been reports of invasive adenocarcinoma in Peutz-Jeghers polyps of the small and large intestine, although the risk is not high. Giardiello et al. (95) did not detect invasive carcinoma within hamartomatous polyps in any of their patients. The polyps containing hamartomatous, adenomatous, and malignant components have been observed in Peutz-Jeghers polyps of the small and large intestine (99–103). Spigelman et al. (102) surveyed 72 patients registered with PJS at St. Mark's Polyposis Registry. Four patients had nine carcinomas in hamartomatous polyps in stomach, duodenum, jejunum, and colon. This observation suggests that a hamartomatous, adenomatous, and carcinomatous progression may be important in the development of malignancy in Peutz-Jeghers polyps.

Genetic analysis showed that STK11/LKB1 acts as a tumor suppressor gene and may be involved in the early stages of PJS carcinogenesis (104,105). The results suggest that Peutz-Jeghers related carcinoma have different molecular genetic alteration compared with those found in sporadic GI carcinomas (103).

Peutz-Jeghers–Like Mucocutaneous Pigmentation

Characteristic mucocutaneous pigmentation is often the clinical clue that heralds the diagnosis of PJS. The melanotic or lentiginous pigmented macules are dark brown, blue, or blue-brown and located on the vermillion border of the lips ($>90\%$), buckle mucosa, digits, and occasionally on the periorbital, auricular, perianal, and vulva skin (106). The relevance of PJS-like hyperpigmentation in the absence of other features of PJS is not known. Boardman et al. (106) coined the terms isolated melanotic mucocutaneous pigmentation (IMMP).

To ascertain the risk of malignancy for patients with IMMP, they identified a group of individuals with

mucocutaneous melanotic macules indistinguishable clinically from PJS hyperpigmentation but who did not manifest the other phenotypic characteristics of PJS. To distinguish those patients with possible or definite PJS from those with pigmentation only, the authors applied the diagnostic criteria of Giardiello et al. (95) to define definite PJS. Patients who had PJS-like oral hyperpigmentation only and none of the other criteria of PJS were classified as IMMP. Of 60 patients who had the diagnosis of PJS or PJS-like pigmentation were identified through the patient registry of the Mayo Clinic from 1945 to 1996. Twenty-six unrelated patients were identified with IMMP. There were 16 men and 10 women.

The results showed that 10 individuals developed 12 noncutaneous malignancies including breast ($n=1$), cervical ($n=3$), endometrial ($n=3$), renal ($n=1$), lung ($n=2$), colon ($n=1$), and lymphoma ($n=1$). The median age of diagnosis of noncutaneous malignancy was 47 years (range 33–84 years); this compared to a median age of carcinoma in the general population of 68 years. In their previous review of carcinoma risk in PJS patients, the median age at diagnosis of carcinoma was 38 years (range 16–59 years) (105). The mean interval from the identification of the pigmentation to the development of carcinoma in IMMP patients was 24.2 years, compared to a mean latency period of 19.9 years in PJS patients (103,106). Although the magnitude and gender associations of carcinomas in patients with IMMP and PJS are remarkably similar, the authors detected no alterations in the LKB1 among IMMP patients. Is IMMP an entity distinct from PJS? The overlap in the two conditions of phenotypic pigmentary features and the increased risk of malignancy, specifically of the breast and gynecologic tract in women, support the notion that they might share a common genetic origin. Though none of nine individuals with IMMP had mutations in LKB1, 14% to 42% of patients with definite PJS lack LKB1 mutations, suggesting that another yet to be identified gene or genes may be responsible for cases of both PJS and IMMP not caused by LKB1 mutations (106). Based on the increased RR for gynecologic and breast carcinomas that they detected in their patient population of IMMP, the authors recommend following current screening guidelines for gynecologic and breast carcinoma with thorough evaluation of PJS-like pigmentation. They recommended examination of the GI tract at age 20 years in asymptomatic individuals with PJS-like hyperpigmentation.

Screening

Given the multitude of carcinomas that these patients are susceptible, aggressive screening protocols are recommended. Upper and lower GI endoscopies are indicated for any adolescent or adult suspected of having PJS. Radiographic studies should also be used to screen for distal small intestinal polyps. Pelvic ultrasound of females and gonadal examination in young men is also recommended.

An at-risk, but unaffected relative is a first-degree relative of an individual with PJS who does not meet clinical criteria for PJS. Guidelines for surveillance of affected patients also apply to these at-risk family members. The current guideline for carcinoma screening is summarized in Table 5.

Management of Peutz-Jeghers Polyps

The clinical course of PJS is characterized by asymptomatic periods interspersed with complications such as abdominal pain, intussusception often leading to frank intestinal obstruction, and hemorrhage that is often occult. Small bowel obstruction is the presenting complaint in half of the cases, and exploratory celiotomy due to polyp-induced complications occurs commonly and may do so at quite short intervals (107). Because this problem is coupled with the significant risk of malignancy in the polyps, the surgical approach is now more aggressive. The current approach is to operate on the patient if the small intestinal polyps are larger than 1.5 cm (107,108).

