Pathology

Doctor 2017 | Medicine | JU | GI

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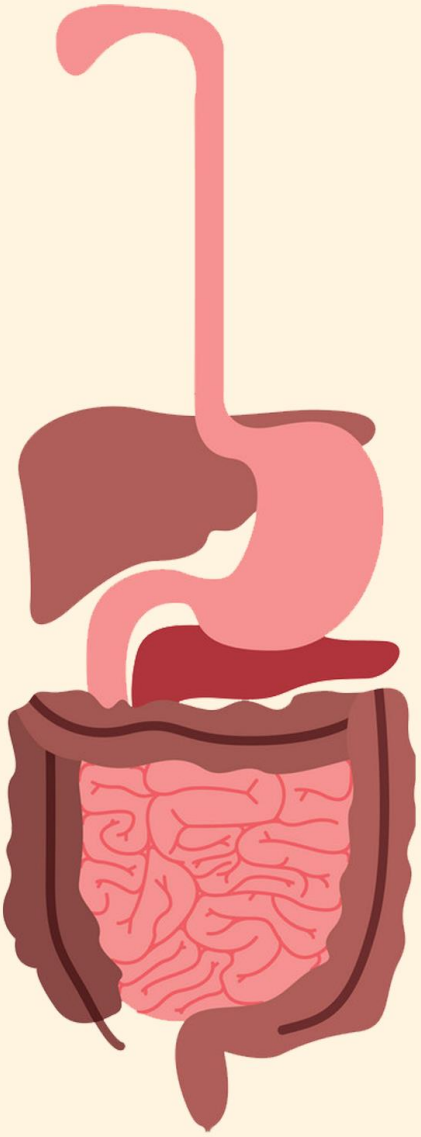


2nd system - GI

We started talking in the last lecture about polyps of the intestines and already discussed two of the nonneoplastic polyp types, Juvenile and Peutz-Jughers polyps. We shall continue here on the last type of nonneoplastic polyp, hyperplastic polyps, and finish our discussion on neoplastic polyps as well.

Hyperplastic Polyps:

Goblet cells are the ones that look the most transparent ↓

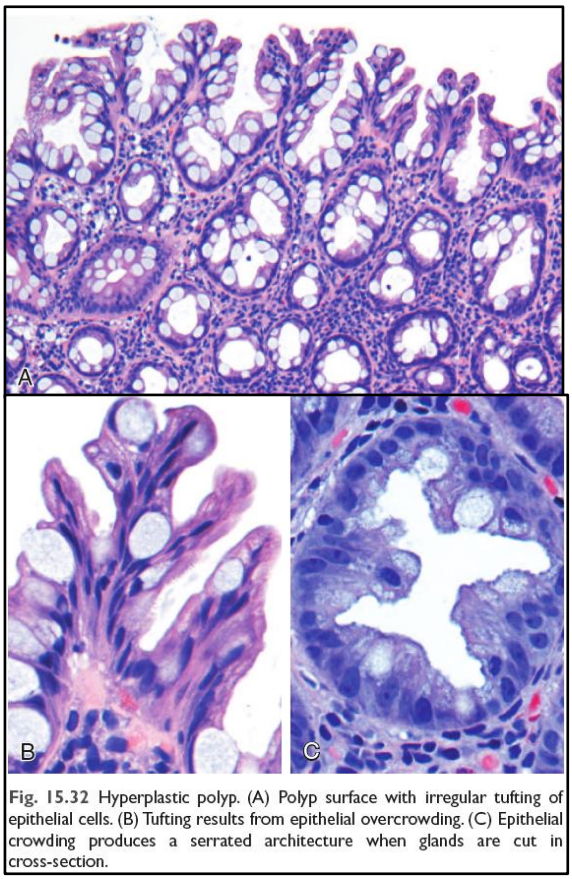


Fig. 15.32 Hyperplastic polyp. (A) Polyp surface with irregular tufting of epithelial cells. (B) Tufting results from epithelial overcrowding. (C) Epithelial crowding produces a serrated architecture when glands are cut in cross-section.

- Pathogenesis: thought to result from decreased epithelial cell turnover and **delayed shedding of surface epithelial cells**, leading to a "pileup" of goblet cells.
- Totally benign with no malignant potential.
- Common in older age (50-60 yrs old).
- Morphology and Histology:
  - Most commonly **found in the left and sigmoid colon**.
  - Usually less than 5 mm in diameter.
  - May occur singly but more frequently are multiple.
  - Composed of mature goblet and absorptive cells.
  - **Morphologic hallmark**: The delayed shedding of these cells leads to crowding that creates a **serrated surface (sawtooth-like) appearance**. The serration appears in crypts as star shaped due to accumulation of cells.

