PATHOLOGY TEAM

Colonic
tumors and polyps

Done by:

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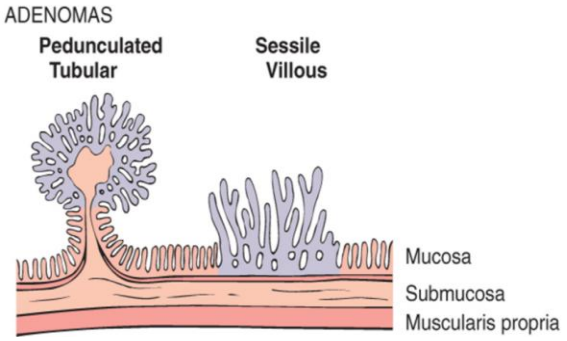
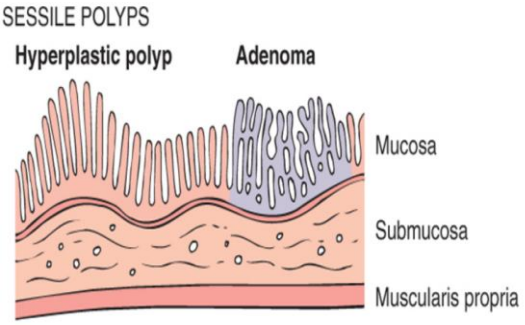
Tumors of the small and large intestines:

