CHAPTER 6

Tumours of the Colon and Rectum

Colorectal carcinomas vary considerably throughout the world, being one of the leading cancer sites in the developed countries. Both environmental (diet) and genetic factors play key roles in its aetiology. Genetic susceptibility ranges from well-defined inherited syndromes, e.g. familial adenomatous polyposis, to ill-defined familial aggregations. Molecular genetic mechanisms are diverse, and recent data suggest two main pathways: a mutational pathway, which involves inactivation of tumour suppressor genes such as APC; and microsatellite instability which occurs in hereditary nonpolyposis colon cancer (HNPCC) and a proportion of sporadic carcinomas.

The main precursor lesion is the adenoma, which is readily detected and treated by endoscopic techniques. Non-neoplastic polyps are not considered precancerous unless they occur in polyposis syndromes. Inflammatory bowel diseases, such as chronic ulcerative colitis, bear resemblance to Barrett oesophagus as a precursor lesion with a potential for control by endoscopic surveillance. Cure is strongly related to anatomic extent, which makes accurate staging very important.

Lymphomas, endocrine tumours, and mesenchymal tumours are quite uncommon at this site.
WHO histological classification of tumours of the colon and rectum

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<th>Epithelial tumours</th>
<th>Non-epithelial tumours</th>
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<td>Tubular</td>
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<td>Villous</td>
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<td>Tubulovillous</td>
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<td>Malignant melanoma</td>
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<td>Intraepithelial neoplasia(^2) (dysplasia)</td>
<td>Malignant lymphomas</td>
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<td>Low-grade glandular intraepithelial neoplasia</td>
<td>Marginal zone B-cell lymphoma of MALT Type</td>
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<td>High-grade glandular intraepithelial neoplasia</td>
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<td>Carcinoma</td>
<td>Diffuse large B-cell lymphoma</td>
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<td>Adenocarcinoma</td>
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<td>Mucinous adenocarcinoma</td>
<td>Burkitt-like/atypical Burkitt-lymphoma</td>
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<td>Signet-ring cell carcinoma</td>
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<td>Carcinoid (well differentiated endocrine neoplasm)</td>
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<td>EC-cell, serotonin-producing neoplasm</td>
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<td>Mixed carcinoid-adenocarcinoma</td>
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TNM classification of tumours of the colon and rectum

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Stage Grouping

- Stage 0
- Tis
- N0
- M0
- Stage I
- T1
- N0
- M0
- T2
- N0
- M0
- Stage II
- T3
- N0
- M0
- T4
- N0
- M0
- Stage III
- Any T
- N1
- M0
- Any T
- N2
- M0
- Stage IV
- Any T
- Any N
- M1

\(^1\) This classification is modified from the previous WHO histological classification of tumours (8453) taking into account changes in our understanding of these lesions. In the case of endocrine neoplasms, it is based on the recent WHO classification (1784) but has been simplified to be of more practical utility in morphological classification.

\(^2\) Morphology code of the International Classification of Diseases for Oncology (ICD-O) (542) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for in situ carcinomas and grade III intraepithelial neoplasia, and /1 for unspecified, borderline or uncertain behaviour. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are available only for lesions categorized as glandular intraepithelial neoplasia grade III (8148/2), and adenocarcinoma in situ (8140/2).

\(^3\) This classification applies only to carcinomas.

\(^4\) A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.

\(^5\) This includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through muscularis mucosae into submucosa.

\(^6\) Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa, e.g. invasion of sigmoid colon by a carcinoma of the cecum.
Carcinoma of the colon and rectum

Definition
A malignant epithelial tumour of the colon or rectum. Only tumours that have penetrated through muscularis mucosae into submucosa are considered malignant at this site. The presence of scattered Paneth cells, neuroendocrine cells or small foci of squamous cell differentiation is compatible with the diagnosis of adenocarcinoma.

ICD-O codes
Adenocarcinoma 8140/3
Mucinous adenocarcinoma 8480/3
Signet-ring cell carcinoma 8490/3
Small cell carcinoma 8041/3
Squamous cell carcinoma 8070/3
Adenosquamous carcinoma 8560/3
Medullary carcinoma 8510/3
Undifferentiated carcinoma 8020/3

Epidemiology
An estimated 875,000 cases of colorectal cancer occurred worldwide in 1996, representing about 8.5% of all new cancers [1531]. The age-standardized incidence (cases/100,000 population) varies greatly around the world, with up to 20-fold differences between the high rates in developed countries of Europe, North and South America, Australia/New Zealand, and Asia and the still lower rates in some recently developed countries (Malaysia, Korea) and in developing countries of Africa, Asia and Polynesia. Significant differences also exist within continents, e.g. with higher incidences in western and northern Europe than in central and southern Europe [336]. Among immigrants and their descendants, incidence rates rapidly reach those of the adopted country, indicating that environmental factors are important. According to the U.S. SEER database, the incidence rate for adenocarcinoma of the colon is 33.7/100,000 and increased by 18% during the period from 1973 through 1987 while the incidence of rectal adenocarcinoma (12.8/100,000) and mucinous adenocarcinoma in the colon and rectum (0.3 and 0.8, respectively) remained relatively constant [1928]. During the last decade of the 20th century, incidence and mortality have decreased [566]. By contrast, the incidence in Japan, Korea and Singapore is rising rapidly [737], probably due to the acquisition of a Western lifestyle. Incidence increases with age [2121]: carcinomas are rare before the age of 40 years except in individuals with genetic predisposition or predisposing conditions such as chronic inflammatory bowel disease. Incidence rates in the 1973-87 SEER data for colonic and rectal adenocarcinoma for males were higher than those for females; whites had higher rates than blacks for rectal adenocarcinoma, but blacks had higher rates for colonic adenocarcinoma [1928]. During 1975-94, a decrease in incidence in whites was evident, while the incidence of proximal colon cancers in blacks still increased [1958].

Aetiology
Diet and lifestyle
A high incidence of colorectal carcinomas is consistently observed in populations with a Western type diet, i.e. highly caloric food rich in animal fat combined
with a sedentary lifestyle. Epidemiological studies have indicate that meat consumption, smoking and alcohol consumption are risk factors. Inverse associations include vegetable consumption, prolonged use of non-steroidal anti-inflammatory drugs, oestrogen replacement therapy, and physical activity (1531, 2121). Fibre may have a protective role, but this has been questioned recently. The molecular pathways underlying these epidemiological associations are poorly understood, but production of heterocyclic amines during cooking of meat, stimulation of higher levels of fecal bile acids and production of reactive oxygen species have been implicated as possible mechanisms (416, 1439).

Vegetable anticarcinogens such as folate, antioxidants and inducers of detoxifying enzymes, binding of luminal carcinogens, fibre fermentation to produce protective volatile fatty acids, and reduced contact time with colorectal epithelium due to faster transit may explain some of the inverse associations.

Chronic inflammation

Chronic inflammatory bowel diseases are significant aetiological factors in the development of colorectal adenocarcinomas (1582). The risk increases after 8-10 years and is highest in patients with early-onset and widespread manifestation (pancolitis).

Ulcerative colitis. This chronic disorder of unknown aetiology affects children and adults, with a peak incidence in the early third decade. It is considered a premalignant disorder, with duration and extent of disease being the major risk factors. Population-based studies show a 4.4-fold increase in mortality from colorectal carcinoma (1504, 448, 1835, 1214). In clinical studies, the increase in incidence is usually higher, up to 20-fold (647, 990). Involvement of greater than one half of the colon is associated with a risk to develop carcinoma of approximately 15%, whereas left sided disease may bear a malignancy risk of 5% (1727, 1045). Ulcerative proctitis is not associated with an increased carcinoma risk.

Crohn disease. Development of carcinoma is seen both in the small intestine and the large intestine. The risk of colorectal malignancy appears to be 3 fold above normal (581). Long duration and early onset of disease are risk factors for carcinoma.

Modifying factors. Non-steroidal anti-inflammatory drugs and some naturally occurring compounds block the biochemical abnormalities in prostaglandin homeostasis in colorectal neoplasms. Some of these agents cause a dramatic involution of adenomas but their role in the chemoprevention of adenocarcinoma is less clear. Polymorphisms in key enzymes can alter other metabolic pathways that modify protective or injurious compounds, e.g. methylenetetrahydrofolate reductase, N-acetyltransferases, glutathione-S-transferases, aldehyde dehydrogenase and cytochrome P-450 (1766, 686, 1300). These polymorphisms may explain individual susceptibility or predisposition among populations with similar exposures (1555).

Irradiation.

A rare but well recognized aetiological factor in colorectal neoplasia is therapeutic pelvic irradiation (1974).

Localization

Most colorectal carcinomas are located in the sigmoid colon and rectum, but there is evidence of changing distribution in recent years, with an increasing proportion of more proximal carcinomas.
Molecular pathology has also shown site differences: tumours with high levels of microsatellite instability (MSI-H) or ras proto-oncogene mutations are more frequently located in the caecum, ascending colon and transverse colon.

Clinical features

Signs and symptoms

Some patients are asymptomatic, especially when their neoplasm is identified by screening or surveillance. Haematochezia and anaemia are common presenting features due to bleeding from the tumour. Many patients experience change in bowel habit; in the right colon, the fluid faeces can pass exophytic masses, whereas in the left colon the solid faeces are more often halted by annular tumours so that constipation is more common. There may be associated abdominal distension. Rectosigmoid lesions can produce tenesmus. Other symptoms include fever, malaise, weight loss, and abdominal pain. Some patients present with the complications of obstruction or perforation.

Imaging

Modern imaging techniques permit non-invasive detection and clinical staging. Conventional barium enema detects large tumours, while air-contrast radiography improves the visualization of less advanced lesions. Cross-sectional imaging by CT, MRI imaging and transrectal ultrasoundography permit some assessment of the depth of local tumour invasion and the presence of regional and distant metastases. Scintigraphy and positron emission tomography are also used.

Endoscopy

The development of endoscopy has had a major impact on diagnosis and treatment. Colonoscopy allows observation of the mucosal surface of the entire large bowel with biopsy of identified lesions. Chromoendoscopy employing dyes to improve visualization of non-protruding lesions and magnification, have been developed. The flat neoplastic lesions
have been designated by Japanese gastroenterologists as 'type II', with three subtypes: IIa, 'en plateau' elevated; IIb, completely flat; and IIc, 'en plateau' depressed. The depressed lesions have, despite a smaller diameter, a poor prognosis with prompt penetration in the submucosa. The pit pattern of the surface at magnification 100 allows a reliable prediction of histology. Therapeutic endoscopy, including snare polypectomy and endoscopic mucosectomy, can be used to remove colorectal neoplasms, especially adenomas, and carcinomas with minimal submucosal invasion. Protruded neoplasms can usually be resected by snare polypectomy. Superficial lesions (flat and depressed) and some protruded lesions may be removed by endoscopic mucosal resection [2121, 2122, 1164].

Macroscopy
The macroscopic features are influenced by the phase in the natural history of tumours at the time of discovery. Carcinomas may be exophytic/fungating with predominantly intraluminal growth, endophytic/ulcerative with predominantly intramural growth, diffusely infiltrative/linnitis plastica with subtle endophytic growth, and annular with circumferential involvement of the colorectal wall and constriction of the lumen. Overlap among these types is common. Pedunculated exophytic lesions have a mural attachment narrower than the head of the tumour, with the stalk consisting of uninvolved mucosa and submucosa, while sessile exophytic tumours have broad attachment to the wall.
Carcinomas of the proximal colon tend to grow as exophytic masses while those in the transverse and descending colon are more often endophytic and annular. On cut section, most colorectal carcinomas have a relatively homogeneous appearance although areas of necrosis can be seen. Adenocarcinomas of the mucinous (colloid) type often have areas with grossly visible mucus. Carcinomas with high levels of microsatellite instability (MSI-H) are usually circumscribed and about 20% are mucinous [842].

Tumour spread and staging
Following transmural extension through the muscularis propria into pericolic or perirectal soft tissue, the tumour may involve contiguous structures. The consequences of direct extension depend on the anatomic site. An advanced rectal carcinoma may extend into pelvic structures such as the vagina and urinary bladder, but cannot gain direct access to the peritoneal cavity when it is located distal to the peritoneal reflection. By contrast, colonic tumours can extend directly to the serosal surface. Perforation can be associated with transcoelomic spread to the peritoneal cavity (peritoneal carcinomatosis). Involvement of the peritoneal surface should only be diagnosed if the peritoneum is ulcerated or if tumour cells have clearly penetrated the mesothelium. Since the peritoneal surface infiltrated by tumour cells may become adherent to adjacent structures, direct extension into adjoining organs can also occur in colonic carcinomas that have invaded the peritoneal portion of the wall [62]. Implantation due to surgical manipulation occurs only occasionally, but has been reported after laparoscopic colectomy for cancer [1106]. Spread via lymphatic or blood vessels can occur early in the natural history and lead to systemic disease. Despite the presence of lymphatics in the colorectal mucosa, lymphogenic spread does not occur unless the muscularis mucosae is breached and the submucosa is invaded. This biological behaviour stands in sharp contrast to carcinomas of the stomach where metastasis occurs occa-
Adenocarcinoma

sionally from purely intramucosal carcinomas. Invasion of portal vein tributaries in the colon and vena cava tributaries in the rectum can lead to haematogenous dissemination.

Staging
The classification proposed by C. Dukes in 1929-35 for rectal cancer serves as the template for many staging systems currently in use. This family of classifications takes into account two histopathological features: depth of penetration into the wall and the presence or absence of metastasis in regional lymph nodes. The TNM classification (66) is replacing the Dukes classification.

Histopathology
The defining feature of colorectal adenocarcinoma is invasion through the muscularis mucosae into the submucosa. Lesions with the morphological characteristics of adenocarcinoma that are confined to the epithelium or invade the lamina propria alone and lack invasion through the muscularis mucosae into the submucosa have virtually no risk of metastasis. Therefore, ‘high-grade intraepithelial neoplasia’ is a more appropriate term than ‘adenocarcinoma in-situ’, and ‘intramucosal neoplasia’ is more appropriate than ‘intramucosal adenocarcinoma’. Use of these proposed terms helps to avoid overtreatment.

Most colorectal adenocarcinomas are gland-forming, with variability in the size and configuration of the glandular structures. In well and moderately differentiated adenocarcinomas, the epithelial cells are usually large and tall, and the gland lumina often contain cellular debris.

Mucinous adenocarcinoma
This designation is used if > 50% of the lesion is composed of mucin. This variant is characterized by pools of extracellular mucin that contain malignant epithelium as acinar structures, strips of cells or single cells. Many high-frequency micro-satellite instability (MSI-H) carcinomas are of this histopathological type.