Endoscopic resection of Peutz-Jeghers polyps throughout the small intestine at double-balloon enteroscopy without exploratory celiotomy has been reported to be successful (109). However, in general, an enteroscopy is performed at the time of exploratory celiotomy with polypectomy or resection of the small bowel (110,111). The indications for surgery included obstructing or intussuscepting polyps, polyps larger than 1.5 cm identified radiologically, or smaller polyps associated with iron deficiency anemia (111).

In order to achieve more complete polyp clearance, Edwards et al. (111) analyzed their experience of using intraoperative enteroscopy in conjunction with explore celiotomy. The enteroscope was introduced through an enterotomy at the site of polypectomy for the largest polyps. Depending on the size of the polyps, snare polypectomy, electrocoagulation, or biopsies were performed. In their experience of 25 patients, enteroscopy identified 350 polyps not detected by palpation or transillumination of the bowel by an operating light. All the polyps were removed. There was one early complication of a delayed small bowel perforation at the site of a snare polypectomy that resulted in an urgent reoperation but no long-term sequelae. No patient in this group had required operative polypectomy within four years of polyp clearance by intraoperative enteroscopy, compared with registry data of 4 of 23 patients who had more than one exploratory celiotomy within a year. It appears that intraoperative enteroscopy for PJS improves polyp clearance without the need for additional enterotomies and may help to reduce the frequency of exploratory celiotomy (112).

TABLE 5 ■ Screening Recommendations for Peutz-Jeghers Syndrome

Organs	Age to Begin	Interval (yr)	Procedure
Colon	25	2	Colonoscopy
Gastrointestinal tract	10	2	Upper endoscopy
Pancreas	30	1–2	Endoscopic ultrasound Transabdominant ultrasound
Breast	20	2	Mammography
		1	Self-breast exam
Uterus	20	1	Transvaginal ultrasound Endometrial biopsy
Cervix	20	1	Pap smear
Testicular	10	1	Physical exam, ultrasound if clinically indicated

Source: From Ref. 96.

Cronkhite-Canada Syndrome

Cronkhite-Canada syndrome is characterized by generalized GI polyposis associated with alopecia, cutaneous pigmentation, and atrophy of fingernails and toenails (Onychotrophia). It was first deducted in two patients and described by Cronkhite and Canada in 1955 (113).

Etiology

The etiology is unknown. There is no familial inheritance pattern and no associated gene or mutation has been identified (114).

Clinical Presentations

Diarrhea is a prominent feature of this syndrome, accounting for 46 of 55 patients in the series of Daniel et al. (115). The cause of diarrhea is unknown. Nardone et al. (116) reported a case of Cronkhite-Canada syndrome associated with achlorhydria and hypergastrinemia causing direct gastric wall invasion by gram-negative *Campylobacter pylori*. This may explain the diarrhea in those patients.

Hair loss was noted in 49 of 55 patients. In most patients, hair loss took place simultaneously from the scalp, eyebrows, face, axillae, pubic areas and extremities, but in some only loss of scalp hair was described (115).

Nail changes were reported in 51 of 55 patients. In most of them, the nails showed varying degrees of dystrophy, such as thinning and splitting, and partial separation from the nail bed (onycholysis). Complete loss of all finger and toenails (onychomadesis), over a period of several weeks, was also noted in some patients (115).

Hyperpigmentation was present in 45 of 55 patients, ranging from a few millimeters to 10 cm in diameter. The distribution of pigmentary skin changes could be anywhere, including extremities, face, palms, soles, neck, back, chest, scalp, and lips (115).

Other manifestations include nausea, vomiting, weakness, weight loss, abdominal pain, numbness and tingling of extremities (115).

Electrolyte disturbances are a prominent feature and appear to reflect malabsorption and losses from the GI tract. Total serum protein is also found to be low in most patients due to excessive enteric protein loss (115).

The Polyps

From radiologic, endoscopic, and autopsy data, the stomach and large intestine were involved in 53 of 55 cases. The actual frequency of small bowel involvement would be inaccurate because the small bowel X-rays and biopsies were not performed in every case, in the series of Daniel et al. (115). From the autopsy data, the number of polyps were greatest in the duodenum, less in the jejunum and proximal ileum, and again increased in the terminal ileum (115).

The polyps consist of cystic dilatation of the epithelial tubules similar to that of juvenile polyps, but the lesions are usually smaller and do not show marked excess of lamina propria (115,117).

Risk of Malignancy in Polyps

The true incidence of GI carcinoma in Cronkhite-Canada syndrome is unknown. In the review of literature by Daniel et al. (115) in 55 cases, they found six cases of carcinoma of the colon and/or rectum, including one case of carcinoma of the stomach. Some of these carcinomas were multiple. Watanabe et al. (118) reported a case of Cronkhite-Canada syndrome associated with triple gastric carcinoma. Histopathologic examination revealed that the polyp underwent malignant transformation without an adenoma component.

Management

There has been no specific treatment. The management is symptomatic and the correction of any deficiencies. A complete spontaneous remission has been reported (119).