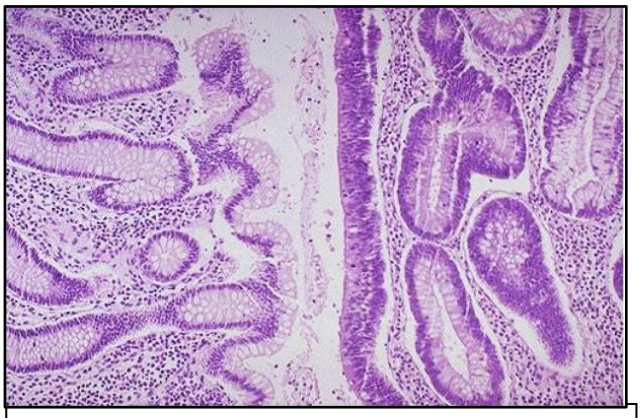
Adenomas:

- The **most common and clinically important** neoplastic polyps are colonic adenomas.
- Colorectal adenomas are **characterized by the presence of epithelial dysplasia** (Dysplasia MUST be present to diagnose as adenoma).
- They are benign polyps that *can* give rise to colorectal adenocarcinomas. Most adenomas, however, **DO NOT** progress to adenocarcinoma.
- Usually begin at age 50 and increase with age. Rare at younger ages, like in a 20-year-old for example, **except** if the adenoma is related to a **F**amilial **P**olyposis **S**yndrome (FPS).
- Adults in the United States undergo screening colonoscopy starting at 50 yrs old.
- Individuals with a family history are screened earlier.

- Can be pedunculated or sessile (sessile adenomas are usually larger with a rough surface). *Recall: Pedunculated means the polyp has a stalk while a sessile polyp doesn't.*

  Being pedunculated or sessile has NO relation to malignancy risk.
- Always **resected** if found during endoscopy and then checked for malignancy.
- **Western diets** (low fibre & high carb/fat diet) increases the risk of adenoma.
- Morphology:
  - We said that the characteristic of an adenoma is dysplasia, so how do we deduce dysplasia from a histological point of view?

    Check the figure to the right!



Note the difference between the right and left halves of the figure, can you guess which half is dysplastic?

The **cytologic hallmark** of epithelial dysplasia:

1. Nuclear hyperchromasia → ↑ basophilia
2. Elongation of nuclei
3. Stratification
4. High N/C ratio.

  - **The two most important factors to evaluate the risk of malignancy in an adenoma are:**
    1. **Size of the polyp**
    2. **Grade of dysplasia (higher → more risk)**
  - Adenomas can be classified on the basis of their architecture:
    - Tubular: usually pedunculated and smaller. Composed of tubular glands.
    - Tubulovillous: mixture between tubular and villous.
    - Villous: usually sessile, larger, and at a higher grade of dysplasia (→ *higher malignancy risk*). Covered by slender villi.

    <u>These categories have little clinical significance in isolation, however, usually the villous adenomas are more frequently associated with colonic carcinoma due to the characteristics mentioned above.</u> The stalk is usually covered by non-neoplastic epithelium.

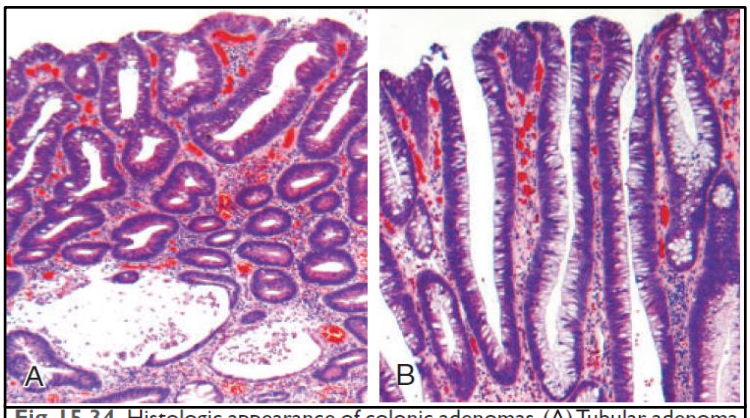


Fig. 15.34 Histologic appearance of colonic adenomas. (A) Tubular adenoma with a smooth surface and rounded glands. In this case, crypt dilation and rupture, with associated reactive inflammation, can be seen at the bottom of the field. (B) Villous adenoma with long, slender projections that are reminiscent of small-intestinal villi. (C) Dysplastic epithelial cells *(top)* with

Again! Architecture has no relation to malignancy, only size and grade do!