Signet-ring cell carcinoma
This variant of adenocarcinoma is defined by the presence of > 50% of tumour cells with prominent intracytoplasmic mucin (1672). The typical signet-ring cell has a large mucin vacuole that fills the cytoplasm and displaces the nucleus. Signet-ring cells can occur in the mucin pools of mucinous adenocarcinoma or in a diffusely infiltrative process with minimal extracellular mucin. Some MSI-H carcinomas are of this type.

Adenosquamous carcinoma
These unusual tumours show features of both squamous carcinoma and adenocarcinoma, either as separate areas within the tumour or admixed. For a lesion to be classified as adenosquamous, there should be more than just occasional small foci of squamous differentiation. Pure squamous cell carcinoma is very rare in the large bowel.
Tumours of the colon and rectum

Medullary carcinoma
This rare variant is characterized by sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant pink cytoplasm exhibiting prominent infiltration by intraepithelial lymphocytes. It is invariably associated with MSI-H and has a favourable prognosis when compared to other poorly differentiated colorectal carcinomas.

Undifferentiated carcinoma
These rare tumours lack morphological evidence of differentiation beyond that of an epithelial tumour and have variable histological features. Despite their undifferentiated appearances, these tumours are genetically distinct and typically associated with MSI-H.

Other variants
Carcinomas that include a spindle cell component are best termed spindle cell carcinoma or sarcomatoid carcinoma. The spindle cells are, at least focally, immunoreactive for cytokeratin. The term carcinosarcoma applies to malignant tumours containing both carcinomatous and heterologous mesenchymal elements. Other rare histopathological variants of colorectal carcinoma include pleomorphic (giant cell), choriocarcinoma, pigmented, clear cell, stem cell, and Paneth cell-rich (crypt cell carcinoma). Mixtures of histopathological types can be seen.

Carcinosarcoma
Carcinomas that include a spindle cell component are best termed sarcomatoid carcinoma or spindle cell carcinoma. The spindle cells are, at least focally, immunoreactive for cytokeratin. The term carcinosarcoma applies to malignant tumours containing both carcinomatous and heterologous mesenchymal elements.

Grading
Adenocarcinomas are graded predominantly on the basis of the extent of glandular appearances, and should be divided into well, moderately and poorly differentiated, or into low-grade (encompassing well and moderately differentiated adenocarcinomas) and high-grade (including poorly differentiated adenocarcinomas and undifferentiated carcinomas). Poorly differentiated adenocarcinomas should show at least some gland formation or mucus production; tubules are typically irregularly folded and distorted.

When a carcinoma has heterogeneity in differentiation, grading should be based on the least differentiated component, not including the leading front of invasion. Small foci of apparent poor differentiation are common at the advancing edge of tumours, but this feature is insufficient to classify the tumour as poorly differentiated.

The percentage of the tumour showing formation of gland-like structures can be used to define the grade. Well differentiated (grade 1) lesions exhibit glandular structures in > 95% of the tumour; moderately differentiated (grade 2) adenocarcin-
adenocarcinoma has 50-95% glands; poorly differentiated (grade 3) adenocarcinoma has 5-50%; and undifferentiated (grade 4) carcinoma has < 5%. Mucinous adenocarcinoma and signet-ring cell carcinoma by convention are considered poorly differentiated (grade 3). Medullary carcinoma with MSI-H appears undifferentiated. Additional studies of the biological behaviour of MSI-H cancers are needed to relate the morphological grade and molecular subtypes of mucinous, signet-ring cell and medullary carcinoma to outcome since MSI-H carcinomas have an improved stage-specific survival (788, 924, 1098).

Precursor lesions
During the past decade the natural history of colorectal carcinomas has been extensively studied in correlation with the underlying accumulation of genetic alterations.

Aberrant crypt foci (ACF)
The earliest morphological precursor of epithelial neoplasia is the aberrant crypt focus (ACF). Microscopic examination of mucosal sheets dissected from the bowel wall and stained with methylene blue, or mucosal examination with a magnifying endoscope, reveal ACFs to have crypts of enlarged calibre and thickened epithelium with reduced mucin content. Microscopy shows two main types: ACFs with features of hyperplastic polyps and a high frequency of ras proto-oncogene mutations, and dysplastic ACFs (micro-adenomas) associated with a mutation of the APC gene (1375). Progression from ACF through adenoma to carcinoma characterizes carcinogenesis in the large intestine (1326).

Adenomas
These precursor lesions are defined by the presence of intraepithelial neoplasia, histologically characterized by hypercellularity with enlarged, hyperchromatic nuclei, varying degrees of nuclear stratification, and loss of polarity. Nuclei may be spindle-shaped, or enlarged and ovoid. Inactivation of the APC/beta-catenin pathway commonly initiates the process and results in extension of epithelial proliferation in dysplastic epithelium from the base of the crypts, where it normally occurs, toward or onto the luminal surface (851, 1528). Polyps appear to grow as a consequence of accelerated crypt fission resulting from APC gene mutation (564). Intraepithelial neoplasia can be low-grade or high-grade, depending on the degree of glandular or villous complexity, extent of nuclear stratification, and severity of abnormal nuclear morphology. Paneth cells, neuroendocrine cells and squamous cell aggregates may be seen in adenomas and may become a dominant constituent of the epithelium.

Macroscopy. Colorectal adenomas can be classified into three groups: elevated, flat, and depressed (973). Elevated adenomas range from pedunculated polyps with a long stalk of non-neoplastic mucosa to those that are sessile. Flat or non-protruding adenomas and depressed adenomas are recognized macroscopically by mucosal reddening, subtle changes in texture, or highlighting by dye techniques. The term adenoma is applied even though the lesions are not polypoid because intraepithelial neopla-

Fig. 6.20 A Signet-ring cell carcinoma arising in an adenoma; intramucosal signet-ring cells adjacent to adenomatous glands. B Signet-ring cells infiltrating muscularis propia. C Lymph node metastasis of a signet-ring cell carcinoma.

Fig. 6.21 Sporadic proximal colonic carcinomas. Comparison of pathology of MSI-H (red) and microsatellite stable MSS (blue) carcinomas.

Fig. 6.22 Frequency of adenocarcinoma in adenomas relative to size and architecture.
Tumours of the colon and rectum

Dysplasia (dysplasia) is the hallmark of these lesions. Depressed adenomas are usually smaller than flat or protruding ones and tend to give rise to adenocarcinoma while still relatively small (mean diameter, 11 mm) due to a greater tendency to progress [1628]. These adenomas have a lower frequency of ras mutation than polypoid adenomas [974].

**Histopathology.**

Tubular adenomas are usually protruding, spherical and pedunculated, or non-protruding (flat). Microscopically, dysplastic glandular structures occupy at least 80% of the luminal surface. Villous adenomas are typically sessile with a hairy-appearing surface. Microscopically, leaf-like projections lined by dysplastic glandular epithelium comprise more than 80% of the luminal surface. Distinction of villous structures from elongated separated tubules is sometimes problematical. Villous architecture is defined arbitrarily by the length of the glands exceeding twice the thickness of normal colorectal mucosa. Tubulovillous adenomas have a mixture of tubular and villous structures with a ratio between 80%/20% and 20%/80%. Serrated adenomas are characterized by the saw-tooth configuration of a hyperplastic (metaplastic) polyp on low power microscopy, but the epithelium lining the upper portion of the crypts and luminal surface is dysplastic. Serrated adenomas can also have a tubular or villous component, but low-levels of microsatellite instability (MSI-L) and altered mucin are characteristic of these serrated lesions [840]. By contrast, mixed hyperplastic polyp adenoma contains separate identifiable areas of each histopathological type [1092]. Occasionally, some villous adenomas show in the slopes of the villi closely packed small glands; those adenomas have been referred to as villo-microglandular adenomas [972].

Although tiny flat or depressed adenocarcinomas are well-described, it is difficult to determine if de novo adenocarcinomas without a benign histopathological precursor lesion ever occur in the large bowel, because adenocarcinoma can overgrow the precursor lesion. The prolonged time interval usually required for progression of intraepithelial to invasive neoplasia offers opportunities for prevention or interruption of the process to reduce mortality due to colorectal carcinoma.

Intraepithelial neoplasia can also occur in the absence of an adenoma, in a pre-existing lesion of another type (such as a hamartomatous polyp in juvenile polyposis syndrome and Peutz-Jeghers syndrome), and in chronic inflammatory diseases.

**Hyperplastic (metaplastic) polyps**

The definition is a mucosal excrescence characterized by elongated, serrated crypts lined by proliferative epithelium in the bases with infolded epithelial tufts and enlarged goblet cells in the upper crypts and on the luminal surface, imparting a saw-tooth outline. In the appendix, diffuse hyperplasia may occur as a sessile mucosal proliferation. The epithelial nuclei in the serrated region are small, regular, round and located at
the base of the cells adjoining the basement membrane, which is often thickened beneath the surface epithelial cells. The cytoplasm contains prominent mucin vacuoles, which are usually larger than normal goblet cells. The proliferative zone often shows increased cellularity and mitotic activity, which can be mistaken for adenoma. Hyperplastic polyps are traditionally considered non-neoplastic, but ras mutation is common, clonality has been demonstrated, and biochemical abnormalities and epidemiological associations that occur in colorectal adenomas and carcinomas have been found (851, 663, 1178). These lines of evidence suggest that hyperplastic polyps may be neoplastic but have a molecular pathogenesis that differs from the adenoma-adenocarcinoma sequence due to absence of inactivation of the APC/beta-catenin pathway.

**Juvenile polyps**

Sporadic juvenile polyps are typically spherical, lobulated and pedunculated and considered hamartomatous. They most commonly occur in children. The surface is often eroded and friable, and the cut surface typically shows mucin-containing cysts. On histology, the abundant stroma is composed of inflamed, often oedematous granulation tissue that surrounds cystically dilated glands containing mucin. The glands are lined by cuboidal to columnar epithelial cells with reactive changes. The juvenile polyps in patients with juvenile polyposis syndrome may have the macroscopic and microscopic appearances of sporadic juvenile polyps, but they often have a frond-like growth pattern with less stroma, fewer dilated glands and more proliferated small glands (microtubular pattern) than their sporadic counterparts. Intraepithelial neoplasia (dysplasia) is rare in sporadic juvenile polyps. Intraepithelial neoplasia in this setting results from inactivation of the APC/beta-catenin pathway analogous to the genetic basis of adenoma formation (2145).

**Peutz-Jeghers polyps**

These are discussed in the small intestine section.

**Reactive lesions**

**Inflammatory polyps.** These non-neoplastic polyps are composed of varying proportions of reactive epithelium, inflamed granulation tissue and fibrous tissue, often with morphological similarity to juvenile polyps; inflammatory polyps are seen in a variety of chronic inflammatory diseases including chronic inflammatory bowel disease and diverticulitis.

**Lymphoid polyps.** These result from aggregates of reactive mucosa-associated lymphoid tissue with conspicuous germinal centres located in the mucosa and/or submucosa.

**Mucosal prolapse.** On occasion, mucosal prolapse can produce morphological features that mimic neoplasia, including polyps, masses and ulcers characterized histologically by elongated, distorted, regenerative glands surrounded by a proliferation of smooth muscle fibres from the muscularis mucosae, together with superficial erosions, inflamed granulation tissue and fibrosis (159). Widening of gland lumina at the surface is common. Examples of this phenomenon include inflammatory cloacogenic polyp (1083), solitary rectal ulcer and cap polyp. The process can extend into the bowel wall, producing colitis cystica profunda.

**Neoplasia in chronic inflammatory bowel disease**

There is evidence that the natural history of colorectal carcinomas associated with chronic colitis differs from that of ordinary adenomas both morphologically and with respect to the type and sequence of genetic alterations.

*Fig. 6.28* Tubulovillous adenoma, partly sessile, partly pedunculated.

*Fig. 6.29* A Adenoma with low-grade dysplasia and well-maintained glandular architecture. B Low-grade dysplasia with regular but slightly elongated, hyperchromatic nuclei. Cytoplasmic mucin is retained.

*Fig. 6.30* Adenomas with high-grade dysplasia. A Loss of normal glandular architecture, hyperchromatic cells with multi-layered irregular nuclei and loss of mucin, high nuclear/cytoplasmic ratio. B Marked nuclear atypia with prominent nucleoli. C Adenoma with focal cribriform pattern.
Ulcerative colitis (UC)

Development of carcinoma is apparently metachronous to the development of intraepithelial neoplasia (classified as low-grade and high-grade) complicating chronic colitis. Because invasion can be associated with intraepithelial neoplasia exhibiting relatively mild morphological changes, high-grade intraepithelial neoplasia is diagnosed in colitis on the basis of abnormalities that are less severe than the criteria for high-grade intraepithelial neoplasia in adenomas. It may be flat or present as a ‘dysplasia associated lesion or mass’ (DALM); the latter is often associated with a synchronous carcinoma arising beneath the dysplastic surface. DALMs are considered high-grade lesions through their architecture alone, and both DALM of any grade of dysplasia and high-grade flat dysplasia are associated with invasive carcinoma in about 40% of cases. The diagnosis of DALM and high-grade flat dysplasia usually leads to total colectomy (1687). It may be difficult to distinguish a DALM from an incidental adenoma in a patient with UC.

Attempts have been made to identify early dysplastic lesions in UC with cell cycle proliferation markers. Topoisomerase II alpha and Ki-67 have been shown to increase significantly over baseline expression in UC related dysplasias. Ki-67 positive cells are found both at the surface and the base of the crypts, indicating a fundamental deregulation of the proliferative cell pool (1368). Alterations of p16 have also been identified in early UC but only very infrequently in adenomas. Both tumour tissue and multiple colorectal cancer cell lines studied showed absence of LOH in 9p 1 (2019, 878).

Microsatellite instability and gene alterations in p16 and p53 may represent early events during the development of dysplasia and carcinoma, and these changes may lead to susceptibility for allelic loss of other genes such as APC and DCC. It has been shown that LOH of genetic areas close to the VHL locus on 3p is frequently present in DALM lesions and, less frequently, in flat dysplastic lesions. These changes are not usually seen in sporadic adenomas (515). This may indicate that dysplasia in UC and sporadic adenomas may follow different genetic pathways.

Crohn disease

Intraepithelial neoplasia, classified as low-grade or high-grade, is associated with a high proportion of Crohn carcinomas, either adjacent to the invasive lesion or at a distance from it (1757). Similar to UC, polyoid dysplastic lesions are diagnosed as DALM in Crohn’s disease. Mucinous adenocarcinomas are seen in Crohn disease more frequently than in sporadic colorectal carcinomas (656). There is an increased frequency of adenocarcinomas within perianal fistulas, and of squamous cell carcinomas of the anal mucosa (992).

Similar to UC, TP53 and c-KRAS mutations are observed earlier in Crohn-associated intraepithelial neoplasia associated with UC, in contrast to the adenoma-carcinoma sequence in sporadic colorectal carcinomas. Some TP53 mutations have even been observed in non-dysplastic mucosa of chronic inflammation (516, 1463, 2175).