Bowel resection is reserved for cases in which complications such as carcinoma, bleeding, intussusception, and rectal prolapse develop (115). Surgery is not usually performed for improvement of protein-losing gastroenteropathy because the protein losing is usually not localized (120). Hanzawa et al. (120) reported a patient with Cronkhite-Canada syndrome with numerous polyps in the stomach, duodenum, and from cecum to transverse colon. The patient had severe hypoproteinemia and peripheral edema, unresponsive to conservative treatment including elemental diet and hyperalimentation. Scintigraphy with technetium TC99m-labeled human albumin (121,122) demonstrated a protein-losing region in the ascending colon. An ileo-right colectomy was performed. After the operation, the protein-losing enteropathy stopped; the ectodermal changes improved, and other polyps that was a secondary cause to malnutrition regressed.

Cowden's Disease

Cowden's disease is an uncommon familial syndrome of combined ectodermal, endodermal, and mesodermal hamartomas. The disease was named after the family name of the propositus by Lloyd and Dennis in 1963 (123).

Eighty percent of patients present with dermatologic manifestations, such as keratosis of extremities, the most common being a benign neoplasm of the hair shaft: a trichilemmoma. If a patient is diagnosed with more than one trichilemmoma, consideration should be given to the diagnosis of Cowden's disease. The second most common area of involvement is the central nervous system. Cowden's disease in concert with cerebella gangliocytomatosis is referred to as the Lhermitte-Duclos syndrome. Approximately 40% of affected individuals have macrocephaly as a component of the syndrome. Only 35% of patients who meet the diagnostic criteria for Cowden's disease have GI polyposis (124).

Polyps in patients with Cowden's disease are small, typically < 5 mm in diameter. Microscopic features are consistent with hamartomas, characterized by disorganization and proliferation of the muscularis mucosa with minimally abnormal overlying mucosa (125).

Genetics

Most patients with Cowden's disease have been shown to subsume germ-line mutations in the PTEN gene located at 10q22 (126). PTEN is a tumor suppressor gene which has been shown to be involved with other forms of carcinoma such as familial thyroid carcinoma, inherited breast carcinoma, prostatic carcinoma, and malignant melanoma (124).

Neoplastic Risk

The majority of patients with Cowden's disease will have some form of benign thyroid or breast disease. In addition,

the projected lifetime risk of thyroid malignancy is 10% and of breast malignancy is approximately 30% to 50% (127–129). There has been no reported increased risk of invasive GI malignancy to date (124).

Management and Surveillance

Screening and surveillance for breast malignancies should include a schedule of monthly breast self-examinations. Clinical examination should be undertaken annually, beginning in the late teen years or as clinically warranted by symptoms. Mammography should be implemented at the age of 25. Although no specific recommendations for thyroid surveillance have been published, annual screening by clinical examination should begin in the late teen years or as symptoms warrant. A thyroid ultrasound may be used in parallel every 1 to 2 years (124).

GI polyposis should be addressed by endoscopic surveillance. Although no definitive increased risk of colorectal carcinoma has been documented, the syndrome is rare; thus, the true risk may be unrecognized (124).

Bannayan-Ruvalcaba-Riley Syndrome

This disease encompasses three previously described disorders: Bannayan-Zonana syndrome, Riley-Smith syndrome, and Ruvalcaba-Myhre-Smith syndrome. In 1960, Riley and Smith noted an autosomal dominant condition in which macrocephaly with a slowed cycle motor development, pseudopapilledema, and multiple hemangiomas were observed (130). In 1971, Bannayan noted the congenital combination of macrocephaly with multiple subcutaneous and visceral lipoma as well as hemangiomas (131). In 1980, Ruvalcaba described two males with macrocephaly, hamartomatous intestinal polyposis, and pigmentary spotting of the penis (132). Given the clinical similarities between the conditions and the autosomal dominant pattern of inheritance, geneticists began to accept the notion of combining the disorders into a single entity as Bannayan-Ruvalcaba-Riley syndrome (96). The syndrome gene is located at chromosome 10q23 (133). Intestinal polyposis affects up to 45% of these patients. Usually multiple hamartomatous polyps are identified with the majority limited to the distal ileum and colon, though they may be seen throughout the GI tract. Histologically, they appear similar to the juvenile polyposis-type polyp (96).

Genetics

Bannayan-Ruvalcaba-Riley syndrome is an autosomal dominant condition and, like Cowden's disease, appears to be associated with genetic alterations in the PTEN gene (133).

Neoplastic Risk

There has been no increased risk of colorectal carcinoma, other GI malignancies, or extraintestinal malignancy documented in these patients (124).

■ INFLAMMATORY AND LYMPHOID POLYPS

Inflammatory polyps, or pseudopolyps, may look grossly like adenomatous polyps. However, microscopic examination shows islands of normal mucosa or mucosa with slight inflammation. They are caused by previous attacks of any form of severe colitis (ulcerative, Crohn's, amebic, ischemic, or schistosomal), resulting in partial loss of mucosa, leaving remnants or islands of relatively normal mucosa.