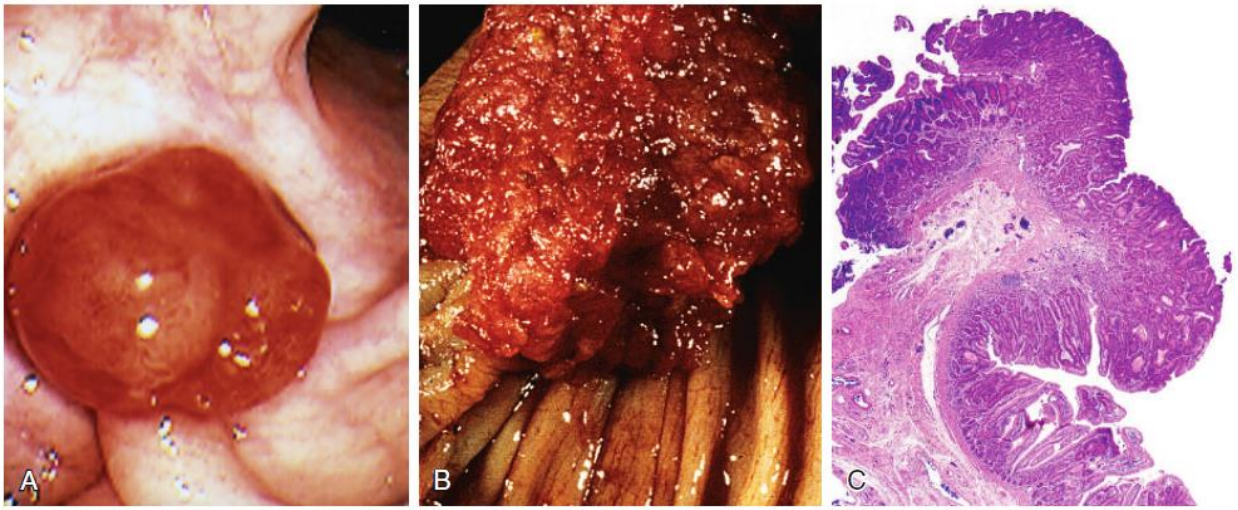


Fig. 15.33 Colonic adenomas. (A) Pedunculated adenoma (endoscopic view). (B) Adenoma with a velvety surface. (C) Low-magnification photomicrograph of a pedunculated tubular adenoma.

Familial Syndromes:

Familial syndromes are inherited conditions characterized by multiple polyps and an increased risk of colorectal carcinoma (also increase gastric adenomas → ↑risk of gastric carcinoma).

1. Familial Adenomatous Polyposis (FAP):
    - An **autosomal dominant** disorder, therefore, if one family member is diagnosed with FAP, the whole family must be screened, if a mutation is found → colectomy.
    - Marked by the appearance of many colorectal adenomas in **teenage** years.
    - Caused by mutations of the *adenomatous polyposis coli* gene (***APC***).
    - At least **100 polyps** are necessary for a diagnosis of **classic** FAP, and as many as several thousand may be present.
    - Morphologically indistinguishable from sporadic adenomas (same morphology).

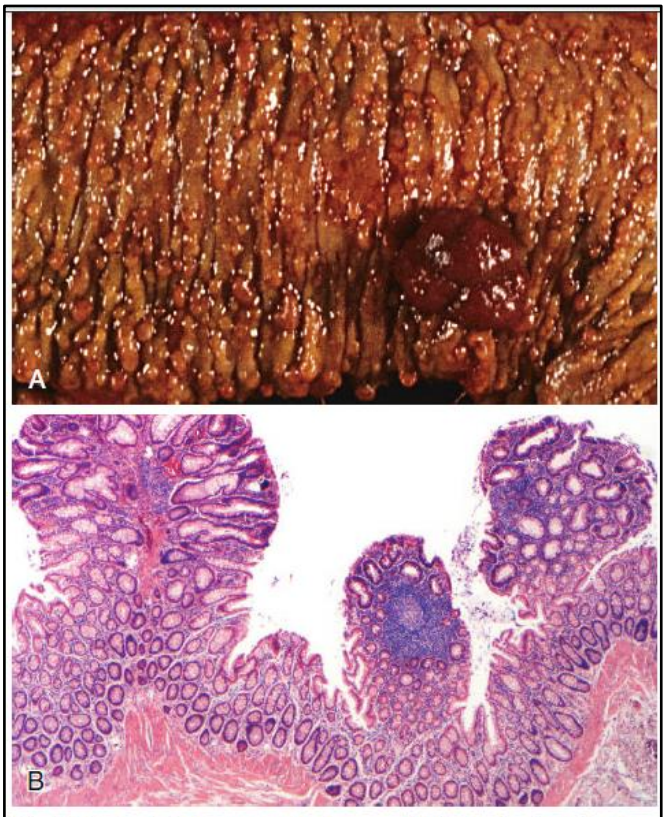


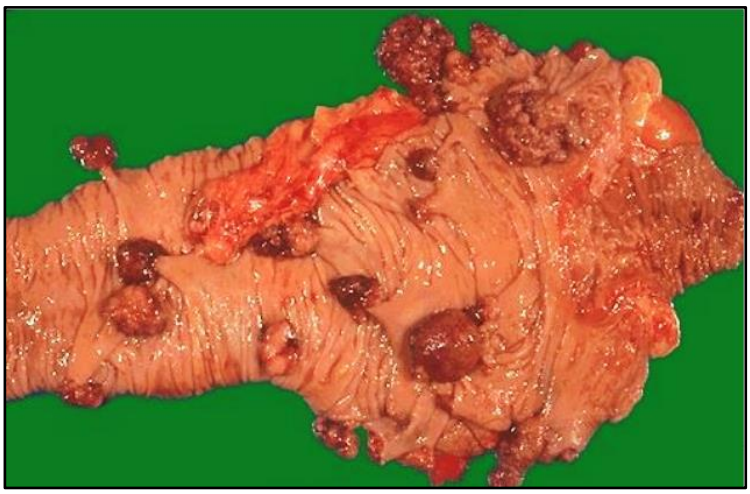
Fig. 15.35 Familial adenomatous polyposis. (A) Hundreds of small colonic polyps are present along with a dominant polyp *(right)*. (B) Three tubular adenomas are present in this single microscopic field.