Genetic susceptibility

The spectrum of genetic susceptibility is broad, ranging from well-defined autosomal dominantly inherited syndromes with known germline genetic mutations to ill-defined familial aggregation (1531, 1928, 642). The diseases are traditionally divided into polyposis syndromes characterized by large numbers of polyps, e.g. familial adenomatosis coli (FAP), and non-polyposis syndromes with a small number of or absence of polyps, e.g. hereditary nonpolyposis colorectal cancer (HNPCC). They are described in the following chapters. A non-truncating polymorphism of the APC gene that induces an unstable polyadenin repeat sequence, occurs in approximately 5% of Ashkenazi Jews.
and carries a modestly elevated risk of colorectal cancer. Only small numbers of adenomas occur in patients with this form of germline APC alteration \(1004\).

**Li-Fraumeni syndrome**  
MIM No: Li-Fraumeni syndrome \(151623\);  
TP53 mutations \(191170\)

Li-Fraumeni syndrome is an autosomal dominant disorder characterized by multiple primary neoplasms in children and young adults, with a predominance of soft tissue sarcomas, osteosarcomas and breast cancer, and an increased incidence of brain tumours, leukaemia and adrenocortical carcinomas \(1403\).

Criteria for proband identification are: (1) occurrence of sarcoma before age 45, (2) at least one first-degree relative with any tumour before age 45, and (3) at least one first- or second-degree relative with cancer before age 45 or with sarcoma at any age \(717, 141, 1066\).

In about 70\% of Li-Fraumeni kindreds, affected family members carry a germline mutation in \(TP53\) \(1151\). From 1990 to 1999, a total of 144 families with a \(TP53\) germline mutation were identified. A database of these mutations is available at [http://www.iarc.fr/p53/Germ.htm](http://www.iarc.fr/p53/Germ.htm) \(699\).

As with somatic mutations, germline mutations cluster in conserved regions of exons 4 to 9, with major hotspots at codons 175, 248 and 273. It has been suggested that cancer phenotype correlates with the position of the mutation within the coding sequence, with lower age of clinical manifestation in probands with mutations falling in the DNA-binding domain of the p53 protein \(142\). The most frequent type of germline mutation is transition (GC to AT) at CpG dinucleotides 556. The molecular basis of tumour predispositions in families within \(TP53\) germline mutations is not known. Recent studies have excluded tumour suppressor genes such as \(PTEN\) and \(CDKN2\) \(214\).

**Gastrointestinal manifestations**

Neoplasms of the digestive tract represent 7\% of the tumours observed in Li-Fraumeni families. Most of these tumours are colorectal carcinoma, with a minority of stomach carcinomas. The male:female ratio is 1.5 and the mean age at clinical manifestation is 45, which correspond to a relatively long latency period as compared to other types of cancers occurring in Li-Fraumeni families \(1403\). Preferential familial occurrence of stomach cancer...
Tumours of the colon and rectum (familial clustering) has been observed only in Japan, a country at high incidence for that type of tumour. Cancers of the liver and of the upper gastrointestinal tract are exceedingly rare (less than 0.5% of all Li-Fraumeni neoplasms). In these neoplasms, sporadic cases often carry somatic TP53 mutations. The low frequency of these tumours in families with germline TP53 mutations suggests that the pre-existence of a TP53 mutation is not sufficient to increase the likelihood of cancer development.

**BRCA 1 and BRCA 2**

In a retrospective analysis of 33 large, high-risk breast and breast/ovarian cancer families linked to the BRCA1 locus, a significantly elevated risk of colon cancer was found, with an estimated relative risk of 4.11 (95% CI 2.36 - 7.15) [518]. This corresponds to a risk of colon cancer by age 70 of about 6%. In this study, there did not seem to be any increased relative risk at younger ages, although power to detect either sex or age effects was somewhat low in this set of data. In a similar study of BRCA2 carriers [69], no increased risk of colorectal cancer was observed. However, there was a significantly elevated risk for both stomach and gallbladder tumours among known or likely mutation carriers with estimated relative risks associated with BRCA2 of 2.6 (95% CI 1.46 - 4.61) and 5.0 (1.50 - 16.5), respectively.

**Molecular genetics**

The development of most colorectal carcinomas is believed to begin in a colorectal epithelial cell with a mutational inactivation of the APC (adenomatous polyposis coli) suppressor gene [922, 636, 186]. This inactivation has multiple consequences, including interference with E-cadherin homeostasis and dysregulation of transcription of genes. Clonal accumulation of additional genetic alterations then occurs, including activation of proto-oncogenes such as c-myc [680] and ras, and inactivation of additional suppressor genes. The genes commonly inactivated during progression include genes on chromosome 18 [1583, 614] and the TP53 gene on the short arm of chromosome 17 [1056, 415]. The mutated TP53 gene product, in turn, fails to regulate normally a variety of genes regulated by wild-type p53, including p21WAF1/CIP1 cyclin-dependent kinase inhibitor which complexes with proliferating cell nuclear antigen [349], and genes leading to apoptosis, including BAX [278]. For many suppressor genes, inactivation of one allele is often caused by loss of all or part of the chromosome where the gene resides. Various other chromosomal loci have high frequencies of loss in colorectal cancer due to chromosomal instability [1044], but the target genes are not yet known.

**Microsatellite instability (MSI)**

Some colorectal cancers are distinguished by extensive nucleotide insertions or deletions in numerous, intrinsically unstable repeated sequences in tumour DNA, termed microsatellite instability (MSI), also termed ubiquitous somatic mutations, DNA replication errors (RER), or nucleotide instability (1540, 860). MSI is defined as a change of any length due to either insertion or deletion of repeating units, in a microsatellite within a...
Adenocarcinoma

It has been recommended that a panel of five microsatellites should be used as a reference standard (BAT25, BAT26, DSS346, D2S123, D17S250) for carcinomas of the large intestine (164). If two or more of these markers show MSI, the lesion is classified as high-frequency microsatellite instability (MSI-H); if only one marker shows MSI, it is classified as low-frequency microsatellite instability (MSI-L); if no markers show MSI it is classified as microsatellite stable (MSS). If more than five markers are used, the criteria should be modified to reflect the percentage of markers demonstrating MSI. Thus, MSI-H lesions would exhibit MSI in more than 30-40% of markers tested.

MSI-H carcinomas are characteristic of hereditary nonpolyposis colorectal cancer syndrome (HNPCC) due to germline mutation of one of a group of DNA mismatch repair genes followed by somatic inactivation of the other allele. Sporadic MSI-H tumours comprise about 15% of colorectal carcinomas. They usually follow transcriptional silencing of both alleles of the hMLH1 mismatch repair gene due to aberrant methylation of cytosine residues in the cytosine and guanine-rich promoter region (886, 696). The alterations that accumulate during progression of both hereditary and sporadic neoplasms characterized by MSI-H include mutations in microsatellites within the coding region of some genes, such as the type II receptor for TGF-beta1 and BAX (548). In contrast to microsatellite-stable cancers, MSI-H cancers display nucleotide rather than chromosomal instability; allelic deletions are rare (1044).

Recent studies indicate a functional link between defective DNA mismatch repair and the Wnt-signalling pathway. Approximately 25% of sporadic colorectal carcinomas with defective mismatch repair (MSI-H) were shown to contain frameshift mutations in the AXIN2 gene, which leads to a stabilization of β-catenin and activation of β-catenin/T-cell factor (TCF). This was associated with an accumulation in tumour cell nuclei which was absent in colorectal cancer without mismatch repair deficiency and in the absence of APC mutations. AXIN2 mutant protein appears to be more stable than the wild-type gene product, suggesting a dominant-negative effect (1079A).

**Prognosis and predictive factors**

**Morphology.** Macroscopic and microscopic features reportedly related to prognosis are summarized in Table 6.01 (2348). Poor prognosis has been associated with both large and small tumour size, with sessile and ulcerated configuration as contrasted with polypoid cancer, with extensive involvement of the bowel circumference, with the presence of complete bowel obstruction, with perforation, and with serosal deposits.
Histopathological features related to poor prognosis include deep infiltration of the layers of the wall, extensive involvement of a particular layer, an infiltrative pattern of the invasive edge of the tumour as contrasted to an expansile pattern, and poor differentiation, including signet-ring cell and mucinous adenocarcinoma, adenosquamous carcinoma, small cell carcinoma and anaplastic carcinoma (1672, 1946, 220, 916, 266). Mucinous adenocarcinomas of the rectum often present at a later stage and have the poorest overall prognosis (1928), but the MSI status influences the aggressiveness of this histopathological subtype (1221). Other studies have shown no significant difference in prognosis between mucinous and non-mucinous varieties of adenocarcinoma (1543).

**Lymph node metastasis.** Metastasis to numerous nodes, those close to the mesenteric margin, at great distance from the primary tumour, or in retrograde lymph nodes, have been associated with poor prognosis while the prognostic value of identification of micrometastasis in lymph nodes by immunohistochemical or molecular techniques is still controversial (1564, 1387, 221).

**Angiogenesis.** Neovascularization of tumour stroma is crucial in supporting tumour growth, and high levels of microvessel density have been interpreted as an adverse prognostic feature (2010).

**Inflammatory response.** The presence of an intense inflammatory infiltrate with polymorphonuclear leukocytes (particularly eosinophils), lymphocytes, plasma cells, mast cells and histiocytes, as well as prominent desmoplasia have been associated with improved prognosis (1352). In the regional lymph nodes, hyperplasia of the paracortical T-lymphocyte areas and the B-cell germinal centers have also been reported as favourable, as has sinus histiocytois.

**Other features of colorectal carcinomas** that have been shown to be of prognostic value in some studies include **angiolympathic invasion**, **perineural space involvement**, **extramural venous involvement**, **peritumoral lymphocytic response**, and **tumour-infiltrating lymphocytes**. Some of these features are evaluated in a classification proposed by Jass (389). A microacinar pattern of growth, defined as discrete, small, relatively regular tubules, is associated with reduced survival (559, 2100).

**Extent of resection.** A short longitudinal surgical resection margin (2-5 cm), reflecting the surgical technique employed, has been associated with poor outcome. In rectal cancer, clearance from the circumferential margin is important. The circumferential margin represents the adventitial soft tissue margin closest to the deepest penetration of the tumour. For all segments of the large intestine that are incompletely enveloped by peritoneum or not enveloped, the circumferential margin is created by blunt or sharp dissection at operation. The mesocolic margin in resection specimens of colon cancer is usually well distant from the primary tumour, but the status of the circumferential margin is particularly important in rectal carcinoma due to the anatomic proximity of pelvic structures (15).

**Genetic predictive markers.** Some of the genetic alterations identified in colorectal cancers are markers for prognosis (313, 1206). Allelic loss of chromosome 18q was found to be an adverse prognostic indicator. Other studies reported that loss of chromosomes 17p, 1p, 5q, 8p or 18q, decreased DCC gene expression, p53
overexpression, reduced p27<sup>kip1</sup> expression, high expression of cyclin A, ras gene mutation, expression of enzymes involved in matrix degradation and their inhibitors (cathepsin-L, urokinase, tissue-type plasminogen activator, tissue inhibitors of metalloproteinases), expression of genes involved in apoptosis (bcl2, bax, survivin), expression of cell surface molecules (CD44 and its variants, ICAM1, galectin 3) and metabolic enzymes (GLUT1 glucose transporter, manganese-superoxide dismutase, thymidylate synthetase, ornithine decarboxylase, cyclooxygenase 2) have prognostic value.

In addition, colorectal cancers manifesting MSI-H have been reported to have a lower frequency of metastasis and improved prognosis when compared to microsatellite-stable tumours.

**Response to therapy.** No pathological features have been reported as predictive of therapeutic response, but some molecular alterations have potential as predictive markers. Studies in cell lines of colonic and other carcinomas have shown that in vitro, the status of TP53 is crucial. The TP53 pathway is closely linked to regulation of the cell cycle and of apoptosis. The presence of wild-type p53 in cell lines is associated with in vitro growth inhibition in response to many chemotherapeutic agents, and with radiation-induced upregulation of p21<sup>WAF1/CIP1</sup> and cell cycle arrest. Tumours manifesting MSI-H may respond to 5-FU-based chemotherapy, while p53 protein accumulation was associated with lack of response to postoperative adjuvant chemotherapy with 5-FU and levamisole. Chromosome 18q loss was associated with an unfavourable survival rate in this setting.

Major problems exist in the interpretation of various pathological features as prognostic and predictive markers. Many of these features are interrelated but have been treated for statistical purposes as independent variables in studies. At present, anatomic staging is the mainstay of clinical decision-making.

### Table 6.01
Prognostic factors in colorectal carcinoma.

<table>
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<tr>
<th>Features of the primary tumour</th>
<th>Evidence of vessel invasion</th>
<th>Evidence of host response</th>
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<td>Distance between resection margin and tumour</td>
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<td>Local inflammatory and desmoplastic response to infiltrating</td>
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<td>Bowel obstruction</td>
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<td>Perforation</td>
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<td>Pattern of invasion</td>
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<td>Grade of differentiation</td>
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</table>

Fig. 6.50 Solitary rectal ulcer. Smooth muscle increased between glands, distorting and displacing them.

Fig. 6.51 Inflammatory cloacogenic polyp with mucous extravasation.
Familial adenomatous polyposis

Definition
Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by numerous adenomatous colorectal polyps that have an intrinsic tendency to progress to adenocarcinoma. It is caused by a germline mutation in the Adenomatous Polyposis Coli (APC) gene which is located on the long arm of chromosome 5 (5q21-22). Gardner syndrome is a variant of FAP that includes epidermoid cysts, osteomas, dental anomalies and desmoid tumours, in addition to colorectal adenomas. Turcot syndrome is a variant that is associated with a brain tumour (medulloblastoma). An attenuated FAP form has been distinguished from classic FAP, where the number of adenomas is less than 100 in the colon.

MIM No.: FAP, including Gardner syndrome, 175100; Turcot syndrome, 276300

Synonyms
Adenomatous polyposis coli, familial polyposis coli, Bussey-Gardner polyposis, Gardner syndrome, familial multiple polyposis, familial adenomatosis, familial polyposis of the colon and rectum, familial adenomatous polyposis coli, etc.

Incidence
Estimates of the incidence of FAP vary between 1 per 7000 and 1 per 30,000 newborns. The mean annual incidence rate has been constantly from 1 to 2 per 1,000,000 in Denmark and Finland while the prevalence has increased to more than 25 per 1,000,000 since the creation of preventive polyposis registries [205; 836]. In general, FAP underlies less than 1% of all new colorectal cancer cases. Between 30 and 50% of new FAP patients are solitary cases, probably representing new mutations of the APC gene. In patients where the clinical criteria remain doubtful and genetic diagnosis is not achieved the finding of extracolonic features of FAP (epidermoid cysts, osteomas, desmoid tumour, gastric fundic gland polyps, etc.) may give additional diagnostic support.