Radiologically, both the acute and chronic forms appear similar. Distinction can be made with the proctosigmoidoscope, but in the chronic stage a biopsy may be necessary to distinguish the condition from familial polyposis. Inflammatory polyps are not premalignant, and their presence in no way influences the potential malignant status of the patient with ulcerative colitis, a development that remains related to the extent, age of onset, and duration of disease. That these polyps are not premalignant in ulcerative colitis is relative; the potential carcinomatous status of the pseudopolyp in this condition is no more or less than that of the adjacent mucosa (134).

Benign lymphoid polyps are enlargements of lymphoid follicles commonly seen in the rectum. They may be solitary or diffuse. Their cause is unknown. Lymphoid polyps must not be confused with familial adenomatous polyposis (FAP).

The histologic criteria set out by Dawson et al. (135) for the diagnosis of benign lymphoid polyps are as follows: the lymphoid tissue must be entirely within the mucosa and submucosa; there must be no invasion of the underlying muscle coat; at least two germinal centers must be present; and if the rectal biopsy fails to include the muscle coat and no germinal centers are seen, the diagnosis is inconclusive.

■ HYPERPLASTIC POLYPS

Hyperplastic polyps, also known as metaplastic polyps, are nonneoplastic polyps commonly found in the rectum as small, pale, and glassy mucosal nodules. Most are 3 to 5 mm located predominately in the left colon (136), although larger ones can be seen in the more proximal part of the colon. Histologic differentiation from neoplastic polyps presents no problem. The characteristic picture is a sawtooth appearance of the lining of epithelial cells, producing a papillary outline (Fig. 16). There is no nuclear dysplasia and thus no potential for malignancy.

Despite the colonoscopic findings of more adenomas than hyperplastic polyps, autopsies from Hawaii, Finland,

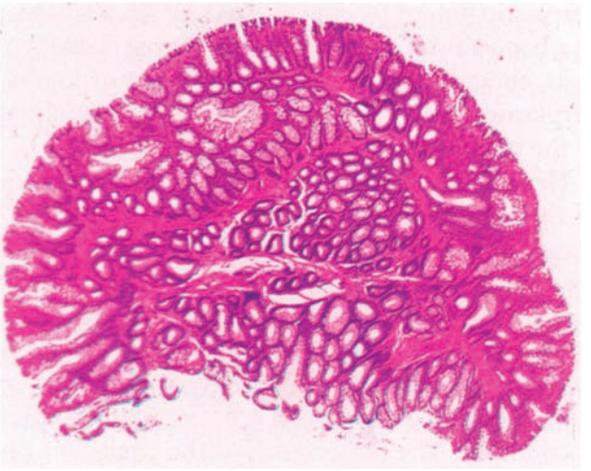

FIGURE 16 ■ Hyperplastic polyp. Note typical sawtooth appearance of the surface epithelium with a papillary appearance.

and England demonstrate hyperplastic polyps in excess upto threefold over adenomas, with the great majority of them occurring in the sigmoid colon and rectum. In contrast adenomas are distributed fairly evenly along the length of the large bowel (137). The possibility of hyperplastic polyps serving as markers for adenomas has been raised in some colonoscopic data. It is clear, though, that the predictive value of the hyperplastic polyp is low, and the clinical usefulness of the marker must be critically questioned (137).

Hyperplastic polyposis is a relatively new entity. The following criteria for hyperplastic polyposis have been proposed: (i) at least histopathologically diagnosed hyperplastic proximal to the sigmoid colon, of which two are greater than 10 mm in diameter; (ii) any number of hyperplastic polyps occurring in proximal to the sigmoid is an individual who has a first-degree relative with hyperplastic polyposis; (iii) more than 30 hyperplastic polyps of any size, but distributed throughout the colon (137). Although Williams et al. (138) found no association between hyperplastic polyposis and colorecal carcinoma, some of the polyps contained mixture of hyperplastic and adenomatous elements which nowadays would have been classified as serrated adenomas. Subsequent case reports and small series recorded the presentation of colorectal carcinoma in patients with hyperplastic polyposis (139,140). Colorectal carcinoma complicating hyperplastic polyposis is characterized by early age at onset multiplicity, frequent location in proximal colon, and greater likelihood of showing the molecular phenotype known as DNA microsatellite instability–high (MSI–H).

The association between colorectal carcinoma and hyperplastic polyposis does not prove that carcinomas orginate within hyperplastic polyposis. Adenomas might coexist with hyperplastic polyposis and might be the precursors of colorectal carcinomas, or these polyposis are infact serrated adenomas.