Notice the 'carpet' of <u>variably sized adenomatous</u> polyps above.

- Colorectal adenocarcinoma develops in **100%** of patients with untreated FAP, often before 30 years of age. **Treatment is prophylactic colectomy at the age of 20 in those found to carry *APC* mutations**.
- Patients remain at risk for **extraintestinal manifestations***,* including neoplasia at other sites, even after the colectomy (they still have the *APC* mutations in the rest of the bodies' cells).
- Specific *APC* mutations are also associated with the development of unique FAP syndromes and explain variants such as:
  - Gardner syndrome: intestinal polyps (<100) and possible osteomas in head/neck bones, cutaneous manifestations, thyroid and desmoid tumours.
  - Turcot syndrome: rarer and is characterized by intestinal adenomas and tumours of the CNS (medulloblastomas >> glioblastomas, both are high grade tumours).

Desmoid tumours: infiltrative tumours of the soft tissue.

2. Hereditary Nonpolyposis Colorectal Cancer (HNPCC)/Lynch syndrome:
   - Was described as familial clustering of cancers at several sites including the colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, and skin.
   - Colon cancers in patients with HNPCC tend to occur at **younger ages than sporadic** colon cancers do.
   - Often located in the **right colon**, <u>unlike sporadic colon carcinomas which usually occur in the left colon (rectosigmoid).</u>
   - Adenomas are present but excessive numbers -***polyposis***- **is not observed**.
   - **Mucin production** is a prominent feature in subsequent adenocarcinomas (mucin production gives poor prognosis.
   - Pathogenesis:
     - HNPCC is caused by inherited **mutations in mismatch repair genes**. At least five such mismatch repair genes have been recognized, but a majority of HNPCC cases involve either **MSH2 or MLH1**.



- Patients with HNPCC inherit one mutated DNA repair gene and one normal allele, therefore, one mutated allele is inherited while the second mutation is acquired (this is commonly referred to as a 'first hit' followed by a 'second hit').
- Mismatch repair genes remove expanded DNA regions caused by mistakes in DNA replications.
- Accumulation of these mutations in microsatellite DNA causes microsatellite instability. Microsatellite (short repeating DNA sequences) will be expanded due to these mutations and lead to further mutations, thus putting the patient in higher risk of multiple cancers. If the mutations occurred in non-coding regions of the microsatellite, then the patient is lucky and there will be no clinical manifestations, however, if the expansion happened in coding or gene promotor areas, the whole gene will be affected leading to microsatellite instability.

Now to compare HNPCC and sporadic colon carcinomas more closely, sporadic cancers of the colon can result from mismatch repair gene mutations; but are not more common in younger ages like HNPCC, nor are the mutations inherited (Both mutations are acquired in sporadic cancers!).

Table 15.7 Common Patterns of Sporadic and Familial Colorectal Neoplasia

Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	*APC*	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%)	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%–15%)	DNA mismatch repair	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

FAP, Familial adenomatous polyposis.

Adenocarcinomas

Adenocarcinoma of the colon is the most common malignancy of the GIT, yet the small intestine in commonly uninvolved by neoplasia. Incidence increases with age and peaks at 60-70 yrs. Only 20% of adenocarcinomas occur in those younger than 50 yrs and those are usually the familial cases only.

Adenocarcinomas are strongly associated with lifestyle and diet. The dietary factors most closely associated with increased colorectal cancer rates are low intake of fibres and high intake of carbs/fat, so they are more common in developed countries.

Aspirin or other NSAIDs have a protective effect. They inhibit cyclooxygenase-2 (COX-2) which was shown to promote epithelial proliferation.

- Pathogenesis:
  - 80% are sporadic while 20% are familial.
  - The combination of molecular events that lead to colonic adenocarcinoma is **heterogeneous** (multiple mutations of multiple genes by multiple mechanisms) and includes genetic and epigenetic abnormalities.
  - Two genetic pathways have been described, both pathways involve the **stepwise accumulation of multiple mutations**, but the genes involved and the mechanisms by which the mutations accumulate differ.
    a) APC/β-catenin pathway: Mutations involving the APC/β-catenin pathway lead to increased WNT signalling.

Also called "**Classic adenocarcinoma sequence**", and accounts for 80% of all sporadic colon tumours. The mutation of the *APC* tumour suppressor is the earliest event in the sporadic APC/β-catenin pathway. Remember that the APC gene is a tumour suppressor gene and thus requires both alleles to be inactivated for a malignancy to develop. *APC* negatively regulates β-catenin*,* a component of the WNT signalling pathway. The **APC protein normally binds to and promotes degradation of β-catenin**, but if *APC* is mutated → β-catenin accumulates and translocate to the nucleus → activates the transcription of genes encoding **MYC and cyclin D1 → promote proliferation**.