The following diagnostic criteria have been established: (1) 100 or more colorectal adenomas or (2) germline mutation of the APC gene or (3) family history of FAP and at least one of the following: epidermoid cysts; osteomas; desmoid tumour.

Colorectal polyps
The colorectal polyps are adenomas, most often tubular, and resemble their sporadic counterparts.

Localization
Colorectal adenomas in FAP occur throughout the colon but follow the general distribution of sporadic adenomas, with greatest density in the rectum and sigmoid colon. The distribution of cancers follows that of the adenomas.

Clinical features
Age at clinical manifestation
Colorectal adenomas become detectable at endoscopic examination (sigmoidoscopy) between the age of 10 and 20 years, increasing in number and size with age. The most important clinical feature of FAP is the almost invariable progression of one or more colorectal adenomas to cancer. The mean age of development of colorectal cancer is about 40 years, but the cancer risk is 1 to 6% already at

Fig. 6.52 Colectomy specimens from patients with familial adenomatous polyposis. A Hundreds of polyps of different size cover the entire mucosal surface. B Multiple adenomas in different stages of development. C Lateral view of polyps. D Numerous small early (sessile) adenomas.
the age of 20 to 25 years (835), and colo-
rectal cancer has been reported even in
children with FAP. Extracolonic manifesta-
tions such as epidermoid cysts, mandi-
bular osteomas, desmoid tumours or
genital hypertrophy of the retinal pig-
ment epithelium (CHRPE) may present in
children and can serve as markers of
FAP.

Symptoms and signs
In the early phase of FAP adenomas do
not cause any symptoms. Specific symp-
toms due to colorectal adenomas are rec-
tal bleeding and diarrhoea often accom-
panied by mucous discharge and
abdominal pain. Symptoms appear gradu-
ally and may be easily overlooked; the
mean age of appearance of symptoms
was 33 years and the mean age of diag-
osis 36 years in about 200 FAP patients
who had no prophylactic screening
arranged [216].

Two thirds of patients diagnosed to have
FAP on the basis of symptoms (propositi)
already have colorectal cancer whereas
in asymptomatic members of known FAP
families cancer is very rare at the time of
the detection of FAP provided that pro-
phylactic endoscopic screening was
arranged in good time, i.e. before the
age of 20 years [836].

Imaging and FAP screening
The appropriate screening method for
diagnosing FAP is flexible sigmo-
doscopy, which should be arranged for
all children of an affected FAP parent
from the age of 10 to 15 years and con-
tinued at 1 to 2 year intervals up to the
age of 40 years if adenomas are not
detected. Endoscopies can be replaced
by genetic testing for the specific APC
mutation in those families where the
mutation has been identified. A positive
test is diagnostic for FAP and signifies
the need for prophylactic colectomy or
proctocolectomy when the colorectal
adenomas become detectable, at the
age of 20 to 25 years at the latest.
If the operation is not performed immedi-
ately after the diagnosis of FAP; colonos-
copy should be undertaken to evaluate
the entire colon because large aden-
omas or cancer may reside beyond the
reach of the flexible sigmoidoscope.
Endoscopic evaluation of the upper gas-
trointestinal tract is recommended at the
time of prophylactic colectomy or procto-
colectomy, and should be repeated at
2 to 5 year intervals depending on the
finding of adenomas in duodenal and
gastric biopsies [888]. Double contrast
barium enema and barium meal may be
used to demonstrate polyps but are infe-
rior to endoscopy because biopsies are
required to provide histological evidence
for a definite diagnosis of FAP.

Macroscopy
Most polyps in FAP are sessile and spheri-
cal or lobulated. Scattered larger pedun-
culated polyps are much less numerous
(205; 835; 836; 688). The colorectal
polyps appear first in adolescence and,
by the late teens, usually number thou-
sands, typically carpeting the lining of the
whole large bowel. Their number varies
between families, in some being little
more than 100, even in adults [1988],
whereas, in the majority of families, there
are profuse polyps, numbering thou-
sands. Typically, the polyps are scattered
evenly along the whole large bowel but, in
over one third of cases, their density is
greater in the proximal colon. Adult
patients with rectal sparing have been
described, even when adenocarcinoma
was present in the right colon (1503).
In any one patient the polyps range from
barely visible mucosal nodules to pedun-
culated polyps of up to 1 cm or more. In
some patients and families the aden-
oma mostly measure only a few millime-
tres while in others they are larger, with
polyps up to several centimetres. In con-
trast, in attenuated FAP, the polyps are so
few that they may not be noticed at rigid
sigmoidoscopy. Polyps rarely appear
until late childhood [216] and are rarely
larger than 1 cm until adulthood.
Adenocarcinomas arise in only a small
percentage of the adenomas.

Histopathology
Adenomas in FAP begin as single dys-
plastic crypts (‘unicryptal’ adenomas). In
practice, to find more than one of these in
a colon is unique to FAP. By excessive
and asymmetrical crypt fission [1086;
433; 2062], probably due to loss of
APC-controlled growth and tissue organi-
ation, they develop into oligocryptal
adenomas, which may not be visible as
polyps before further growth into grossly
visible adenomatous polyps. Most
adenomas in FAP display a tubular archi-
tecture; infrequently they are tubulovil-
ious or villous. Non-polypoid, flat adeno-
mas account for approximately 5% of
adenomas in the colon of affected family
members [1181]. AF adenomas and carci-
nomas in FAP are histologically identical
to sporadic lesions.
Proliferation
The histologically normal intestinal mucosa in FAP shows no increase in the rate of epithelial cell proliferation (2062). Mitotic activity is not increased (1315) except in the adenomatous epithelium, in which cell proliferation is identical with that in sporadic adenomas.

Small intestinal polyps
Small bowel polyps, particularly duodenal polyps, are also adenomas. They develop preferentially in the periampullary region of the duodenum, probably due to a co-carcinogenic effect of bile (1679, 1805). They become evident ten years later than the colorectal polyps. Using side-viewing endoscopy, adenomas have been found in 92% of patients with FAP at routine screening (1809). They increase in size and number with time and carry a lifetime risk of duodenal or periampullary cancer of about 4% (688). Ampullary and periampullary adenocarcinoma is one of the principal causes of death in patients who have undergone prophylactic proctocolectomy (1809).

Extra-intestinal manifestations
Several other organs are involved in FAP but extra-intestinal manifestations rarely determine the clinical course of the disease.

Stomach
Gastric adenomas do occur with increased frequency (425) but the most common abnormality is the fundic gland polyp. This is a non-neoplastic mucus retention type of polyp, grossly visible as a smooth dome-shaped nodule in the gastric body and fundus, usually multiple. Histologically, the lesion is characteristically undramatic, consisting of gastric body mucosa that is often normal apart from cystic dilatation of glands. There is evidence of increased cell proliferation and dysplasia developing in these polyps (2144) but progression to adenocarcinoma is only a rare occurrence (2214).

Liver and biliary tract
There is an increased incidence of hepatoblastoma in the male infants of families with FAP (563, 578). Dysplasia has been demonstrated in the bile duct and gallbladder epithelium in patients with FAP (1377) and these patients are at risk of developing adenocarcinoma of the biliary tree (1806).

Extra-gastrointestinal manifestations

Soft tissues
Tissues derived from all three germ layers are affected in FAP. As well as the endodermal lesions so far described, mesodermal lesions in the form of a fibromatosis unique to FAP, usually referred to as desmoid tumour, develop in a substantial minority of patients (315). Desmoid tumours arise in either the retroperitoneal tissues or in the abdominal wall, often after trauma or previous surgery involving that site.

A desmoid is a mass of firm pale tissue, characteristically growing by expansion, usually rounded in shape. Desmoids begin as small scar-like foci of fibrosis in the retroperitoneal fat and, when large, typically extend around and between other structures such as the small or large bowel, ureters and major blood vessels. Histologically, these lesions are composed of sheets of elongated myofibroblasts, arranged in fascicles and whorls. The lesions have a dense, tough consistency and there is a variable amount of collagen. They are well vascularized and contain numerous small blood vessels that bleed profusely when incised.

Bones
Bone lesions include exostoses and endostoses. Endostoses of the mandible are found in the majority of patients (203). They are almost always small and symptomless. Exostoses may be solitary or multiple and tend to arise in the long bones.

Teeth
Dental abnormalities have been described in 11 to 80% of individuals with FAP (241). The abnormalities may be impaction, supernumerary or absent teeth, fused roots of first and second molars or unusually long and tapered roots of posterior teeth.

Eye
In 75-80% of patients, ophthalmoscopy reveals multiple patches of congenital
hypertrophy of retinal pigment epithelium (CHRPE) [280]. Ultrastructurally, they are freckle-like plaques of enlarged melanin-containing retinal epithelial cells [1466]. Their value for diagnosis is limited by inconsistency and variation between families.

Skin
Epidermal cysts, usually of the face and often multiple, were first described in FAP by Gardner [565].

Endocrine system
There is a definite but relatively slight increase in the incidence of endocrine tumours in FAP, including neoplasia of pituitary, pancreatic islets and adrenal cortex [1160], as well as multiple endocrine neoplasia syndrome, type 2b [1500] but these are of insufficient frequency or gravity to form part of a routine screening protocol. The best documented endocrine association is papillary carcinoma of thyroid [268], largely restricted to women [202].

Nervous system
The concurrent presence of a brain tumour and multiple colorectal polyps constitutes Turcot syndrome. Some individuals affected in this way are victims of FAP, with a germline defect of APC. These are infants or young children who present with medulloblastoma and colorectal polyps (658). Other individuals present later in life with a glioma, usually an astrocytoma or glioblastoma multiforme and are usually associated with hereditary non-polyposis colon cancer (HNPCC) rather than FAP [262].

Genetics
FAP is an autosomal dominant disease with almost complete penetrance by 40 years of age. APC germline mutations are the only known cause of FAP.

Gene structure and expression
The APC gene was localized to chromosome 5q21-22 by Bodmer et al. [156] and Leppert et al. [1047]. It was isolated by the group of White [868; 629] and by the laboratories of Nakamura and Vogelstein [920; 1364]. It spans over a region of 120 Kb and is composed of at least 21 exons, 7 of which are alternatively expressed [1658]. 16 APC transcripts that differ in their 5’-most regions and arise by the alternative inclusion of 6 of these exons have been identified. The APC gene is ubiquitously expressed in normal tissues, with highest levels in the central nervous system. Tissue-specific differences were observed in the expression of APC transcripts without exon 1, a coding region for a heptad repeat that supports homodimerization of the APC protein.

Gene product and function
The APC protein is a 2,843-amino acid polypeptide that is a negative regulator in the Wnt signaling pathway. The protein contains several functional domains that act as binding and degradation sites for β-catenin and control the β-catenin intracellular concentration. A protein-binding domain near the carboxy-terminal of APC mediates phosphorylation by glycogen synthase kinase 3β (GSK3β) and stabilizes the formation of a complex between the two proteins [1627]. In an unstimulated cell, GSK3β promotes phosphorylation of the protein conductin/axin which is added to the APC GSK3β complex [2107; 124]. Phosphorylated axin recruits β-catenin, which is in turn phosphorylated and targeted for degradation through an APC-dependent ubiquitin-proteasome pathway [11]. Normal Wnt signalling inhibits GSK3β activity and dephosphorylates axin. As a result, β-catenin is released from the complex [2107]. In the cytoplasm, β-catenin is involved in cytoskeletal organization with binding to microtubules. It also interacts with E-cadherin, a membrane protein involved in cell adhesion. Free β-catenin shuttles to the nucleus where it binds to the transcription factors of the TCF/LEF family. The resulting complexes activate c-MYC [680] and cyclin D1 transcription [1753; 1922]. Lack of functional APC causes unregulated intracellular accumulation of β-catenin and thereby constitutive expression of c-MYC and of the cyclin D1 gene (CDD1).
Gene mutations

The germline mutation rate leading to a new deleterious APC allele is estimated to be 5 to 9 per million gametes. As a result, most families exhibit unique mutations, and individuals with no previous family history of FAP are not uncommon. They may represent up to one fourth of propositi. A deleterious APC mutation may be found in about 95% of FAP patients. The vast majority of the mutant alleles lead to the synthesis of a truncated protein. About 10% of the mutations are large interstitial deletions that may involve the entire gene. Rare missense mutations, most with uncertain functional consequences, have been described. Mutations at codons 1061 and 1309 account for 20% of all identified germline mutations in the APC gene. In up to 5% of families, the genetic defect causing FAP is not yet known.

Genetics of FAP associated tumours

Consistent with the 2-hit model of carcinogenesis by tumour suppressor genes, the wild type APC allele is lost or mutated in the vast majority of FAP associated tumours, including colorectal adenomatous polyps and carcinoma, desmoid tumours (1245), medulloblastoma (202), gastroduodenal tumours (1949), thyroid carcinoma (822) and hepatoblastoma (980). Each colorectal adenomatous polyp is a premalignant lesion that may progress to carcinoma in an unpredictable fashion. In addition to APC mutations, colon carcinomas in FAP patients contain somatic mutations that are similar to those found in the most frequent type of sporadic colon cancers not associated with replication errors. TP53 mutation and 17p allele loss have been observed in 40% of invasive carcinomas (910). However, in some families TP53 may not be involved (30). Loss of alleles on chromosome 18 and 22 were observed in 46% and 33% respectively. The KRAS mutation frequency increases from 11% in moderately to 36% in severely dysplastic adenomas (30). KRAS mutations may potentiate cyclin D1 transcription (680). Interestingly, the type of APC germline mutation may influence the mode of inactivation of the second APC allele (30).

Animal model

Heterozygous mutant mice for a defective Apc allele develop multiple intestinal neoplasia (1245). The homozygous mutant embryos die prior to gastrulation (1811). Expression of the secretory phospholipase Pla2g2a is associated with a decreased number and size of adenoma in heterozygous mutant Apc mice (1283). Implication of PLA2G2A polymorphism in FAP expressivity has not been demonstrated in humans.

Genotype / phenotype relationships

There are well documented relationships between the location of the mutation on the APC gene and the FAP phenotype. APC mutations in the first or last third of the gene are associated with attenuated colorectal polyposis (AAPC) characterized by the occurrence of less than 100 polyps and a late onset (1284). Fundic gland polyposis is prevalent in the attenuated form of FAP but desmoids may be present only if the AAPC causing mutation lies in the 3’ end of the APC gene. Indeed, mutations after codon 1444 are associated with an increased susceptibility to desmoid tumours (340). CHRPE

Fig. 6.60 Mesenteric fibromatosis (desmoid tumour) in a patient with FAP. A The lesion entraps loops of small intestine. B Collagen bands and small vessels.