Little has been reported on the risk of metachronous adenomas in patients with hyperplastic polyps. Benson et al. (141) examined data from two large randomized colorectal chemoprevention trials for possible associations of hyperplastic polyps and adenomatous polyps with subsequent development of these lesions. Of the 1794 patients randomized in two trials, 1583 completed two follow-up colonoscopies, and are considered in their analysis. They computed rates of incidence on hyperplastic polyps and adenomas over the three-year follow-up after the first surveillance examination with polyp status (type and number) at that examination as predictors. During the three-year follow-up, 320 (20%) had one or more hyperplastic polyps detected, and 564 (36%) had one or more adenomas. Patients with hyperplastic polyps at the first surveillance examination had a higher risk of any hyperplastic polyp recurrence on follow-up than those without hyperplastic polyps (odds ratio 3.67). Similarly, patients with adenomas at the first surveillance examination had a higher risk of adenoma recurrence than those without adenomas (odds ratio 2.08). However, the presence of hyperplastic polyps at the first surveillance examination was not significantly associated with adenoma occurrence during follow-up, nor was the presence of adenoma significantly associated with subsequent hyperplastic polyp occurrence.

FAMILIAL ADENOMATOUS POLYPOSIS

DEFINITION AND NATURAL HISTORY

Familial adenomatous polyposis (FAP) is an inherited, non-sex-linked and Mendelian–dominant disease characterized by the progressive development of hundreds or thousands of adenomatous polyps throughout the entire large bowel. The clinical diagnosis is based on the histologic confirmation of at least 100 adenomas (Fig. 17). However, with the widespread practice of family counseling and the genetic testing, this number of adenomas is no longer rigidly applied. In the absence of a family history of FAP, the number 100 or more is still good to entertain the diagnosis. The important feature of the disease is the fact that one or more of these polyps will eventually develop into an invasive adenocarcinoma unless a prophylactic proctocolectomy is undertaken. The disease has high penetrance, with a 50% chance of development of the disease in the affected family. Approximately 20% of patients with FAP have no family history and their condition represents spontaneous mutation (142). The term ''FAP'' is now used to replace the term ''familial polyposis coli'' because the disease also affects other organs. The older terms Gardner's syndrome, familial polyposis of the gastrointestinal (GI) tract, familial multiple polyposis, and many other names should be avoided.

The incidence of FAP is one in 7000 live births (143). Although the disease is congenital, there is no evidence that adenomas have ever been present at birth. In his extensive experience with the St. Mark's Hospital, London, Polyposis Registry, Bussey (144) summarized the natural course of FAP in the average untreated patient as follows:

Age of appearance of adenomas:	25 years
Age of onset of symptoms:	33 years
Age of diagnosis of adenomas:	36 years
Age of diagnosis of carcinoma:	39 years
Age at death from carcinoma:	42 years

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms usually do not develop until there is a full-blown development of polyposis. Bleeding from the rectum and diarrhea are the most common symptoms. The diagnosis is made by endoscopic examination of the colon and rectum or by barium enema studies. It must be confirmed by histologic findings of adenomatous polyps.

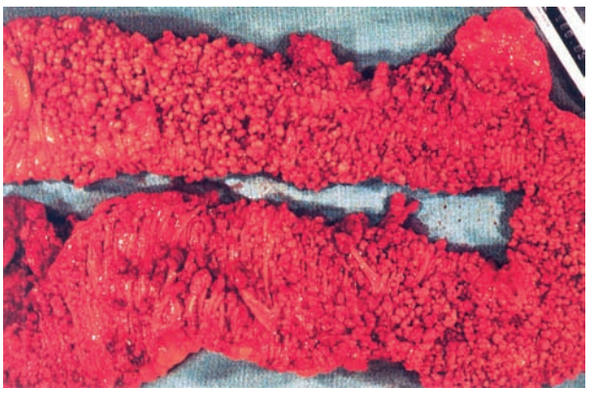

FIGURE 17 ■ Numerous small adenomatous polyps of the colon and rectum in a patient with familial adenomatous polyposis.

Only occasionally are tubulovillous adenomas found and villous adenomas are rare. The smallest possible microadenoma consists of only a single crypt, obviously not visible by examination with the naked eye (145).

The average age at which the disease is diagnosed is 36 years. The adenomas actually appear much earlier, as is seen by comparison with the age of diagnosis in family members called for examination. In this group of patients, the average age is 24 years.

Nearly two of three patients (65%) who were present because of symptoms already have carcinoma. The average age of colorectal carcinoma in these patients is 39 years, compared with 65 years in the normal population.

Since most of the polyps in FAP are small, the best methods of diagnosis are colonoscopy and biopsy. A complete colonic examination has become important since rectal sparing has been reported, even when adenocarcinoma is present in the proximal colon (146).

■ DISTRIBUTION OF POLYPS AND CARCINOMAS

Although the rectum is almost invariably involved with polyps, the number of polyps in each segment of the colon and rectum varies from person to person. In general, the left colon has a higher density of polyps than the right colon (144). In any one patient, the polyps vary in size from barely visible mucosal nodules 1 or 2 mm in diameter, to up to 1 cm or larger. In some patients and families, the adenomas are mostly small, while in others they are large. Most patients with FAP have myriads of polyps, frequently up to 5000 (147). In a series from Denmark, the risk of developing carcinoma was highest in the rectum, followed by the sigmoid colon (Table 6) (147).

■ ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS

This is a variant of FAP that has only relatively recently been recognized (148,149). The majority of patients who were present with between 1 and 50 adenomas, primarily located proximal to the splenic flexure and often morphologically flat. The polyps are diagnosed at the mean age of 44 years, and carcinomas at the mean age of 56 years. Thus, diagnosis of polyps and carcinomas in attenuated familial adenomatous polyposis (AFAP) is generally 10 to 15 years later than in FAP. However, because these data are based on when these lesions are detected and not necessarily on when they arise, the true age of development of polyps and carcinomas in AFAP is unclear. Certainly, lack of recognition of AFAP by patients and by physicians results in fewer patients presenting for voluntary surveillance, perhaps contributing to a delay in diagnosis in these patients (150).

TABLE 6 ■ Distribution of Colorectal Carcinoma in 109 Propositions

	No. of Carcinomas	(%)
Right colon	8	6
Transverse colon	6	5
Descending colon	8	6
Sigmoid colon	31	24
Rectum	77	59
Total	130	100

Source: From Ref. 147.

Clinical Features

A striking feature of AFAP is the variability in number of polyposis within members of the same kindred. Some affected members have few polyps, while others have several hundred. This variability presents difficulties in classifying members of the same kindred as AFAP or FAP. Similar to FAP, colorectal carcinomas in patients with AFAP are generally accompanied by synchronous adenomas (150). The extracolonic manifestations in AFAP are similar to FAP. Church (151) argues that AFAP is not a distinct clinical entity. It is not distinct generally because a large number of different APC mutations can be expressed as AFAP. It is not distinct clinically because patients with fewer than 100 adenomas may have FAP, HNPCC, or multiple sporadic adenomas. It is not even distinct in a familial sense, because members of AFAP family may vary widely in the severity of their polyposis. The definition of AFAP, multiple but fewer than 100 synchronous colorectal adenomas, is arbitrarily one that suffers from its imposition of a finite number on a disease with a spectrum of subtle variations. He would rather regard AFAP as some patients with FAP with a mild expression of the colonic polyposis. This mild form of the colonic disease is most common with mutations at either end of the gene, and in many cases, the polyps are predominantly right sided. However, the underlying disease remains FAP.

Diagnosis and Genetic Test

The clinical diagnosis of AFAP is more difficult than that of classic FAP because of the wide variability of phenotypic expression, and overall lack of awareness of this syndrome. In addition, screening with flexible sigmoidoscopy, the recommended modality for classic FAP, is inadequate because the majority of colonic lesions in patients with AFAP are right-sided.

For asymptomatic at-risk individuals belonging to known FAP or AFAP kindreds, genetic testing should be ideally performed between the ages of 10 and 15 years to determine the presence or absence of an APC mutation. A baseline colonoscopy and esophagoduodenoscopy at the time of genetic testing or by the age of 15 years should be performed (151). In patients with true-negative APC test results (a mutation has been demonstrated in an affected member but not in an at-risk member), a colonoscopy should be performed at the time of genetic testing or by the age of 15. Although the protein truncation test (PTT) is nearly 100% accurate in this setting, endoscopic evaluation serves as confirmation of a negative test. Because polyps occur later in AFAP individuals than in classic FAP, a second colonoscopy at age 20 should be considered to detect late, appearing polyps. If both examinations are negative, no further surveillance is necessary, and the patient may undergo future colorectal carcinoma screening as an average-risk individual (150). Church (151), however, has the opinion that people who test negative when their affected relatives test positive should be recognized that they do not have FAP and can be excluded from surveillance.

Surgical Management

Patients with AFAP are at increased risk for the development of colorectal carcinoma, although the exact risk remains unknown at this time. They do not have the near certainty of developing colorectal carcinoma that classic patients with FAP have. Thus, the indications for prophylactic colectomy differ between these two entities. In patients with few adenomas, colonoscopic polypectomy is sufficient to clear the affected bowel segments. When multiple polyps are clustered within a single segment of the colon, especially the cecum, resection may be the safest option. When resection is required, a total abdominal colectomy can be performed with an IRA. Because the rectal segment is generally uninvolved in these patients, total proctocolectomy with IPAA does not seem to be required. The rectal segment does need continued surveillance because this mucosa is still at risk. Total abdominal colectomy with IRA may also be required in patients who are difficult to examine fully by colonoscopy and, thus, unable to undergo proper surveillance (151).

AFAP has two forms: patients with mutations at the five prime of APC are at minimal risk for desmoid disease, whereas patients with mutation in exon 15 are at high risk. This risk of desmoids, often manifest in other relatives who have had an operation, may encourage deferment of surgery. The alternative to colectomy, endoscopic polypectomy with or without chemoprevention, is risky especially when the patient has been shown to carry a germline APC mutation. Colonoscopic surveillance does not prevent carcinoma in all patients with HNPCC, the same can be applied to AFAP; this must be reserved for truly compliant patients who realize the risks (151).