This is *followed* by additional mutations, including **activating mutations in *KRAS* (late event)***,* which also promote growth and prevent apoptosis. The neoplasm is further progressed by **mutations of other tumour suppressor genes such as *SMAD2* and *SMAD4***. The tumour suppressor gene ***TP53*** is mutated in 70% to 80% of colon cancers, but it's commonly unaffected in adenomas, because ***TP53* mutations occur at late stages of tumour progression**. Expression of telomerase also increases as lesions become more advanced.

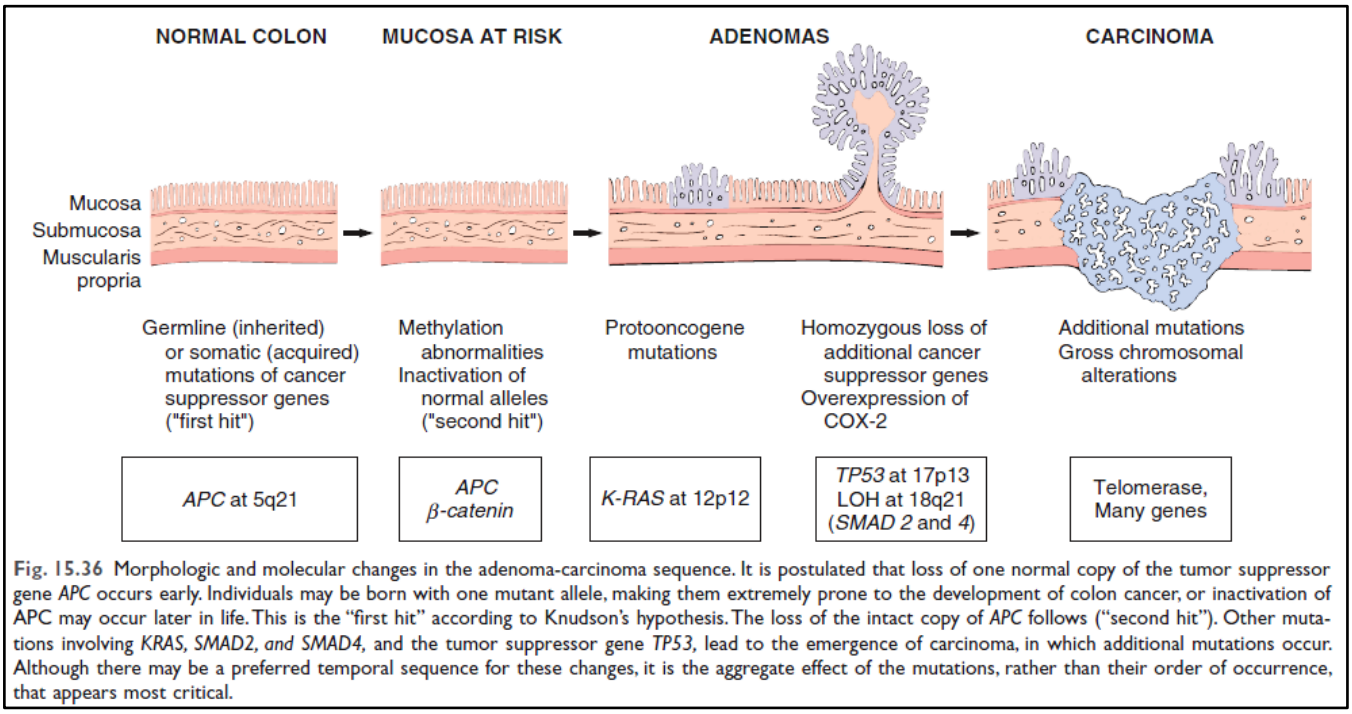


Fig. 15.36 Morphologic and molecular changes in the adenoma-carcinoma sequence. It is postulated that loss of one normal copy of the tumor suppressor gene *APC* occurs early. Individuals may be born with one mutant allele, making them extremely prone to the development of colon cancer, or inactivation of APC may occur later in life. This is the "first hit" according to Knudson's hypothesis. The loss of the intact copy of *APC* follows ("second hit"). Other mutations involving *KRAS, SMAD2, and SMAD4,* and the tumor suppressor gene *TP53,* lead to the emergence of carcinoma, in which additional mutations occur. Although there may be a preferred temporal sequence for these changes, it is the aggregate effect of the mutations, rather than their order of occurrence, that appears most critical.

b) Microsatellite instability pathway: Mutations involving the microsatellite instability pathway are associated with defects in DNA mismatch repair.

Account for 20% of sporadic adenocarcinomas. Due to mutations in DNA mismatch repair genes, mutations accumulate in microsatellite repeats → **microsatellite instability**. These mutations are usually silent, because microsatellites are typically located in noncoding regions, but other microsatellite sequences are located in the coding/promoter regions of genes involved in cell growth and apoptosis, such as TGF-β receptor and BAX respectively. This pathway is very similar to that in HNPCC, except that both mutations are acquired in sporadic adenocarcinoma. As in the APC pathway, other gene mutations usually follow.