Fig. 6.61 Structure of the APC gene and location of somatic and germline mutations. From: P. Polakis, Biochim Biophys Acta 1332: F127-F147 (1997)
lesions are a consistent feature, except if the APC mutation is located before exon 9 and after codon 1387 (1810; 340). Mutations in the central region of the gene, including the mutational hotspot at codon 1309, correlate with a severe phenotype characterized by development of thousands of polyps at a young age (258). In contrast to mutant APC proteins truncated at codon 1309, which interfered only weakly with wild-type APC activity in an in vitro system, a mutant APC protein truncated at codon 1309 was shown to be a strong inhibitor and may thus have dominant negative properties (1422). These observations point to a possible mechanism that could contribute to the genotype/phenotype relationships observed in FAP. There may also be a correlation between slow acetylation genotypes and extracolonic manifestations of the disease (1308).

Application of genetic testing in the clinical setting

In the absence of systematic, family based screening programs, the presenting features are usually those of malignancy, such as weight loss and an inanition, bowel obstruction, or bloody diarrhoea. In such cases, patient evaluation will frequently find a colorectal carcinoma. Occasionally, the extracolonic features of the condition may lead to presentation and diagnosis. Cases of new mutation still present in these ways, but in areas with well organized registers, gene carriers among relatives of affected patients are identified prior to symptoms either by DNA-based genetic tests or by bowel examination.

The most commonly used commercially available genetic testing for FAP involves identification of the mutant APC allele by in vitro detection of truncated APC protein (414). This approach is referred to as in vitro protein synthesis (IVPS) testing. IVPS testing is able to detect mutation carriers in about 80% of families. Once evidence of a disease-causing mutation is found in an index case by this method, testing is near 100% predictive in other family members. It is imperative that genetic counselling be undertaken throughout the process of genetic testing. Without this, genetic testing and the use of the results are poorly applied in the clinical setting (1703).

Screening in gene carriers is similar to that in families where genetic testing is not applied or does not work and usually involves sigmoidoscopy every 1 to 2 years, beginning between age 10 and 12 years. If a genetic diagnosis is made after that age, full colonoscopy should probably be done in view of the risk of lesions higher in the colon. Preventive total colectomy is proposed to gene carriers when polyposis becomes conspicuous. Genotype/phenotype correlations may be used to adapt clinical management to individual FAP patients. A family member who has a negative DNA based genetic test can forgo screening if (1) the mutation found in other affected family members is obviously deleterious and (2) if the individual with a negative test has been unambiguously shown to be a non-gene carrier by DNA testing. Such individuals need no further screening as their risk to develop colon cancer is similar to that of the general population.
Hereditary nonpolyposis colorectal cancer

Definition
Hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) is an autosomal dominant disorder, characterized by the development of colorectal carcinoma, endometrial carcinoma, and cancer of the small intestine, ureter, or renal pelvis.

MIM No. 120435-6

Diagnostic criteria
In 1990, the International Collaborative Group on HNPCC (ICG-HNPCC) proposed a set of selection criteria to provide a basis for uniformity in collaborative studies [2003]. These criteria, referred to as Amsterdam Criteria I (ACI), have been widely used since then. Recently, the criteria have been revised to include the extracolonic cancers that are part of the syndrome. The new set of diagnostic criteria (ACII), is shown in Table 6.02 [2004]. They identify families that are very likely to represent HNPCC. On the other hand, they are not intended to serve as a guide to exclude suspected families from genetic counselling and mutation analysis.

Clinical features
Predisposed individuals from HNPCC families have a high lifetime risk of developing colorectal carcinoma (70-85%), endometrial carcinoma (50%), as well as certain other cancers (below 15%) [5, 2071, 2005]. Colorectal lesions are often diagnosed at an early age (mean, 45 years), and are located in the proximal part of the colon in about two-thirds of the patients. Synchronous or metachronous colorectal carcinoma is present in 35% of patients. In over 90% of the cases, it shows microsatellite instability (MSI) (Table 6.04) [839, 1166, 1129]. The adenomas that occur in HNPCC tend to develop at an early age, to have villous components and to be more dysplastic than adenomas detected in the general population. Although multiple adenomas may be observed in HNPCC, florid polyposis is not a feature. Extracolonic lesions include cancer of the endometrium, renal pelvis/ureter, stomach, small bowel, ovary, brain, hepatobiliary tract, and also sebaceous tumours. Among these tumours, carcinoma of the endometrium, ureter, renal pelvis, and small bowel have the highest relative risk, and are therefore the most specific for HNPCC (Table 6.03). The occurrence of sebaceous gland tumours together with HNPCC type internal malignancy is referred to as the Muir-Torre syndrome [322]. The association of primary brain tumours (usually glioblastomas) with multiple colorectal adenomas is referred to as the Turcot syndrome [1979]. The latter has a shared genetic basis with HNPCC on the one hand and FAP on the other hand [658].

Pathology
The pathology of HNPCC tumours is similar to that of sporadic colorectal carcinoma showing high levels of instability at short tandem repeat sequences, microsatellites (MSI-H). Many studies make no distinction between familial and non-familial MSI-H carcinomas. The following descriptions apply to all MSI-H carcinomas, but highlight subtle differences between HNPCC cancers and their sporadic counterparts where these are known.

Fig. 6.62 Mucinous adenocarcinoma from a patient with HNPCC.

Fig. 6.63 Abundant lymphocytes infiltrate the neoplastic epithelium in these poorly differentiated (A) and moderately differentiated (B) adenocarcinomas from patients with HNPCC.

126 Tumours of the colon and rectum
Macroscopy
HNPPC cancers show a predilection for the proximal colon including caecum, ascending colon, hepatic flexure and transverse colon [1130]. At least 60% occur in the proximal colon. The gross appearances have not been studied in detail. However, since HNPPC and MSI-H colorectal carcinomas show a consistent trend towards good circumscript (842, 1723), they are more likely to present as polypoid growths, plaques, ulcers or bulky masses and less likely to present as diffuse growths or tight strictures.

Adenomas are not numerous but are likely to be more frequent in HNPPC subjects than age-matched controls [846]. Colonooscopy studies indicate that the distribution of adenomas in HNPPC may not mirror the proximal colonic predilection of carcinoma [846]. This could be due to the occurrence of sporadic distal adenomas in older HNPPC subjects or because proximal adenomas are more likely to progress to cancer.

Histopathology
No individual microscopic feature is specific to HNPPC, but particular groups of features are diagnostically useful [1723]. Identical features are found in the 10 to 15% of sporadic colorectal cancers that show high levels of DNA microsatellite instability (MSI-H) [842]. However, sporadic MSI-H cancers present in older subjects lacking a family history of bowel cancer. HNPPC and sporadic MSI-H colorectal cancers fall into three groups based on site and microscopic criteria.

Proximally located mucinous adenocarcinomas. These are usually well circumscribed and well or moderately differentiated. Lymphocytic infiltration is not prominent but tumour infiltrating (intraepithelial) lymphocytes (TIL) may be evident in non-mucinous areas. Tubulo-villous or villous adenomatous remnants adjacent to the cancer may be present. Mucin production may be more common in subjects with an MSH2 germline mutation [1723].

Proximally located, poorly differentiated adenocarcinomas. Poor differentiation indicates a failure of gland formation, the malignant epithelium being arranged in small clusters, irregular trabeculae or large aggregates. Tumours are well circumscribed and lack an abundant desmoplastic stroma. Some are peppered with TIL. A Crohn-like lymphocytic reaction may be present. This subtype has been described as medullary or ‘undifferentiated’, though the majority contains subclones in which glandular differentiation is evident. This subtype may be more common in subjects with an MSH2 mutation [1723]. In general, colorectal cancers showing TIL and/or a Crohn-like lymphocytic reaction may appear to be more common in subjects with an MLH1 germline mutation [1723].

Adenomas in HNPPC. These are more likely to show features indicative of increased cancer risk including villosity and high-grade intraepithelial neoplasia [846]. Immunohistochemical staining to demonstrate loss of expression of MLH1 or MSH2 may assist in pinpointing the underlying germline mutation. However, antigenicity may be retained in the case of MLH1, even if genetic changes have resulted in a non-functioning protein [1924A: 1924B]. Virtually all sporadic MSI-H carcinomas lose MLH1 through methylation.

Immunohistochemical staining of MSI-H colorectal cancers confirms that the majority of TIL are CD3 positive T-cells and most, in turn, are cytotoxic (CD8 positive) [423]. In H&E sections, lymphocytes are difficult to discern when the percentage of CD3 positive lymphocytes (out of all epithelial nuclei) is less than about 5%. CD3 counts in excess of 5% occur in around 70% of MSI-H cancers. CD3 counts in excess of 10% are highly specific for MSI-H cancers. The nodular arrangements of lymphocytes occurring peri-tumourally or within the serosa (Crohn-like reaction) are B-lymphocytes surrounded by T-lymphocytes.

Genetics
Acquired genetic changes in HNPPC cancers
The demonstration of DNA microsatellite instability serves as an important biomarker for HNPPC cancers. Bandshifts in BAT26 are highly sensitive for both familial and sporadic MSI-H cancers [3], though some cases may be missed [548].

<table>
<thead>
<tr>
<th>Table 6.03</th>
<th>Summary of clinical, pathological and genetic features of HNPPC (Lynch syndrome)</th>
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<tbody>
<tr>
<td>– Familial clustering of colorectal and/or endometrial cancer</td>
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<tr>
<td>– Excess risk of cancer of the ovary, uterus/renal pelvis, small bowel, stomach, brain, hepatobiliary tract, and skin (sebaceous tumours)</td>
<td></td>
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<tr>
<td>– Development of multiple cancers at an early age</td>
<td></td>
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<tr>
<td>– Features of colorectal adenoma include: (1) variable numbers from one to a few; (2) increased proportion of adenomas with a villous growth pattern (3) a high degree of dysplasia; (4) rapid progression from adenoma to carcinoma and (5) high frequency of microsatellite instability (MSI-H)</td>
<td></td>
</tr>
<tr>
<td>– Features of colorectal cancer include: (1) predilection for proximal colon; (2) improved survival; (3) multiple colorectal cancers (4) increased proportion of mucinous tumours, poorly differentiated tumours, and tumours with marked host-lymphocytic infiltration and lymphoid aggregation at the tumour margin.</td>
<td></td>
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</table>
A panel of five markers (BAT25, BAT26, D2S123, D5S346 and D17S250) has been recommended for screening purposes [164]. Bandshifts at two or more microsatellite loci are indicative of MSI-H. Around 60% of HNPCC adenomas are MSI-H [2]. Most MSI-H cancers are diploid or near diploid and the frequency of loss of heterozygosity (LOH) is low for the traditional loci 5q, 17p and 18q [962, 841]. The frequency of APC, KRAS and TP53 mutation is reduced [962, 841]. Conversely, mutations are encountered in TGFRII, IGF2R, BAX, E2F-4, MSH3, MSH6 and caspase 5 [548, 1165, 1699, 1793, 2156, 1558]. In general, the driving force for colorectal cancer development and progression may be DNA instability (mutator pathway) or chromosomal instability (suppressor pathway). HNPCC cancers and sporadic MSI-H cancers share the mutator pathway.

Mode of inheritance, chromosomal location, and structure
HNPCC is transmitted as an autosomal dominant trait. It is associated with germline mutations in five genes with verified or putative DNA mismatch repair function, namely MSH2 (MutS homologue 2), MLH1 (MutL homologue 1), PMS1 (Postmeiotic segregation 1), PMS2 (Postmeiotic segregation 2), and MSH6 (MutS homologue 6). Structural characteristics of these genes are given in Table 6.04. Homozygous MLH1 mutations confer to a neurofibromatosis 1 like phenotype [2048, 1580].

Gene product
HNPCC genes are ubiquitously expressed in adult human tissues, and therefore, the expression pattern does not seem to explain the selective organ involvement in this syndrome. Expression is particularly prominent in the epithelium of the digestive tract as well as in testis and ovary (505, 1030, 2120). In the intestine, expression is confined to the replicating compartment, i.e. the bottom half of the crypts. Immunohistochemical staining against these proteins is nuclear.

Function
The protein products of HNPCC genes are key players in the correction of mismatches that arise during DNA replication [957]. Two different MutS-related heterodimeric complexes are responsible for mismatch recognition: MSH2-MSH3 and MSH2-MSH6. While the presence of MSH2 in the complex is mandatory, MSH3 can replace MSH6 in the correction of insertion-deletion mismatches, but not single-base mispairs. Following mismatch binding, a heterodimeric complex of MutL-related proteins, MLH1-PMS2 (and possibly another alternative complex formed by MLH1-MLH3) is recruited, and this larger complex, together with numerous other proteins, accomplishes mismatch repair. The observed functional redundancy in the DNA mismatch repair protein family may help explain why mutations in MSH2 and MLH1 are prevalent in HNPCC families, while mutations in PMS1, PMS2, and MSH6 are much less frequent, and no germline mutations in MSH3 or MLH3 have been reported, so far (see below). Mismatch repair deficiency gives rise to microsatellite instability, and as such may aid in the diagnosis of this syndrome [3].
However, microsatellite instability is not specific to HNPCC, occurring in 10 to 15% of apparently sporadic colorectal and other tumours as well [164]. Correction of biosynthetic errors in the newly synthesized DNA is not the only function of the DNA mismatch repair system. In particular, it is also able to recognize lesions caused by exogenous mutagens, and has been shown to participate in transcription-coupled repair [134, 1215].

Gene mutations
The International Collaborative Group on HNPCC maintains a database for HNPCC-associated mutations and polymorphisms (http://www.nfdht.nl). The great majority is found in MLH1 and MSH2, with a few mutations in MSH6, PMS1 and PMS2. These mutations occur in over 400 HNPCC families from different parts of the world [485].

Most MSH2 and MLH1 mutations are truncating [1488]. However, one-third of MLH1 mutations is of missense type, which constitutes a diagnostic problem concerning their pathogenicity. Commonly used theoretical criteria in support of pathogenicity include the following: the mutation leads to a nonconservative amino acid change, the involved codon is evolutionarily conserved, the change is absent in the normal population, and it segregates with the disease phenotype. A subset of such mutations was directly assessed for pathogenicity using a yeast-based functional assay, and there was a good correlation [1745]. As a rule, the mutations are scattered throughout the genes, but exon 12 in MSH2 and exon 16 in MLH1 constitute particular hot spots [1488].

Mutations in the five DNA mismatch repair genes account for two-thirds of all classical HNPCC families meeting the Amsterdam criteria and showing MSI in tumours [1078]. Occurrence of these mutations is clearly lower (< 30%) in HNPCC kindreds not meeting the Amsterdam criteria [1379, 2103]. Moreover, clinically indistinguishable phenotype (non-polypotic colon cancer plus variable extracolonic cancers) may be associated with germline mutations in genes that are not involved in DNA mismatch repair, such as TGFβRII (1103) and E-Cadherin (1581). As expected, tumours from such families do not characteristically show MSI.