■ MOLECULAR GENETICS

Using genetic-linkage analysis, it has been determined that FAP is caused by a mutation in the tumor suppressor gene *APC* located on the long arm of chromosome 5q21–22. The term FAP is not used to describe this gene because familial amyloidotic polyneuropathy takes historical precedence in the genetic literature (152). The genetic alterations found in the FAP patient's colon and rectal carcinoma are similar to those noted in sporadic carcinoma, except that an *APC* mutation is already present constitutionally at birth (a germline mutation).

There are correlations between the location of the APC mutation and the clinical phenotype. Figure 18 (153) shows the correlation between the APC genotype and the clinical phenotype. The 15 exons of the APC gene are shown. The locations of germ-line mutations associated with specific clinical phenotypes indicated by the dark horizontal lines. Thirty-four mutations causing AFAP have been reported to date; these are clustered either at the five prime ends (before codon 436) or at the three prime end (after codon 1596) of the APC gene. In contrast, mutations causing classic FAP are located in the central region, and mutations between codons 1250 and 1464 are associated with particularly severe polyposis. Abdominal desmoid tumors are more likely in persons with mutations between codons 1445 and 1578.

The molecular mechanisms that explain why certain APC mutations result in a classic phenotype and others in an attenuated phenotype are currently being elucidated. Most models are predicated on the "two-hit hypothesis"—which states that both alleles of APC must be inactivated in order to initiate tumorigenesis. In Figure 19 (153), both copies of chromosome 5 are shown. In classic FAP (panel A), the biallelic inactivation of APC is typically achieved by the combination of an inherited germ-line mutation in one allele (black X) and a chromosomal deletion of the remaining wild-type allele; this is called loss of heterozygosity. In some cases, the germ-line APC mutation (red X) can result in the production of a protein that can inhibit the activity of the wild-type protein (white X). This dominant negative effect functionally results in biallelic inactivation.

In AFAP (panel B), the mechanism of APC inactivation is different. Germ-line mutations involved in AFAP may lead to the formation of alternative APC proteins that are initiated from an internal translation site that is located distal to the truncating mutation. This alternative APC protein does have functional activity. Because of this residual gene activity, an additional "hit" is necessary to fully inactivate APC (panel C). This third "hit" is indicated by the blue X. The second hit is often an intragenic mutation (green X) that inactivates the wild-type APC allele, rather than a large

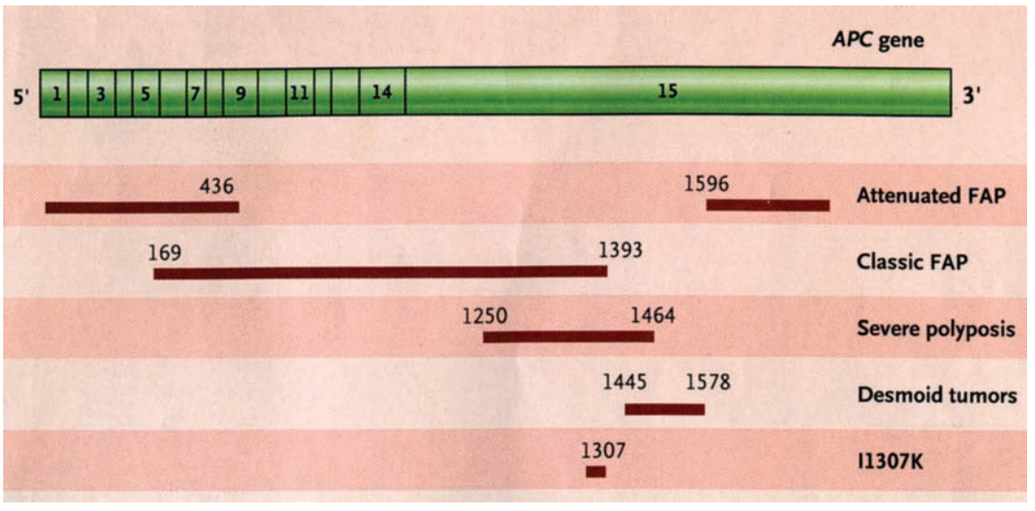

FIGURE 18 ■ Correlation between the APC genotype and the clinical phenotype. (See details in text.) *Source*: From Ref. 153.