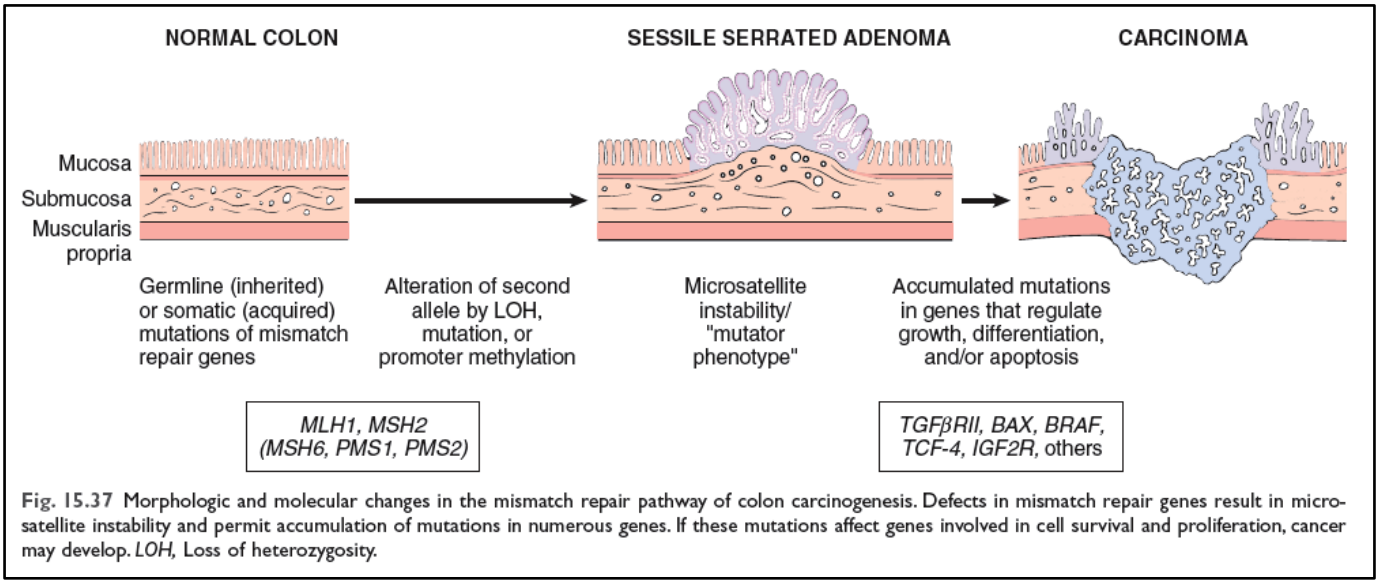
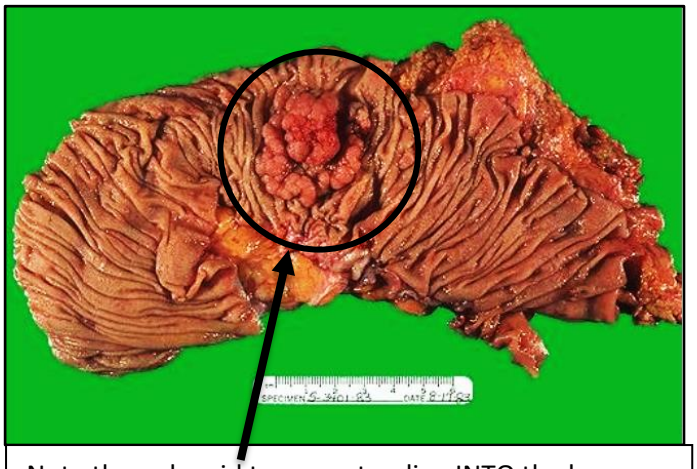
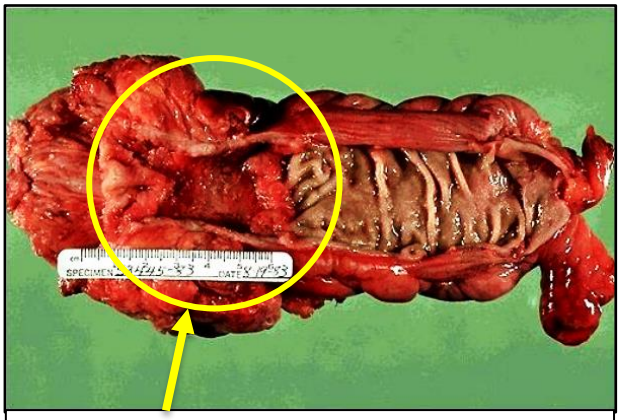


Fig. 15.37 Morphologic and molecular changes in the mismatch repair pathway of colon carcinogenesis. Defects in mismatch repair genes result in microsatellite instability and permit accumulation of mutations in numerous genes. If these mutations affect genes involved in cell survival and proliferation, cancer may develop. *LOH,* Loss of heterozygosity.