- Polyps → benign
- Carcinoma
- Carcinoid tumor malignant
- Lymphoma

Tumors are more commonly seen in the colon

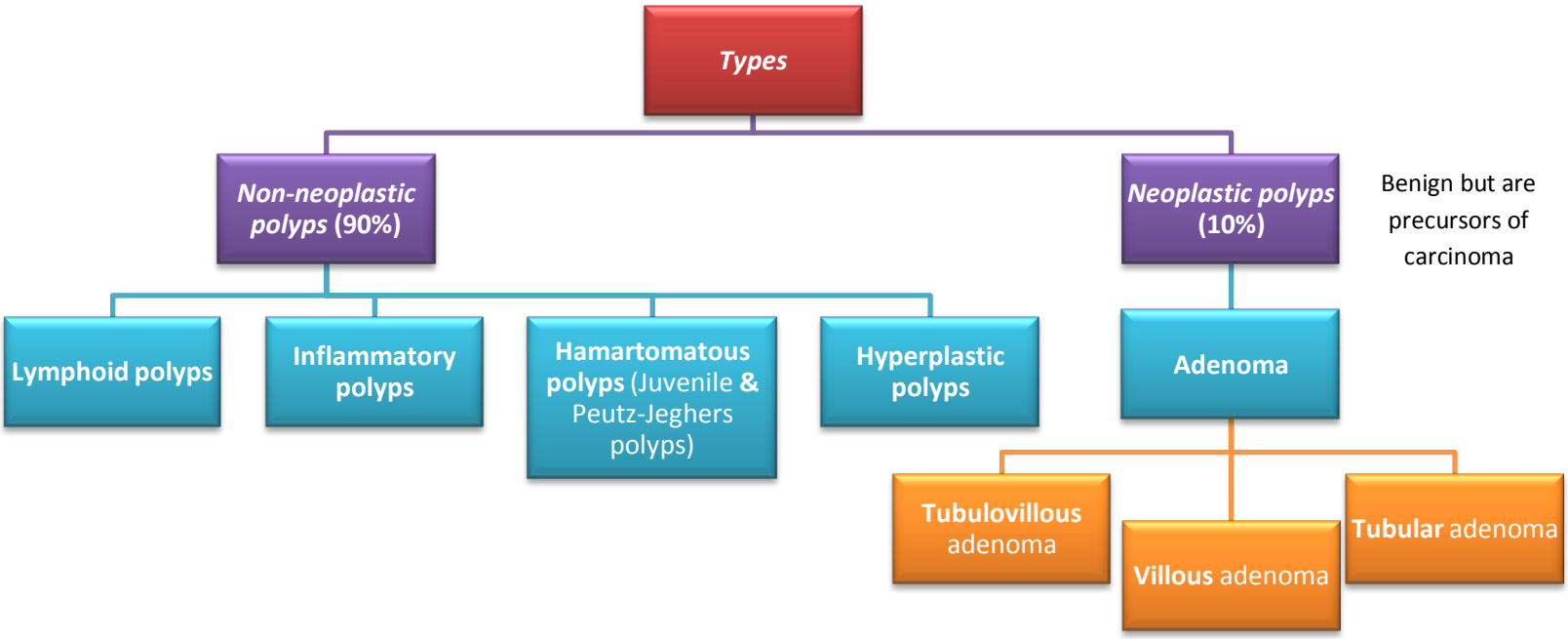




Polyps: -Benign tumors-

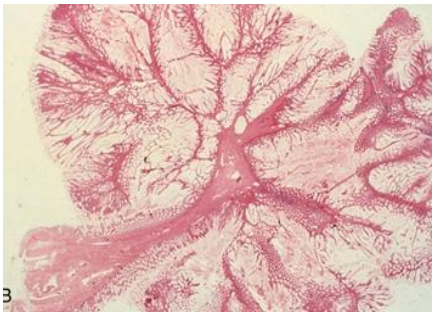
A polyp is a mass of mucosa that protrudes into the lumen of the gut. Polyps are generally formed as the result of abnormal mucosal maturation, inflammation, or architecture. Polyps can be sessile or pedunculated.

What is the difference between pedunculated and sessile polyps?
Pedunculated: has a stalk or a neck
Sessile: lacks the stalk.



Non-neoplastic polyps (90%):

1. Hyperplastic Polyps:



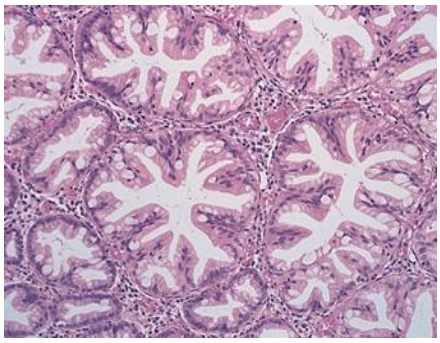
Definition:

is a polyp formed from hyperplasic proliferation of lining that has no dysplastic changes.

Is the most common type in adults

Locations:

> 50% are located in the rectosigmoid



Characteristics:

- Asymtomatic (usually found in patients when performing endoscopy for other reasons)
- Sawtooth surface because of the ↑ number of cells.
- Star shaped crypts
- Composed of well-formed glands and crypts lined by normal differentiated goblet and absorptive cells surrounded by scant lamina propria.

Prognosis:

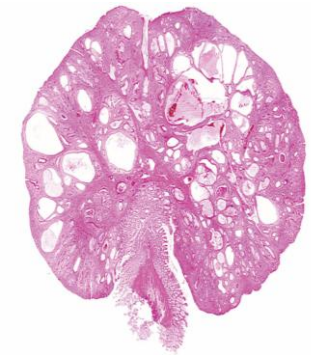
Usually they are benign except in one location, the right side of colon where there is mixture of hyperplastic polyps and neoplastic polyps, which is called serrated adenoma.
Do not have malignant transformation tendencies nor occurs as polyposis syndrome (mentioned in more detail later)

2. Hamartomatous polyps:

a- Juvenile Polyps (retention polyp):

Characteristics:

Most common type of polyp in children



Single often pedunculated developmental malformations affecting:

1. Glands: become cystic and dilated containing large amounts of mucus, hence called retention polyp
2. lamina propria: becomes edematous with inflammation

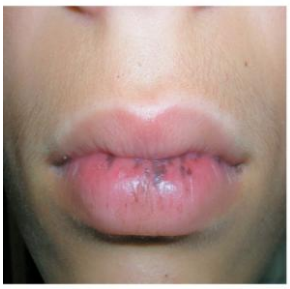
appears as a smooth surface with enlarged cystic spaces on cut section

Age group: commonly occur in children under 5 years old. In adults → called retention polyp.