### Table 6.04
Characteristics of HNPCC-associated human DNA mismatch repair genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal location</th>
<th>Length of cDNA (kb)</th>
<th>Number of exons</th>
<th>Genomic size (kb)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSH2</td>
<td>2p21</td>
<td>2.8</td>
<td>16</td>
<td>73</td>
<td>(509, 956, 1029, 1079, 1686, 1486)</td>
</tr>
<tr>
<td>MLH1</td>
<td>3p21-2p23</td>
<td>2.3</td>
<td>19</td>
<td>58-100</td>
<td>(193, 660, 955, 1077, 1075, 1453)</td>
</tr>
<tr>
<td>PMS1</td>
<td>2q31-q33</td>
<td>2.8</td>
<td>not known</td>
<td>not known</td>
<td>(1350)</td>
</tr>
<tr>
<td>PMS2</td>
<td>7p22</td>
<td>2.6</td>
<td>15</td>
<td>16</td>
<td>(1347, 1350)</td>
</tr>
<tr>
<td>MSH6</td>
<td>2p21</td>
<td>4.2</td>
<td>10</td>
<td>20</td>
<td>(13, 1686, 1451, 1349)</td>
</tr>
</tbody>
</table>

Prognosis and predictive factors
HNPCC mutations generally have a high penetrance. There is no clear-cut correlation between the involved gene, mutation site within the gene, or mutation type vs. clinical features. MSH2 mutations may confer higher risk for extracolonic cancer as compared to MLH1 mutations [2005]. MSH6 mutations may be associated with atypical clinical features, including common occurrence of endometrial cancer [2102] and late age of onset [29]. Finally, capability of the mutant protein to block the normal homologue by a dominant negative fashion may lead to a severe phenotype, in which even normal cells may manifest mismatch repair deficiency [1475, 1348]. Conversely, inability to do so may be associated with a milder phenotype and lack of extracolonic cancers [828]. Kindreds with the Muir-Torre phenotype [971] as well as a subset of those with Turcot syndrome [658] show mutations similar to those observed in classical HNPCC.
Juvenile polyposis

Definition
Juvenile polyposis (JP) is a familial cancer syndrome with autosomal dominant trait, characterized by multiple juvenile polyps of the gastrointestinal tract, involving predominantly the colorectum, but also the stomach and the small intestine. In addition to colorectal cancer, JP patients carry an increased risk for the development of tumours in the stomach, duodenum, biliary tree and pancreas.

Synonyms
Generalized juvenile polyposis; juvenile polyposis coli; juvenile polyposis of infancy; juvenile polyposis of the stomach; familial juvenile polyposis; hamartomatous gastrointestinal polyposis.

Diagnostic criteria
Following the initial report by Stemper in 1975 (1831), the following diagnostic criteria have been established: (1) more than 5 juvenile polyps of the colorectum, or (2) juvenile polyps throughout the gastrointestinal tract, or (3) any number of juvenile polyps with a family history of JP (847). Other syndromes that display hamartomatous gastrointestinal polyps should be ruled out clinically or by pathological examination.

Epidemiology
Incidence
JP is ten-fold less common than familial adenomatous polyposis (838), with an incidence of from 0.6 to 1 case per 100,000 in Western nations (297, 215). JP may be the most common gastrointestinal polyposis syndrome in developing counties (1576, 2109), and approximately half of cases arise in patients with no family history (316).

Age and sex distribution
Two-thirds of patients with juvenile polyposis present within the first 2 decades of life, with a mean age at diagnosis of 18.5 years (316). Some present in infancy, and others not until their seventh decade (749). Though extensive epidemiological data do not exist, incomplete penetrance and approximately equal distribution between the sexes can be presumed.

Localization
Polyps occur with equal frequency throughout the colon and may range in number from one to more than a hundred. Some patients develop upper gastrointestinal tract polyps, most often in the stomach, but also in the small intestine. Generalized juvenile gastrointestinal polyposis is defined by the presence of polyps in the stomach, small intestine and colon (1643).

Clinical features
Signs and symptoms.
Patients with juvenile polyposis usually present with gastrointestinal bleeding, manifesting as haematochezia. Melaena, prolapsed rectal polyps, passage of tissue per rectum, intussusception, abdominal pain, and anaemia are also common.

Imaging.
Air contrast barium enema and upper gastrointestinal series may demonstrate filling defects, but are non-diagnostic for juvenile polyps.

Endoscopy.
Biopsy or excision of polyps by colonoscopy can be both diagnostic and therapeutic. Small juvenile polyps may resemble hyperplastic polyps, while larger polyps generally have a well-defined stalk with a bright red, rounded head, which may be eroded. In the stomach, polyps are less often pedunculated and are more commonly diffuse.

Macroscopy
Most subjects with juvenile polyposis have between 50-200 polyps throughout the colorectum. The rare and often lethal form occurring in infancy may be associated with a diffuse gastrointestinal polyposis (1643). In cases presenting in later childhood to adulthood, completely unaffected mucosa separates the lesions. This is unlike the dense mucosal carpeting that is characteristic of familial adenomatous polyposis. The polyps are usually pedunculated, but can be sessile in the stomach. Smaller examples have the spherical head of a typical solitary juvenile polyp. They may grow up to 5 cm in diameter, with a multilobated head. The individual lobes are relatively smooth and separated by deep, well-defined clefts. The multilobated polyp therefore appears like a cluster of smaller juvenile polyps attached to a common stalk. Such multilobated or atypical juvenile polyps account for about 20% of the total number of polyps (847).

Fig. 6.67 A – C Multiple polyps in juvenile polyposis. The contour of polyps is highly irregular, fronded, in contrast to solitary sporadic juvenile polyps.

L.A. Aaltonen
J.R. Jass
J.R. Howe

Tumours of the colon and rectum

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Histopathology
Smaller polyps are indistinguishable from their sporadic counterparts. In the multi-lobated or atypical variety the lobes may be either rounded or finger-like. There is a relative increase in the amount of epithelium versus stroma. Glands show more budding and branching but less cystic change than the classical solitary polyp [847].

Cancer in juvenile polyposis
There are two histogenetic explanations for the well documented association between colorectal cancer and juvenile polyposis. Cancers could arise in co-existing adenomas. Alternatively, they may develop through dysplastic change within a juvenile polyp. While both mechanisms may apply, pure adenomas are uncommon in juvenile polyposis. By contrast, foci of low-grade dysplasia may be demonstrated in 50% of atypical or multi-lobated juvenile polyps. The dysplastic areas may increase in size, generating a mixed juvenile polyp/adenoma. The adenomatous component may be tubular, tubulovillous or villous. Carcinomas are more likely to be poorly differentiated and/or mucinous [847].

Extraintestinal manifestations
Congenital anomalies have been reported in 11 to 15% of JP patients [316, 727], with the majority occurring in sporadic cases [217]. These anomalies most commonly involve the heart, central nervous system, soft tissues, gastrointestinal tract and genitourinary system [316, 1202]. Several patients have been reported with ganglieneuromatous proliferation within juvenile polyps [428, 1218, 1513, 2081], and others with pulmonary arteriovenous malformations and hypertrophic osteoarthropathy [348, 1760, 101, 333].

Fig. 6.68 A, B Juvenile polyposis. The bizarre architecture differs from the round, uniform structure of sporadic juvenile polyps.

Fig. 6.69 Juvenile polyp with intraepithelial neoplasia and early adenocarcinoma.

Fig. 6.70 A, B Intraepithelial neoplasia in a juvenile polyp.

Fig. 6.71 TGF-β superfamily signaling through signal-transducing SMAD (1,2,3,4,5 and 8) and inhibitory SMAD (6 and 7) proteins. SMAD4, the protein defective in juvenile polyposis, plays a key role in the network. After type I receptor activation, SMADs 1,2,3,5 and 8 become phosphorylated, form homomeric complexes with each other, and assemble into heteromeric complexes with SMAD4. The complexes translocate into the nucleus, where they regulate transcription of target genes. Inhibitory Smads act opposite from R-Smads by competing with them for interaction with activated type I receptors or by directly competing with SMADs 1,2,3,5 and 8 for heteromeric complex formation with SMAD4. From: E. Piek et al. FASEB J 13: 2105 (1999).
Genetics
JP is autosomal dominant. Germline mutations in SMAD4/DPC4 tumour suppressor gene account for some of the cases (748, 751). SMAD4 maps to chromosome 18q21.1 (651), i.e. a region that is often deleted in colorectal carcinomas.

Gene structure and product
SMAD4 has 11 exons, encoding 552 amino acids. It is expressed ubiquitously in different human organ systems, as well as during murine embryogenesis. The gene product is an important cellular mediator of TGF-β signals relevant for development and control of cell growth and an obligate partner for SMAD2 and SMAD3 proteins in the signalling pathway from the TGF-β receptor complex to the nucleus (2099).

Gene mutations
While relatively few germline mutations have been described thus far, three studies have confirmed, in different white populations, the frequent occurrence of a four base pair deletion in SMAD4 exon 9 (531, 751, 1622). Haplotype analyses indicate that this is due to a mutation hotspot, rather than an ancient founder mutation (531, 751). The families segregating this particular mutation tend to be large, perhaps indicating high penetrance.

It seems likely that SMAD4 is not the only gene underlying JP since only a subset of the families have SMAD4 germline mutations (531, 748, 751, 1622), and many families are not compatible with 18q linkage (748, 751, 1622). The PTEN gene has also been proposed as underlying JP (1421), but this report has not been confirmed by other studies and the present notion is that individuals with PTEN mutations should be considered having Cowden syndrome, with a risk of breast and thyroid cancer (469).

Cowden syndrome

Definition
Cowden syndrome (CS) is an autosomal dominant disorder characterized by multiple hamartomas involving organs derived from all three germ cell layers. The classical hamartoma associated with CS is the trichilemmoma. Affected family members have a high risk of developing breast and non-medullary thyroid carcinomas. Clinical manifestations further include mucocutaneous lesions, thyroid abnormalities, fibrocystic disease of the breast, gastrointestinal hamartomas, early-onset uterine leiomyomas, macrocephaly, mental retardation and dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos). The syndrome is caused by germline mutations of the PTEN/MMAC1 gene.

MIM No. 158350
Synonyms
Cowden disease; multiple hamartoma syndrome.

Diagnostic criteria
Because of the variable and broad expression of CS and the lack of uniform diagnostic criteria prior to 1996, the International Cowden Consortium (1334) compiled operational diagnostic criteria for CS (Table 6.05), based on the published literature and their own clinical experience (467). Trichilemmomas and papillomatous papules are particularly important to recognize; CS usually presents by the late 20s. It has variable expression and an age-related penetrance although the exact penetrance is unknown. By the third decade, 99% of affected individuals have developed the mucocutaneous stigmata although any of the other features could be present already (see Table 6.05). Because the clinical literature on CS consists mostly of reports of the most florid and unusual families or case reports by subspecialists interested in their respective organ systems, the spectrum of component signs is unknown. Despite this, the most commonly reported manifestations are mucocutaneous lesions, thyroid abnormalities, fibrocystic disease and carcinoma of the breast, gastrointestinal hamartomas, multiple, early-onset uterine leiomyoma, macrocephaly (specifically, megencephaly) and mental retardation (1819, 665, 1152, 1096).

Epidemiology
The single most comprehensive clinical epidemiological study estimated the prevalence to be 1 per million population (1819, 1334). Once the gene was identified (1071), a molecular-based estimate of prevalence in the same population was 1:200 000 (1333). Because of the difficulty in recognizing this syndrome, prevalence figures are likely underestimates.

Intestinal neoplasms
Hamartomatous polyps. In a small but systematic study comprising 9 well documented CS individuals, 7 of whom had a

Prognostic factors
The most severe form of juvenile polyposis presents in infancy, with diarrhoea, anemia, and hypoalbuminemia; these patients rarely survive past 2 years of age. Although polyps in juvenile polyposis patients have classically been described as hamartomas, they do have malignant potential. The risk of colorectal carcinoma is approximately 30-40% and that of upper gastrointestinal carcinoma is 10-15% (749). Typical age of colon carcinoma diagnosis is between 34 and 43 years (range 15-68 years), and upper gastrointestinal carcinoma 58 years (range 21-73 years) (749, 847, 834). Most cases occur in patients who have not been screened radiologically or endoscopically, suggesting that cancers may be preventable through close surveillance.
Cowden syndrome

The two most commonly recognized cancers in CS are carcinoma of the breast and thyroid [1819]. In the general population, lifetime risks for breast and thyroid cancers are approximately 11% (in women), and 1%, respectively. Breast cancer has been rarely observed in men with CS [1167]. In women with CS, lifetime risk estimates for the development of breast cancer range from 25 to 50% [1819, 665, 1096, 467]. The mean age at diagnosis is likely 10 years earlier than breast cancer occurring in the general population [1819, 1096]. Although Rachel Cowden died of breast cancer at the age of 31 [196, 1081] and the earliest recorded age at diagnosis of breast cancer is 14 [1819], the great majority of breast cancers are diagnosed after the age of 30–35 (range 14 – 65) [1096]. The predominant histology is ductal adenocarcinoma. Most CS breast carcinomas occur in the context of DCIS, atypical ductal hyperplasia, adenosis and sclerosis [1691].

Thyroid cancer. The lifetime risk for thyroid cancer can be as high as 10% in males and females with CS. Because of small numbers, it is unclear if the age of onset is truly earlier than that of the general population. Histologically, the thyroid cancer is predominantly follicular carcinoma although papillary histology has also been rarely observed [1819, 665, 1152] (Eng, unpublished observations). Medullary thyroid carcinoma has not been observed in patients with CS [1445, 468, 932]. Other malignancies and benign tumours have been reported in patients or families with CS. Some authors believe that endometrial carcinoma could be a component tumour of CS as well. It remains to be shown whether other tumours (sarcomas, lymphomas, leukaemia, meningiomas) are true components of CS.

Genetics

Chromosomal location and mode of transmission

CS is an autosomal dominant disorder, with age related penetrance and variable expression [468]. The CS susceptibility gene, PTEN, resides on 10q23.3 [1071, 1334, 1068].

Gene structure

PTEN/MMAC1/TEP1 consists of 9 exons spanning 120-150 kb of genomic distance [1167, 1820, 1068]. It is believed that intron 1 occupies much of this (approximately 100 kb). PTEN is predicted to encode a 403-amino acid phosphatase. Similar to other phosphatase genes, PTEN exon 5 specifically encodes a phosphatase core motif. Exons 1 through 6 encode amino acid sequence that is homologous to tensin and auxilin [1065, 1820, 1068].