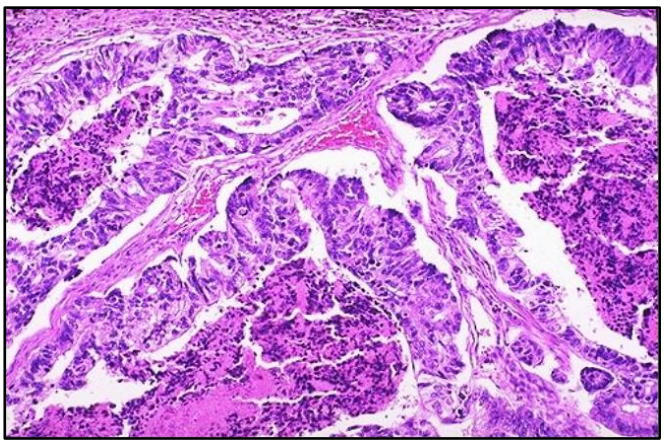
- Morphology: overall, adenocarcinomas are distributed approximately equally over the entire length of the colon.
    - Tumours in the proximal colon often grow as polypoid, exophytic masses that extend into the WIDE lumen of the cecum or ascending colon; therefore, they rarely cause obstruction → late clinical presentation → tumour is very advanced at diagnosis.
    - On the other hand, carcinomas in the distal colon tend to be annular lesions (forming a ring) that produce "napkin ring" constrictions and luminal narrowing, sometimes to the point of obstruction → earlier clinical presentation → symptoms such as abdominal pain, distention, constipation and vomiting.
    - Under the microscope, notable **dysplastic** columnar epithelium forming glands, anaplasia, necrosis, and invasion is present. Invasion starts through the mucosa then submucosa and so on. Some form signet cells (like in diffuse gastric adenocarcinoma).
    - Necrosis is very common in colon adenocarcinomas.
    - Abundant mucin production especially in the right colon.
    - Commonly associated with **strong desmoplastic response** (fibrotic invasion of surrounding soft tissue).
    - Metastasis is usually through lymphatics and the most common sites of metastasis are to the liver and lung.



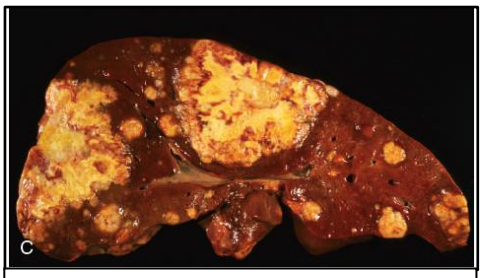
Note the polypoid tumor extending INTO the lumen. These polyps make it hard to differentiate in endoscopy from nonneoplastic adenomas.



Note the annular tumor (napkin ring) constricting the lumen.



- Clinical features: heavily depends on the site.
  - Left-side: More symptomatic with early narrowing/obstruction. Manifested with fresh coloured bloody stool, a positive occult bleeding test, changes in bowel habits (suddenly appearing constipation/diarrhoea/bloody stool), or cramping in left lower-quadrant and discomfort.
  - Right-side: since obstruction is rare, there is usually no clinical presentation until much later, usually many months or years. When clinical presentation does occur however, it is usually in the form of fatigue and weakness due to continuous (chronic) occult bleeding that causes iron-deficiency anaemia. This bleeding is due to continuous friction with this large polypoid tumour, leading to chronic blood loss.
    Occult bleeding: bleeding in small amounts that isn't enough to produce faecal colour change/melena, and can only be detected by lab tests.
  - **Thus, it is a clinical rule that the underlying cause of iron-deficiency anaemia in an older male or postmenopausal female (>50 yrs old) is gastrointestinal cancer until proven otherwise**.
  - The two most important prognostic factors are **depth of invasion**, and **lymph node metastasis**. It is argued though that **distant metastasis** should be another factor, but since this metastasis is usually easily resectable, it is not a common cause of death.



Metastasis to the liver with central necrosis.

SUMMARY

COLONIC POLYPS, ADENOMAS, AND ADENOCARCINOMAS

- *Intestinal polyps* can be classified as *nonneoplastic* or *neoplastic*. The nonneoplastic polyps can be further defined as *inflammatory, hamartomatous,* or *hyperplastic*.
- *Inflammatory polyps* form as a result of chronic cycles of injury and healing.
- *Hamartomatous polyps* occur sporadically or as a part of genetic diseases. In the latter case, they often are associated with increased risk for malignancy.
- *Hyperplastic polyps* are benign epithelial proliferations most commonly found in the left colon and rectum. They are not reactive in origin, in contrast with gastric hyperplastic polyps; have no malignant potential; and must be distinguished from sessile serrated adenomas or polyps.
- *Benign epithelial neoplastic polyps* of the colon are termed *adenomas*. The hallmark feature of these lesions, which are the precursors of colonic adenocarcinomas, is cytologic dysplasia.
- In contrast with traditional adenomas, *sessile serrated adenomas*, or polyps, lack cytologic dysplasia and share some morphologic features with hyperplastic polyps.
- *Familial adenomatous polyposis (FAP)* and *hereditary nonpolyposis colorectal cancer (HNPCC)* are the most common forms of familial colon cancer. FAP is caused by *APC* mutations, and patients typically have over 100 adenomas and develop colon cancer before 30 years of age.
- HNPCC is caused by mutations in DNA mismatch repair genes. Patients with HNPCC have far fewer polyps and develop cancer at an older age than that typical for patients with FAP but at a younger age than in patients with sporadic colon cancer.
- The vast majority of colonic cancers are adenocarcinomas. They arise either by APC-β-catenin pathway or the microsatellite instability pathway. The two most important prognostic factors are depth of invasion and the presence or absence of metastases to lymph nodes or distant organs.