Location: rectum, may prolapse out of the rectum causing bleeding

Prognosis: it doesn't progress to malignancy
May be present as multiple polyps in case of Juvenile polyposis

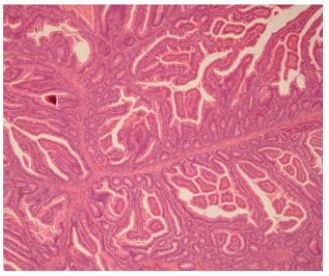
b- Peutz-Jehgers syndrome: (PJP)



Characteristics:

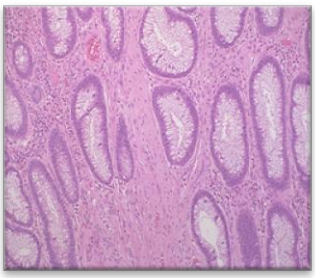
rare, hereditary, autosomal dominant
Polyps tend to be multiple, large and pedunculated
multiple polyps found throughout the GIT (stomach, large and small intestine) but predominant in the small intestines rather than stomach and colon.

Hamartomatous polyps are accompanied by melanotic mucosal and cutaneous pigmentation around the lips, oral mucosa, face and genitalia.



Histologically:

Smooth muscle (spindle-shaped) cells invading the lamina propria
Glands appear to be separated by large amounts of smooth muscle instead of connective tissue.

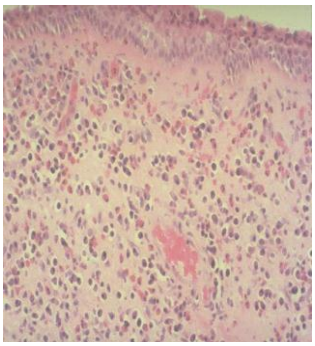


Prognosis: No malignant transformation of the polyp itself
Increased risk of developing carcinoma (not in the GIT, due to mutation in one of the tumor suppressor gene) of the pancreas, breast, lung, ovary and uterus.

3. Inflammatory Polyps:

Characteristics:

Psuedopolyps

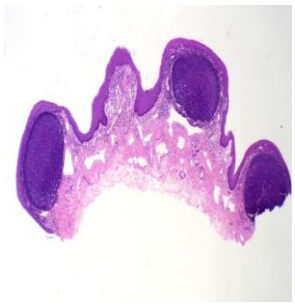


Contain large amounts of inflammatory cells (lymphocyte, macrophages, neutrophils, eosinophils) along with edema.

Represent an exuberant reparative response (healing response of inflammation and granulation tissue) to longstanding mucosal injury or tissue within the ulcerated area that has not been affected.

Cause:
Longstanding IBD (inflammatory bowel disease), especially in chronic ulcerative colitis.

4. Lymphoid polyps:



Characteristics:
Lymphoid collection below the lining epithelium.

It has lymphoid follicles with germinal center in biopsy,

NO neoplastic significance

Not related to hyperplasia of peyer's patches.

Neoplastic Polyps (10%):

Adenomatous Polyp (adenoma):

Definition:

it is benign tumor of the glands

Location:

occur mainly in large bowel.

Subtypes:

1. sporadic (usually 1 or 2 polyps are seen only)
2. Familial (multiple polyps are present; >100 polyp).