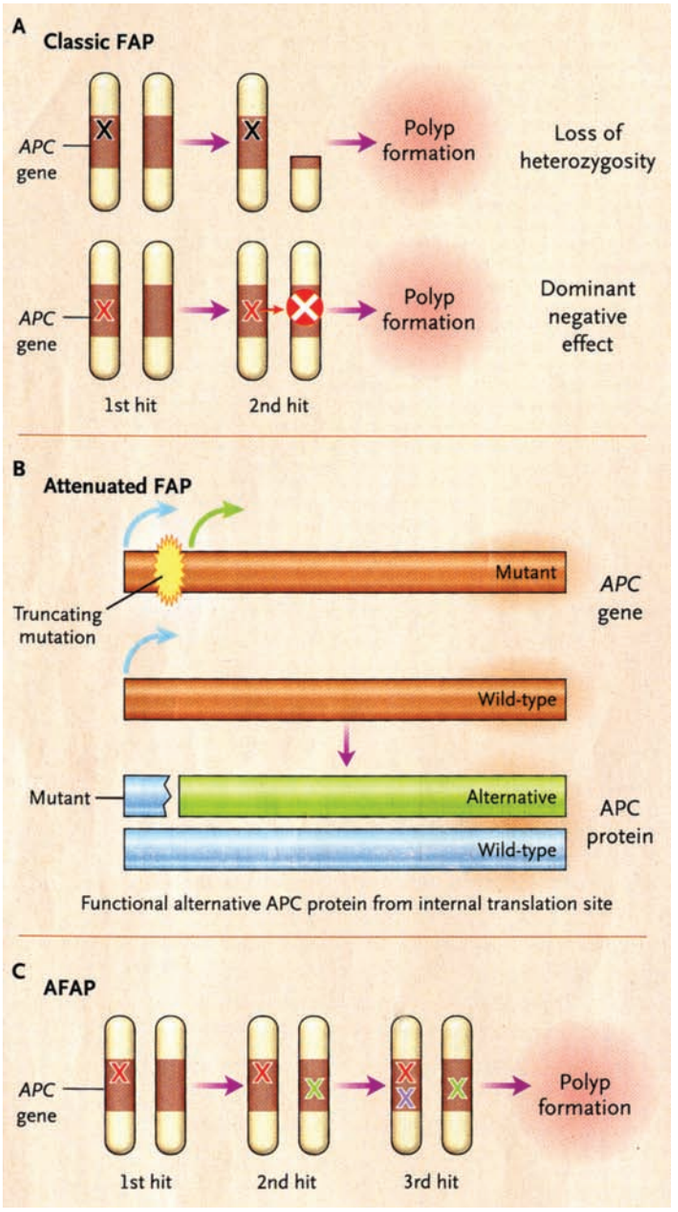

FIGURE 19 ■ Mechanisms of inactivation of the APC gene in classic and attenuated familial adenomatous polyposis (FAP). (See details in text.) *Source*: From Ref. 153.

chromosomal deletion as in classic FAP. The red X represents the inherited APC mutation (153).

■ EXTRACOLONIC EXPRESSIONS

In 1951, Gardner (154) reported finding osteomatosis, epidermoid cysts, and fibromas of the skin, a triad in FAP known as Gardner's syndrome. The detection of identical mutations in individuals with FAP and Gardner's syndrome helps confirm that at the genetic level they are variants of a common entity (155). The disease affects the whole body, involving tissues derived from all three germ layers (145). Factors that contribute to the extracolonic manifestations are unresolved. Modifying genetic factors (e.g., other genes or different genetic backgrounds) or environmental variables probably play a role in the final phenotype. Likewise, the role that APC plays in the development of various extracolonic neoplasms and manifestations remains to be defined. There have been some indications that the location of the APC mutation itself may have an effect on the phenotype, although conclusive evidence for this proposal is lacking (155).

Endodermal Abnormalities

Gastric Polyps

With improved survival rates following colorectal resection, gastric polyps or upper GI lesions have become increasingly important because of the risk of malignant change in duodenal polyps. The introduction of flexible endoscopy has provided more ready access to the upper GI tract, although at present the course of the disease is not precisely known (156).

The prevalence of gastric polyps ranges from 34% to 100%; most of them are hyperplastic type in the fundus of the stomach, and a few adenomatous types have been reported in the anturm (157,158).

Of the 102 patients screened prospectively, in the series of Spigelman et al. (159), 56 had gastric polyps. Gastric fundus polyps were small (mean 4.7 mm) and multiple, whereas antral polyps, when present, were larger (mean 6.4 mm) and less numerous. Only 6 of 73 patients who had gastric biopsy revealed adenoma. When gastric adenomas are present they seem to be in patients who have duodenogastric reflux, in an area, exposed to bile (160).

Duodenal Polyp and Carcinoma

In most series, duodenal adenomas occur in more than 90% of FAP patients, particularly in the periampullary region (161–163). The macroscopic appearance of duodenal polyps is very different to that of colonic polyps. The number of the former varies from invisible to over 100. They may present as multiple discrete adenomas (1–10 mm in diameter) or as flat confluent plagues. Sometimes no lesion can be seen and the only clinical abnormality is a prominent ampulla, or the mucosa may appear pale and seem to have a white covering which cannot be removed by rubbing. Biopsy of apparently normal mucosa frequently showed microadenomas (160). The lifetime risk of adenoma in FAP patients is high. Mutations downstream from coden 1051 seem to be associated with severe periampullary adenomas (164). Spigelman et al. (159) staged the duodenal polyposis according to polyp number, polyp size, and histologic type. The criteria provided a four-stage scoring system (Table 7). The classification allows estimation of the severity of duodenal polyposis.

In a prospective study conducted by Domizio et al. (165), over 102 asymptomatic FAP patients were screened

TABLE 7 ■ **Staging of Duodenal Polyposis**

	Grade Points		
Criteria	**1**	**2**	**3**
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Note: Stage 0, 0 point; stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–12 points.
Source: From Ref. 159.