Gene product

PTEN is virtually ubiquitously expressed [1820]. Detailed expression studies in...
development have not been performed. However, early embryonic death in pten⁻/⁻ mice would imply a crucial role for PTEN in early development {1526, 1868, 407}.

PTEN is a tumour suppressor and is a dual specificity phosphatase {1304}. It is a lipid phosphatase whose major substrate is phosphatidylinositol-3,4,5-triphosphate (PIP3) which lies in the PI3 kinase pathway {553, 1814, 1142, 364, 1067}. When PTEN is ample, PIP3 is converted to 4,5-PIP2, which results in hypophosphorylated Akt/PKB, a known cell survival factor. Hypophosphorylated Akt is apoptotic. Transient transfection studies have shown that ectopic expression of PTEN results in apoptosis in breast cancer lines mediated by Akt {1067} and G1 arrest in glioma lines {553, 554}. The G1 arrest is not fully explained by the PTEN-PI3K-Akt pathway. It is also believed that PTEN can dephosphorylate FAK and inhibit integrin and MAP kinase signalling {637, 1892}.

Gene mutations

Approximately 70-80% of CS cases, as strictly defined by the Consortium criteria, have a germline PTEN mutation {1167, 1071}. If the diagnostic criteria are relaxed, mutation frequencies drop to 10-50% {1335, 1964, 1124}. A formal study which ascertained 64 unrelated CS-like cases revealed a mutation frequency of 2% if the criteria are not met, even if the diagnosis is made short of one criterion {1168}. A single research centre study involving 37 unrelated CS families, ascertained according to the strict diagnostic criteria of the Consortium, revealed a mutation frequency of 80% {1167}. Exploratory genotype-phenotype analyses revealed that the presence of a germline mutation was associated with a familial risk of developing malignant breast disease {1167}. Further, missense mutations and/or mutations 5’ of the phosphatase core motif seem to be associated with a surrogate for disease severity (multi-organ involvement). A small study comprising 13 families with 8 PTEN mutation-positive members could not find any genotype-phenotype associations {1333} but this may be due to the small sample size. Bannayan-Riley-Ruvalcaba syndrome (BRR). Previously thought to be clinically distinct, BRR (MIM 153480), characterized by macrocephaly, lipomatosis, haemangiomatosis and speckled penis, is likely allelic to CS {1169}. Approximately 60% of BRR families and isolated cases combined carry a germline PTEN mutation {1170}. There were 11 cases classified as true CS-BRR overlap families in this cohort, and 10 of these had a PTEN mutation. The overlapping mutation spectrum, the existence of true overlap families and the genotype-phenotype associations which suggest that the presence of germline PTEN mutation is associated with cancer strongly suggest that CS and BRR are allelic and part of a single spectrum at the molecular level. The aggregate term of PTEN hamartoma tumour syndrome (PHTS) has been suggested {1170}.

The identification of a germline PTEN mutation in a patient previously thought to have juvenile polyposis {1421} excludes that diagnosis, and points to the correct designation as CS or BRR {469, 751, 983, 750, 1171}.

Prognosis

There have been no systematic studies to indicate if CS patients who have cancer have a prognosis different from that of their sporadic counterparts.

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Operational diagnosis in an individual</th>
<th>Operational diagnosis in a family where one individual is diagnostic for Cowden</th>
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</thead>
<tbody>
<tr>
<td><strong>Pathognomonic Criteria</strong></td>
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<tr>
<td>Mucocutaneous lesions:</td>
<td>1. Mucocutaneous lesions alone if: a) there are 6 or more facial papules, of which 3 or more must be trichilemmoma, or b) cutaneous facial papules and oral mucosal papillomatosis, or c) oral mucosal papillomatosis and acral keratoses, or d) palmoplantar keratoses, 6 or more</td>
<td>1. At least one pathognomonic criterion</td>
</tr>
<tr>
<td>Trichilemmomas, facial acral keratoses Papillomatous papules Mucosal lesions</td>
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<tr>
<td><strong>Major Criteria</strong></td>
<td>2. Two major criteria but one must include macrocephaly or LDD</td>
<td>2. Any one major criterion with or without minor criteria</td>
</tr>
<tr>
<td>Breast CA</td>
<td>3. One major and three minor criteria</td>
<td>3. Two minor criteria</td>
</tr>
<tr>
<td>Thyroid CA, esp. follicular carcinoma Macrocephaly (Mencecephaly) (≥ 97%ile) Lhermitte-Duclos disease (LDD)</td>
<td>4. Four minor criteria</td>
<td></td>
</tr>
<tr>
<td><strong>Minor Criteria</strong></td>
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<tr>
<td>Other thyroid lesions (e.g. adenoma or multinodular goiter) Mental retardation (IQ ≤ 75) Gastro-intestinal hamartomas Fibrocystic disease of the breast Lipomas Fibromas Genitourinary tumours (e.g. uterine fibroids) or malformation</td>
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</table>
Hyperplastic polyposis

Definition
Multiple or large hyperplastic (metaplastic) polyps of the large intestine, typically located proximally, and often exhibiting familial clustering.

Synonyms and historical annotation
The term metaplastic polyposis has been used synonymously. Early descriptions emphasized a multiplicity of hyperplastic polyps throughout the colorectum and caused diagnostic confusion with familial adenomatous polyposis (FAP) (2114). The condition was also reported to occur in young male subjects. These descriptions (predating the colonoscopic era) were biased towards cases mimicking FAP or showing unusual aspects such as young age of onset. In the colonoscopic era, the features of large polyp size and/or distribution throughout the colorectum serve to distinguish hyperplastic polyposis from the far more common occurrence of small hyperplastic polyps in the distal colon and rectum. Hyperplastic polyposis should be distinguished from sporadic hyperplastic polyps in view of its association with colorectal neoplasia (1198, 126) and reports of familial clustering (849).

Diagnostic criteria
In the absence of generally accepted guidelines on what would constitute the minimum number of polyps or polyp size to warrant a diagnosis of hyperplastic polyposis, the following criteria are recommended: (1) At least five histologically diagnosed hyperplastic polyps proximal to the sigmoid colon of which two are greater than 10 mm in diameter, or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first degree relative with hyperplastic polyposis, or (3) more than 30 hyperplastic polyps of any size, but distributed throughout the colon.

Clinical features
Unless there is associated malignancy, hyperplastic polyposis is generally asymptomatic. Larger hyperplastic polyps may occasionally present with rectal bleeding. The condition may be diagnosed in adults of all ages. Although considered as rare, the condition is probably under-reported. Firm management guidelines have not been developed. The rather frequently observed association with adenomatous polyps and colon carcinomas suggests that some surveillance of patients is required, with generous biopsy sampling and polypectomy as appropriate, particularly of larger polyps, to determine if neoplasia is present. Subtotal colectomy is occasionally necessary in patients with multiple adenomatous polyps if there are numerous and rapidly growing hyperplastic polyps that make it nearly impossible to selectively eliminate neoplastic lesions.

Imaging
Small polyps may be indistinguishable from diminutive adenomas. High resolution videoendoscopy, combined with dye spraying, will demonstrate the diagnostic star-shaped crypt opening (1191). Larger hyperplastic polyps may either present as pale flat lesions on the crest of a mucosal fold or may become protuberant. The head may darken and become lobulated, simulating an adenoma. The colonoscopic phenotype in some patients simulates FAP with scores to hundreds of 1mm to 5mm in diameter polyps, while others exhibit a smaller number of centimeter sized darker sessile lesions that grossly may be confused with multiple villous adenomas. With either phenotype, one or several adenomas may be found in addition to the hyperplastic polyps. High resolution videoendoscopy suggests that a mixed hyperplastic and cerebriform pattern may be indicative of serrated adenoma (1191).

Histopathology
Most hyperplastic polyps are indistinguishable from their common counterparts, apart from their large size. As in the sporadic hyperplastic polyp, the proliferative zone is increased but remains confined to the lower crypt. There is abnormal retention of cells in the upper maturation zone associated with the characteristic appearance of serration. A small proportion contains foci of intraepithelial neoplasia (dysplasia) that may
either resemble a tubular, tubulovillous, or vilous adenoma, or retain a serrated architecture supporting a diagnosis of serrated adenoma (1987, 1092, 337). Hyperplastic polyps and serrated adenomas show a similar mucinous phenotype exemplified by upregulation of the goblet cell mucin MUC2, reduction of the intestinal mucin MUC4 and neo-expression of the gastric mucin MUC5AC. This suggests that hyperplastic polyps and serrated adenomas represent a histogenetic continuum (139). Unusual growth patterns, including inversion and pseudoinvasion, with associated disorganization of the muscularis mucosae, are more characteristic of large polyps (1729, 1773) and will therefore be over-represented in hyperplastic polyposis. It has been suggested that hyperplastic polyposis be distinguished from ‘serrated adenomatous polyposis’ (1944). However, the histological distinction between a large hyperplastic poly and a serrated adenoma is not straightforward and there is probably no sharp division between hyperplastic polyposis and ‘serrated adenomatous polyposis’.

Genetics
Despite being regarded as non-neoplastic, hyperplastic polyps may show clonal genetic changes, including chromosomal rearrangements at 1p, KRAS mutation and low levels of DNA microsatellite instability (775). Mutations of TP53 and increased immunexpression of p53 are limited to areas of high-grade intraepithelial neoplasia in serrated adenomas (720). In hyperplastic polyposis, microsatellite instability is seen in areas of intraepithelial neoplasia. High levels of microsatellite instability (MSI-H) are associated with loss of expression of the DNA mismatch repair protein hMLH1 in these lesions (844). This observation fits with the suggestion that DNA microsatellite instability may be caused by the silencing of DNA mismatch repair genes by methylation of the promoter region (361). A mutation affecting a gene that controls methylation might account for familial and non-familial cases of hyperplastic polyposis, placing this condition within the spectrum of colorectal lesions showing mismatch repair deficiency (1950). An epigenetic mechanism involving disordered methylation would explain polyp multiplicity and the tendency for hyperplastic polyps to regress spontaneously (986).

Prognosis
Sporadic hyperplastic polyps are generally believed not to be associated with an increased cancer risk. Evidence for hyperplastic polyposis being a precancerous lesion includes the observation of mixed hyperplastic/adenomatous polyps in this condition and the synchronicity of hyperplastic polyposis and colorectal cancer (1198, 126). The genetic changes noted above offer further evidence for a direct relationship between hyperplastic polyposis and colorectal carcinoma, and support the concept of a hyperplastic polyp-adenoma-carcinoma sequence (775).
Endocrine tumours of the colon and rectum

Definition
Endocrine tumours of the large intestine are defined as in the small intestine.

Epidemiology
Incidence and time trends
Endocrine tumours of the colon have an incidence of 0.07-0.11 up to 0.21 cases per 100,000 population per year [1251]. In a recent series, carcinoids from caecum to transverse colon (midgut) represented about 8% and descending colon and rectosigmoid (hindgut) carcinoids about 20% of 5973 gastrointestinal carcinoids [1251]. Rectal carcinoids had a reported incidence of 0.14-0.76 cases per 100,000 population per year. In the 40-year time period (from 1950 to 1991) the percentage of caecal carcinoids, among carcinoids of all sites, nearly doubled, as did the percentage of rectosigmoid lesions [1251].

Age and sex distribution
The reported average age at diagnosis is 58 years, for rectal, and 66 years, for colonic carcinoids, and the M/F ratio is 1.06, for rectal, and 0.66, for colonic carcinoids [1251].

Aetiology
Some colorectal carcinoids have been reported in the large bowel of patients with ulcerative colitis [584, 622] or Crohn disease [722, 622]. In association with these conditions, the tumours tend to be multiple [1208]. However, there appears to be no evidence to substantiate a direct association between inflammatory bowel disease and carcinoid tumours, because almost all cases were found incidentally after surgery for inflammatory bowel disease [622].

Localization
Endocrine tumours are more common in the rectum (54% of the cases), followed by the caecum (20%), sigmoid colon (7.5%), rectosigmoid colon (5.5%) and ascending colon (5%) [1251, 1784].

Clinical features
Patients with colonic carcinoid tumours most commonly present in the seventh decade with symptoms of abdominal pain and weight loss, though some present late with liver metastases [1616]. Less than 5% of patients present with the carcinoid syndrome [1616, 128]. Carcinoids of the colon are associated with metachronous or synchronous non-carcinoid neoplasms in 13% of cases [1251]. Half of rectal endocrine tumours are asymptomatic and are discovered at routine rectal examination or endoscopy, while the other half give rise to symptoms, typically rectal bleeding, pain or constipation [857, 1836]. Rectal carcinoids are practically never associated with the carcinoid syndrome [857, 1836, 212]. Small cell carcinomas are aggressive neoplasms and can present with symptoms due to local disease or to widespread metastases.

Macroscopy
The majority of colonic carcinoids are detected in the right colon [1616, 128] and are larger than carcinoids of the small intestine, appendix, and rectum. The average size was 4.9 cm in cases reviewed by Berardi [128]. Rectal carcinoids appear as submucosal nodules, sometimes polypoid, often with apparently intact overlying epithelium [968]. Larger lesions tend to be somewhat fixed to the rectal wall. In the great majority of cases the tumour is found 4 to 13 cm above the dentate line and on the anterior or lateral rectal walls [222]. The majority of rectal endocrine tumours are solitary and measure less than 1 cm in diameter [222]. Reviewing 356 cases reported in the literature, Caldarola et al. [222] found that only 13% of rectal carcinoids measured more than 2 cm in diameter.

Histopathology
Carcinoid – well differentiated endocrine neoplasm
Colonic serotonin-producing EC-cell tumours show histological, cytological, cytochemical, and ultrastructural features that are identical to those of jeuno-ileal EC-cell tumours, including the absence of S100 protein positive sustentacular cells [1784]. L-cell, glucagon-like peptide and PP/PYY-producing tumours are characterized histologically by a predominance of a type B [1775] ribbon pattern, often admixed with type C (tubuloacin) or broad, irregular trabeculae with rosettes and only occasionally with areas of type A solid nest structures. These patterns are different from

Fig. 6.77 Endoscopically resected carcinoid tumour of rectum.

Fig. 6.78 A, B Carcinoid tumour of rectum. Trabecular pattern, typical of L-cell tumour.

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E. Solcia
L.H. Sobin
R. Arnold
those of EC-cell tumours, in which type A structures prevail. The argentaffin reaction is usually negative [146], while consistently positive results are obtained with Grimelius stain [488]. Immunohistochemically, they stain for panendocrine markers (neuron-specific enolase, synaptophysin, chromogranins) and for a variety of peptide hormones [488]. Among 62 rectal carcinoids derived from surgical pathology files, about 80% displayed more or less abundant glucagon-like peptide (GLP-1, GLP-2, glicentin) and/or PP/PYY immunoreactivities typical of intestinal L-cells, whereas only 30% showed serotonin immunoreactivity and 20% somatostatin immunoreactivity, usually in only few cells [1780, 507]. Although there is a prevalence of L-cells in these tumours, minority populations of substance P, insulin, enkephalin, beta-endorphin, neurotensin, and motilin immunoreactive cells have also been identified [1780, 488, 212]. The vast majority (82%) of colorectal carcinoids tested in one series of 84 cases showed immunoreactivity for prostatic acid phosphatase, a finding that is unusual in other gut carcinoids and possibly is related to the common origin of the rectum and prostate from cloacal hindgut (488). Ultrastructurally, rectal L-cells show round to slightly angular secretory granules similar to those of L-cells of the normal human intestine (506).