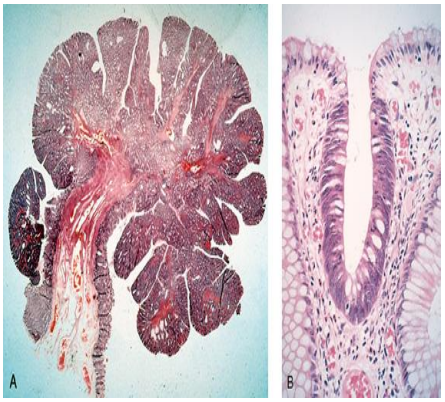
Characteristics:

Vary from small pedunculated to large sessile.
Epithelium proliferation and features of dysplysia (hyperchromatism, pleomorphism, ↑ nuclear cytoplasmic ratio and mitotic figures).
There is overcrowding of glands, nuclei become dark and striated occupying ½ it's thickness

Adenoma is further divided into:

- Tubular adenoma: less than 25% villous architecture
- Villous adenoma: villous architecture over 50%
- Tubulovillous adenoma: villous architecture between 25% and 50%.

1. Tubular Adenoma:

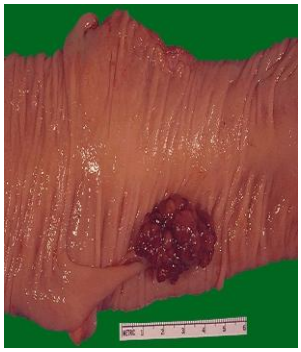


Characteristic:
Small (<1-2cm) pedunculated with smooth surface (only few villi)
usually it's benign

Incidence:
represents 75% of all neoplastic polyps (most common)

Location:
75 % occur in the distal colon and rectum

2. Villous Adenoma: (Most Dangerous)



Description:
broad based sessile with multiple villi (finger like projections) lined by dark elongated striated cells
largest (10-15 cm)
most ominous (malignant transformation)

Location: 75% located in rectosigmoid area.

Incidence:
the least common

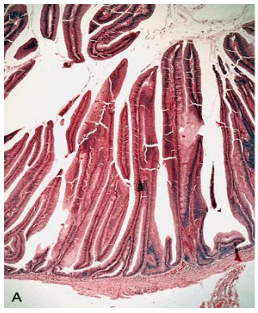
Age group: 60 to 65 years

Features:

presents with rectal bleeding and/or anemia
large ones may secrete copious amounts of mucoid material rich in proteins and potassium ions resulting in hypoproteinemia (hypoalbuminemia), hypokalemia and osmotic type of diarrhea.

3. Tubulovillous Adenoma:

Intermediate in size
degree of dysplasia and malignant potential between tubular and villous adenomas.



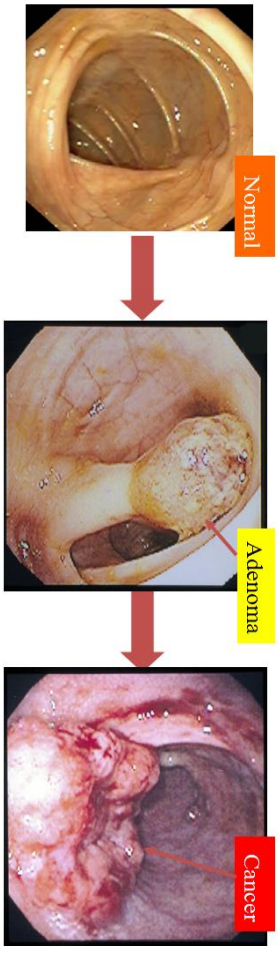
Relationship of Neoplastic Polyps to Carcinoma:

Adenoma to carcinoma sequence is documented by several genetic alterations and morphological changes as well.
Polyp removal is mandatory as it helps prevention from developing to CRC (colorectal cancer)