Appendix

The appendix is a normal true diverticulum of the cecum. Its wall has the same layers as cecum (mucosa – submucosa – muscularis propria – serosa) and contains lymphoid structures so is considered as a part of the immune system. Acute appendicitis is the most common medical emergency, while tumours of the appendix are rare.

Acute Appendicitis: is most commonly seen in adolescents and young adults but may occur in any age group. Despite its prevalence, the **diagnosis can be difficult to confirm preoperatively**, and the condition may be confused with other diseases that mimic its pain signals like:

- Mesenteric lymphadenitis: most important in children when they have viral enterogastritis → enlargement of intestinal lymph nodes → pain similar to that of acute appendicitis.
- Acute salpingitis: inflammation of the fallopian tubes.
- Ectopic pregnancy: pregnancy outside of the uterus.
- Mittelschmerz: pain associated with ovulation.
- Meckel diverticulitis (discussed in sheet 3)
- Crohn's disease,

Therefore, the **only real diagnosis is in the form of postoperative microscopy**, any claim preoperatively is seen as high suspicion only.

Pathogenesis: Acute appendicitis is thought to be initiated by an **increase in intraluminal pressure that compromises venous outflow**.

- In 50% to 80% of cases, acute appendicitis is associated with **luminal obstruction**, usually by a small, stone-like mass of stool (***fecalith***), or, less commonly, a gallstone, tumour (in the cecum for example), or mass of worms.
- Obstruction of lumen's neck → ↓venous drainage → blood stasis/congestion → ischemia & oedema.
- Ischemic injury and stasis of luminal contents (like trapped faeces) →bacterial proliferation → inflammatory responses → severe inflammation can progress to suppurative inflammation/abscess → perforation → peritonitis.
- Necrosis and ulceration → acute gangrenous appendicitis.

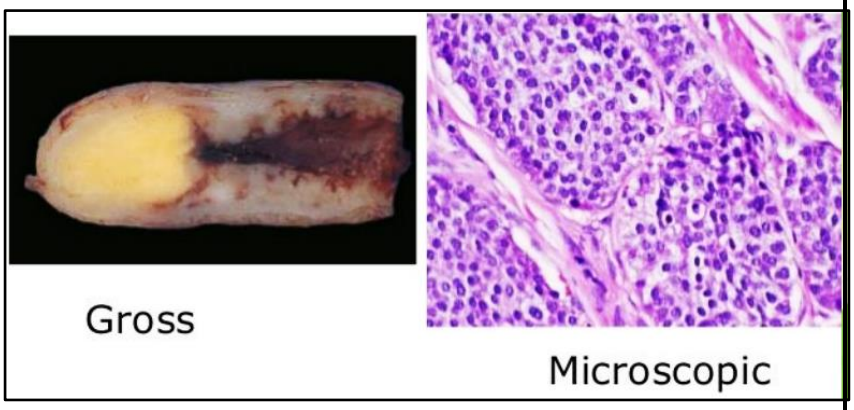
Diagnosis: postoperative microscopic observation of **neutrophilic infiltration into the muscularis propria**.

Clinical Features:

- Early acute appendicitis produces **periumbilical pain**.
- Later, the pain localizes to the right lower quadrant.
- Followed by nausea, vomiting, low-grade fever, and a mildly elevated peripheral white blood cell count.
- A classic physical finding is *McBurney's sign,* deep tenderness noted at a location two-thirds of the distance from the umbilicus to the right anterior superior iliac spine (McBurney's point).
- These signs and symptoms, however, are often absent, creating difficulty in clinical diagnosis.

Tumours of the Appendix:

- The most common tumour of the appendix is the **carcinoid** (similar to that in the stomach).
- Usually discovered incidentally at the time of surgery or on examination of a resected appendix.
- Most commonly involves the distal tip of the appendix.
- A rounded yellowish benign tumour. Nodal metastases and distant spread are exceptionally rare.



SUMMARY

APPENDIX

- Acute appendicitis is most common in children and adolescents. It is thought to be initiated by increased intraluminal pressure consequent to obstruction of the appendiceal lumen, which compromises venous outflow.
- The most common tumor of the appendix, the *carcinoid,* or *well-differentiated neuroendocrine tumor,* is most often discovered incidentally and is almost always benign
- The clinical presentation of appendiceal adenocarcinoma can be indistinguishable from that of acute appendicitis, although the former tends to present in older patients.