Small cell carcinoma (poorly differentiated neuroendocrine neoplasm)

These are morphologically identical to small cell carcinomas of the lung, and correspond to grade 3 tumours according to Rindi et al. [1589]. They are usually found in the right colon, and are frequently associated with an overlying adenoma or adjacent adenocarcinoma [2085], but are not associated with carcinoid tumours. Small cell carcinomas typically express neuroendocrine markers (e.g. chromogranin, synaptophysin) by immunohistochemistry. Patients usually have liver metastases at the time of original surgery, and the prognosis is poor [207].

Large cell neuroendocrine carcinoma is a malignant neoplasm composed of large cells having organoid, nesting, trabecular, rosette-like and palisading patterns that suggest endocrine differentiation, which can be confirmed by immunohistochemistry and electron microscopy. In contrast to small cell carcinoma, cytoplasm is more abundant, nuclei are more vesicular and nucleoli are prominent [1954]. These tumours have not been well described in the gastrointestinal tract because of their apparent low frequency.

Genetics

Loss of heterozygosity at MEN-1 locus has been reported in two sporadic colonic and two sporadic rectosigmoidal carcinoids [829]. However, this finding has not been confirmed by more recent studies [394, 1938]. Colorectal carcinoids do not represent an integral part of MEN-1 [1444]. A case of rectal carcinoid tumour associated with Peutz-Jeghers syndrome has been reported [2032].

Prognosis

Colonic EC-cell carcinoids are frequently malignant, local spread of the tumours was found in 36-44% of patients and distant metastases in 38% [1251, 1616]. The reported 5-year survival rate was 25-42% and the 10-year survival rate was 10% [1251, 1616]. Modlin found malig-
B-cell lymphoma of the colon and rectum

Definition
Primary lymphoma of the colorectum is defined as an extranodal lymphoma arising in either the colon or rectum with the bulk of disease localized to this site (1251). The alleged poor prognosis of colonic carcinoids has been questioned as possibly the result of a proportion actually being poorly differentiated adenocarcinomas with carcinoid-like growth patterns (1928).

For rectal carcinoids, an overall malignancy rate of 11% to 14% has been calculated in some studies (1251, 488). Recognised malignancy criteria include: a size of the tumour greater than 2 cm (857, 1328, 930), invasion of the muscularis propria (857, 212, 1328), atypical histology (964), presence of more than 2 mitoses per 10 high power (X 400) microscopic fields, and DNA aneuploidy (1963). Patients with rectal carcinoids generally have a good prognosis, showing a 5-year survival rate of 72%-89% (1251, 1931), which is better than the 5-year survival rate of 60% for patients with jejun-ileal carcinoids (211). The prognosis is excellent if the tumour diameter is 1 cm or less (294).

Epidemiology
Primary lymphomas arising in the large intestine are less frequent than either gastric or small bowel lymphomas (792). Primary colorectal lymphomas account for about 0.2% of all neoplasms at this site. The lymphoma subtypes that present in the colorectum are similar to those that involve the small intestine, with the exception of immunoproliferative small intestinal disease (IPSID). Mucosa-associated lymphoid tissue (MALT) lymphomas of both small and large cell type account for the majority of lymphomas of the colorectum (1733). Mantle cell lymphoma (MCL), often in the form of multiple lymphomatous polyposis, is less frequent but accounts for a larger proportion of primary lymphomas in the colorectum than in the small bowel (1733). Most colorectal lymphomas occur in older patients without a clear sex predominance. Amongst acquired immunodeficiency syndrome (AIDS) patients, the median age is lower and the majority of cases occur in homosexual men. Involvement of the colorectum by Burkitt lymphoma is distinctly uncommon in immunocompetent individuals.

Aetiology
The factors involved in the aetiology of colorectal lymphomas are similar to those in the small intestine. Inflammatory bowel disease, particularly ulcerative colitis, is a recognized predisposing factor (1733). Diverticular disease does not appear to be a risk factor for the development of lymphoma. Immunodeficiency disorders giving rise to lymphoma have a predilection for the gastrointestinal tract. The frequency of colorectal lymphomas has significantly increased, partly due to the AIDS epidemic.

Localization
Most colorectal lymphomas involve the distal large bowel, rectum and anus. There is a preference for rectal lymphoma in patients infected with the human immunodeficiency virus (HIV) (787, 1057). Multifocal involvement is uncommon with the exception of multiple lymphomatous polyposis (1733).

Clinical features
The presenting features are very similar to epithelial neoplasms at this site. Rectal bleeding is the most common symptom, followed by diarrhoea, abdominal pain, passage of mucus per rectum, constipation, abdominal mass, weight loss, irregular bowel habit, anal pain and worsening of ulcerative colitis symptoms. Occasional cases are found incidentally, while an acute presentation with rupture of the colon is distinctly uncommon (1733, 611).

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A. Chott
R.D. Gascoyne
A. Wotherspoon
extent of disease. Multiple lymphomatous polyposis has a characteristic radiological picture with numerous polyps of variable size throughout the colon. Transrectal ultrasonography may also be a useful adjunct for diagnosis.

**Macroscopy**

Most low-grade lymphomas present as well defined protuberant growths that deeply invade the bowel wall. Diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma tend to form larger masses with stricture and ulcer formation involving long segments of the colorectum. Low-grade and aggressive MALT lymphomas typically remain localized for prolonged periods, but may spread to involve loco-regional lymph nodes. Mantle cell lymphoma (MCL) may present as an isolated mass or as multiple polyps producing the clinical picture of multiple lymphomatous polyposis (2084). In most cases, the colon is more significantly involved than the small bowel. Importantly, other histological subtypes of lymphoma can produce this clinicopathological entity (see below). The polyps range in size from 0.5 cm to 2 cm with much larger polyps found in the ileocaecal region (791, 1292). MCL frequently spreads to involve the spleen, extra-abdominal lymph nodes, bone marrow and peripheral blood.

**Histopathology**

**MALT lymphoma**

The majority of intestinal lymphomas involving the large bowel are B-cell lymphomas of MALT type, including both low-grade and aggressive histologies (796). The histological and immunophenotypic features are discussed in detail in the section describing lymphomas of the stomach. Colorectal low-grade MALT lymphomas resemble those of the small intestine in that lymphoepithelial lesions are less prominent than in the stomach. Precise criteria for defining a MALT lymphoma of large cell type are lacking, as are the criteria for distinguishing transformation within a low-grade MALT lymphoma. When both histologies are evident, the neoplasm is best described as composite. When small foci of large transformed cells or early sheeting-out of large cells are detected within a background of low-grade intestinal MALT lymphoma, their presence should be noted (383). Currently, the prognostic impact of these findings and their effect on treatment are undetermined. DLBCLs arising in the large bowel that lack a background of low-grade MALT lymphoma are best classified as extranodal diffuse large B-cell lymphoma, not otherwise specified, until such time as confirmatory tests can be established to clearly determine the histogenesis of these neoplasms from the mucosal immune system.

**Burkitt lymphoma**

The details of the histology, immunophenotype, cytogenetics and molecular genetics are described in detail in the small intestinal lymphoma section (Chapter 4).

**Burkitt-like lymphoma**

The histological and cytogenetic features have been previously described in the small intestinal lymphoma section. AIDS patients have a preponderance of cases with this histology. Many are of small non-cleaved cell type with the typical molecular and cytogenetic changes associated with classical Burkitt lymphoma, and compressed by the surrounding lymphoma cells, imparting the appearance of replacing the normal mantle zones. Intestinal glands may be destroyed by the lymphoma, but typical lymphoepithelial lesions are not seen. The low power appearance is monotonous with frequent epithelioid histiocytes, mitotic figures and fine sclerosis surrounding small blood vessels. The lymphoma cells are small to medium sized with irregular nuclear outlines, indistinct nucleoli and scant amounts of cytoplasm. Large transformed cells are typically not present.

The lymphoma cells are mature B-cells and express both CD19 and CD20. Characteristically the cells co-express CD5 and CD43. Surface immunoglobulin is found including both IgM and IgD. Light chain restriction is present in most cases, with some studies demonstrating a predominance of lambda. CD10 and CD11c are virtually always negative. Bcl-1 (cyclin D1) is found in virtually all cases and can be demonstrated within the nuclei of the neoplastic lymphocytes in paraffin sections.

**Figure 6.82** MALT lymphoma of rectum with lymphoepithelial lesions.

**Figure 6.83** Malignant lymphoma of rectum.

**Figure 6.84** Burkitt lymphoma of colon. The malignant cells infiltrate the lamina propria and produce lymphoepithelial lesions.
are best considered to be part of the same biological entity [236]. However, patients with AIDS have also been recognized to have another lymphoma, with features intermediate between small non-cleaved cell lymphoma with plasmablastic differentiation and immunoblastic lymphoma, plasmacytoid type. This latter lymphoma subtype is strongly associated with EBV infection and TP53 mutations [236].

**Other B-cell lymphomas**

Any subtype of B-cell lymphoma can arise in a colorectal site, including those thought to arise from peripheral lymph node equivalents. *De novo* DLBCLs are equal in frequency to low-grade MALT lymphomas in the colorectum [1733], and are particularly common in the setting of HIV infection. Rectal involvement in AIDS patients typically demonstrates DLBCL with either centroblastic or immunoblastic cytology. These lymphoma subtypes can be distinguished using phenotypic markers including Bcl-6, CD138 (syndecan-1) and EBV-related protein, latent membrane protein (LMP-1). Small non-cleaved and centroblastic lymphomas express Bcl-6, but fail to express CD138 or LMP-1 in the majority of cases. Immunoblastic lymphomas in the HIV setting do not express Bcl-6, but are positive for both CD138 and LMP-1, in keeping with a non-germinal center histogenesis [237].

**Genetics**

*MALT lymphoma*

Cytogenetic and molecular features of intestinal low-grade MALT lymphomas are incompletely understood. The presence of either t(1;14)(p22;q32) or t(11;18)(q21;q21) and the corresponding molecular abnormalities, rearrangement of *bcl-10* or *AP12-MLT*, have not been described at this site, thus the relationship of these lesions to gastric MALT lymphomas is unclear [2116, 412]. Furthermore, trisomy 3 is common in gastric MALT lymphomas, but the frequency of this cytogenetic abnormality in primary intestinal lymphoma is unknown. Some of these DLBCLs may have a low-grade MALT component evident, providing compelling evidence that their histogenesis is related to the mucosal immune system.

**Mantle cell lymphoma**

MCL is characterized by a recurrent cytogenetic abnormality, the t(11;14) (q13;q32). This translocation deregulates expression of the *bcl-1* oncogene on chromosome 11. Rearrangement can be detected using Southern blot analysis, PCR or fluorescent in situ hybridization (FISH).

**Prognosis**

The relevant prognostic factors in colorectal lymphomas are similar to those for the small intestine, and have been described in detail in that section. MCL is an aggressive lymphoma, which typically presents in advanced stage; there is often involvement of mesenteric and peripheral lymph nodes, spleen, bone marrow and peripheral blood [670].
Mesenchymal tumours of the colon and rectum

Definition
A variety of benign and malignant mesenchymal tumours that arise in the large intestine as a primary site.

Classification
The morphological definitions of these lesions follow the WHO histological classification of soft tissue tumours (2086). Stromal tumours are described in detail in the chapter on gastric mesenchymal tumours.

Epidemiology
Sarcomas accounted for 0.1% of malignant large intestinal tumours in SEER data (1928). Males were affected slightly less than females. Adults between the 6th and 8th decades were primarily affected.

Aetiology
Aetiological factors are poorly understood for most colorectal mesenchymal tumours. Kaposi sarcoma usually occurs in association with AIDS, but it has also been described in connection with inflammatory bowel disease, in one case following immunosuppressive therapy (1930, 1584). Human herpesvirus 8 is usually demonstrable by PCR in Kaposi sarcoma cells. An angiosarcoma has been reported in the colon, related to a persistent foreign body (149).

Pathological features
Lipomas are composed of mature adipose tissue and are surrounded by a fibroblastic capsule. They usually arise in the submucosal layer of the caecum or the sigmoid colon. When ulcerated, the lipocytes may become irregular and hyperchromatic. Lipomas should be distinguished from lipohyperplasia of the ileocaecal valve (1726). Neurofibromas and schwannomas occur in the colorectum. Most patients with the former have neurofibromatosis, and in these cases plexiform neurofibromas are common. Ganglioneuromas occur rarely in the mucosa. Vascular tumours are classified into benign (such as haemangiomas, lymphangiomas and angiomatosis) and malignant (such as haemangioendotheliomas and angiosarcomas). Kaposi sarcoma is mostly asymptomatic; a few present with GI-bleeding (319). Intestinal lesions may be observed without cutaneous disease (114). The tumours are often multiple mucosal or submucosal nodules. Histologically typical are sheets of spindle cells interspersed by clusters of extravasated erythrocytes. Cytoplasmic hyaline PAS-positive globules are usually seen. The spindle cells are generally positive for CD31 and CD34 and are negative for actin, desmin and c-kit.

Leiomyomas usually are detected in the rectum and colon as small polyps arising from the muscularis mucosae, and consist of well-differentiated smooth muscle cells with a similar immunohistochemical profile as observed in oesophageal leiomyomas (1227). Leiomyomatosis has been described in the colon with a circumferential semiconstrictive growth in a 35 cm long segment (529). It is not known whether colorectal leiomyomas and leiomyomatosis have the same colla-
Mesenchymal tumours

Gastrointestinal stromal tumours (GISTs) of the colorectum are similar to those in the stomach and small intestine and are discussed in the section on gastric mesenchymal neoplasms. Most reports antedate the separation of GISTs and leiomyosarcoma. GISTs occur mainly between the 6th and 8th decades, and most are malignant \(^{89}\). Many tumours grow beyond the rectal wall making radical surgery difficult and recurrences common. Histologically, the examples reviewed by us have all been of the spindle cell variety, all have been c-kit positive, and most of them CD34-positive. Actin-positivity occurs, but the tumours are desmin-negative. C-kit mutations have been shown in rectal GISTs \(^{1018}\). The survival from large bowel stromal/smooth muscle sarcomas appears to be slightly higher than that of the small bowel and lower than that of the stomach and oesophagus \(^{461}\).