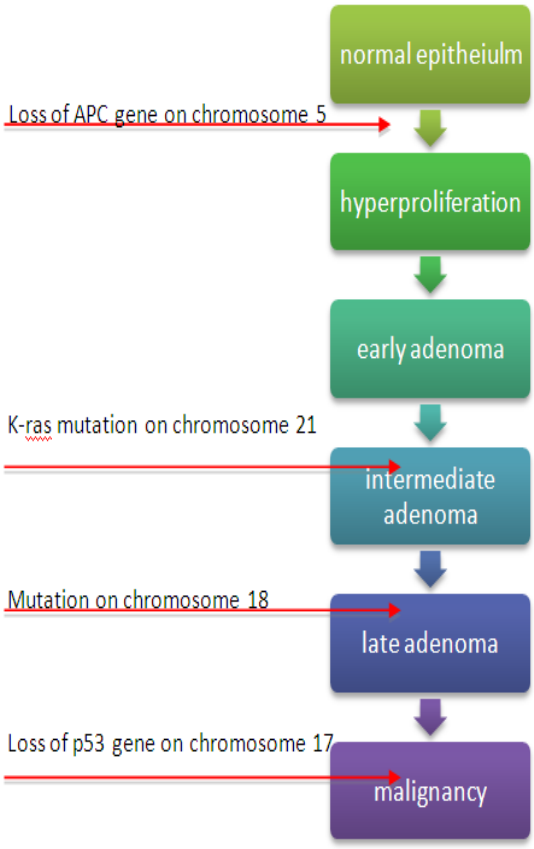
<u>The probability of carcinoma occurring in a neoplastic polyp is related to:</u>

1. The size of the polyp: ↑size → more chance to develop to cancer.
   >2 cm → 40% risk of malignancy
2. The number of polyps: multiple → higher risk
3. The relative proportion of its villous features: ↑ villous architecture → more chance to develop to cancer.
   Villous-type adenomas have a 30-40% risk for malignancy
4. The presence of significant cytologic atypia (dysplasia) in the neoplastic cells: ↑dysplasia → more chance to develop to cancer.

Pathway:

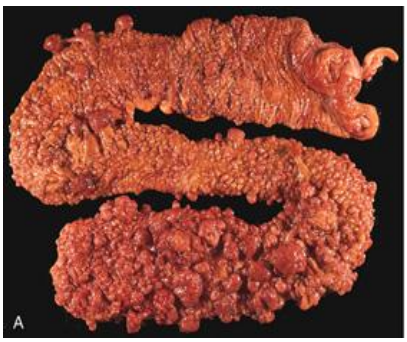


<u>Genetic factors:</u>



Familial Polyposis Syndrome:

Patients have genetic tendencies to develop neoplastic polyps (such as mutation in chromosome 5, note that the two alleles must be mutated to develop malignancy)
Presented as multiple polyps (>500)



1. Familial polyposis coli (FPC):

Cause:
- genetic defect of Adenomatous polyposis coli (*APC*).
- inactivation of *APC* gene located on the long arm of chromosome 5 (5q21).
  → *APC* gene is a tumor suppressor gene
- Autosomal dominant

Location: innumerable neoplastic polyps in the colon (500 to 2500). However, polyps are also found elsewhere in alimentary tract

Prognosis:

Polyps begin to dezelop between 10 to 20 years of age

The risk of colorectal cancer is 100% by midlife (the age of 30-40).

Treatment: patients need total colectomy. Prophylactic colectomy is recommended

The next two types have similar genetic defects as FPC in addition to other genetic factors and manifestations:

2. Gardener's syndrome:

Polyposis coli, multiple osteomas (bone tumors), epidermal cysts (skin lesions), and fibromatosis (soft tissue tumors).

3. Turcot syndrome:

Polyposis coli, glioma (brain tumors) and fibromatosis (soft tissue tumors).

> Polyp removal leads to CRC prevention.
> Polyp is surrogate marker.

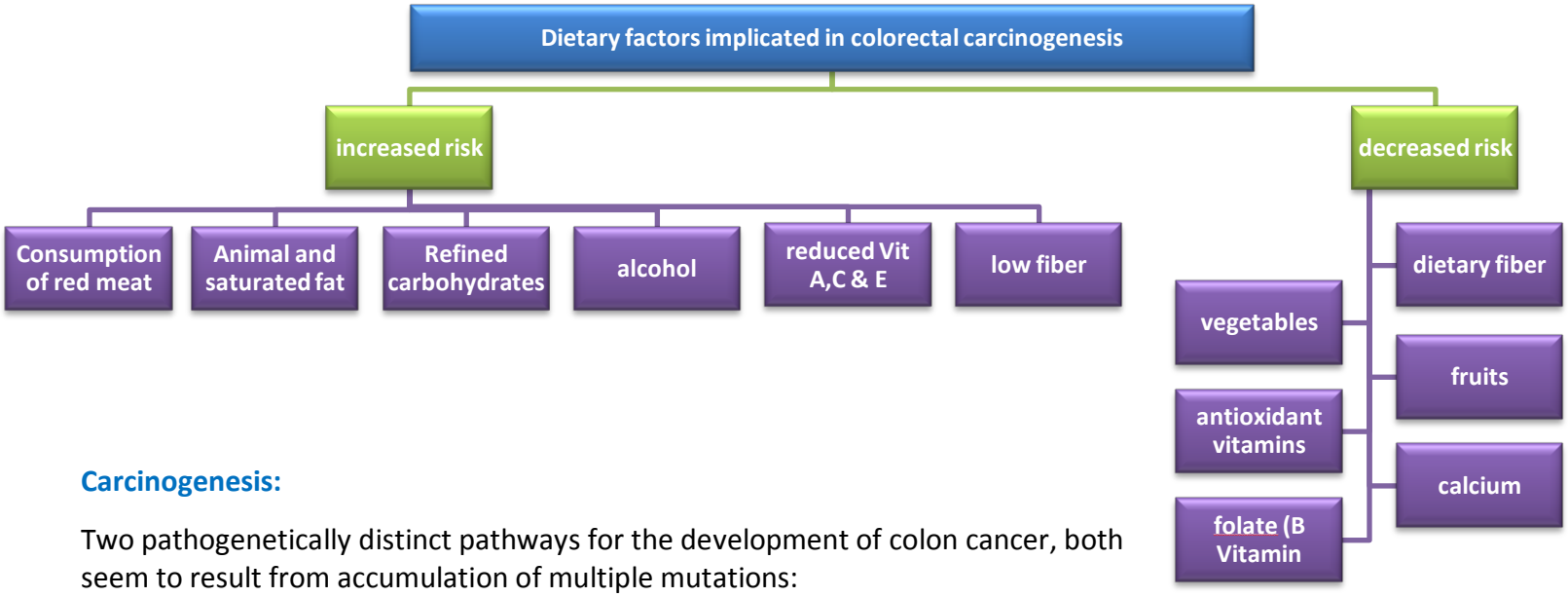
Malignant Tumors of Large Intestine:

Adenocarcinoma:

Incidence:
Adenocarcinoma of the colon is the most common malignancy of the GI tract and is a major cause of morbidity and mortality worldwide. (3rd common cause of cancerous deaths among both women and men)
Constitutes 98% of all cancers in the large intestine.
More common among elderly → peaks at 60-70 years of age

Predisposing factors:

1. Age: >50 years of age
2. Sedentary lifestyle, Diet, Obesity
3. Cigarette smoking
4. Family History of CRC:
   - First degree relatives with colon cancer
   - No specific pattern of dominance
5. Hereditary Syndromes
   - familial adenomatous polyposis (FAP)
   - hereditary polyposis syndrome
   - heridetary non-polyposis colon cancer
   - family cancer syndrome → mutation in P53 gene
6. Inflammatory Bowel Disease (IBD): ulcerative colitis > Crohn's disease
7. Adenomas, Polyps
8. Diet appears to play an important role in the risk for colon cancer:



Carcinogenesis:

Two pathogenetically distinct pathways for the development of colon cancer, both seem to result from accumulation of multiple mutations:

1- The APC/B-catenin pathway (85 %)

It is a chromosomal instability that results in stepwise accumulation of mutations in a series of oncogenes and tumor suppressor genes.

Gives rise to hereditary polyposis syndromes

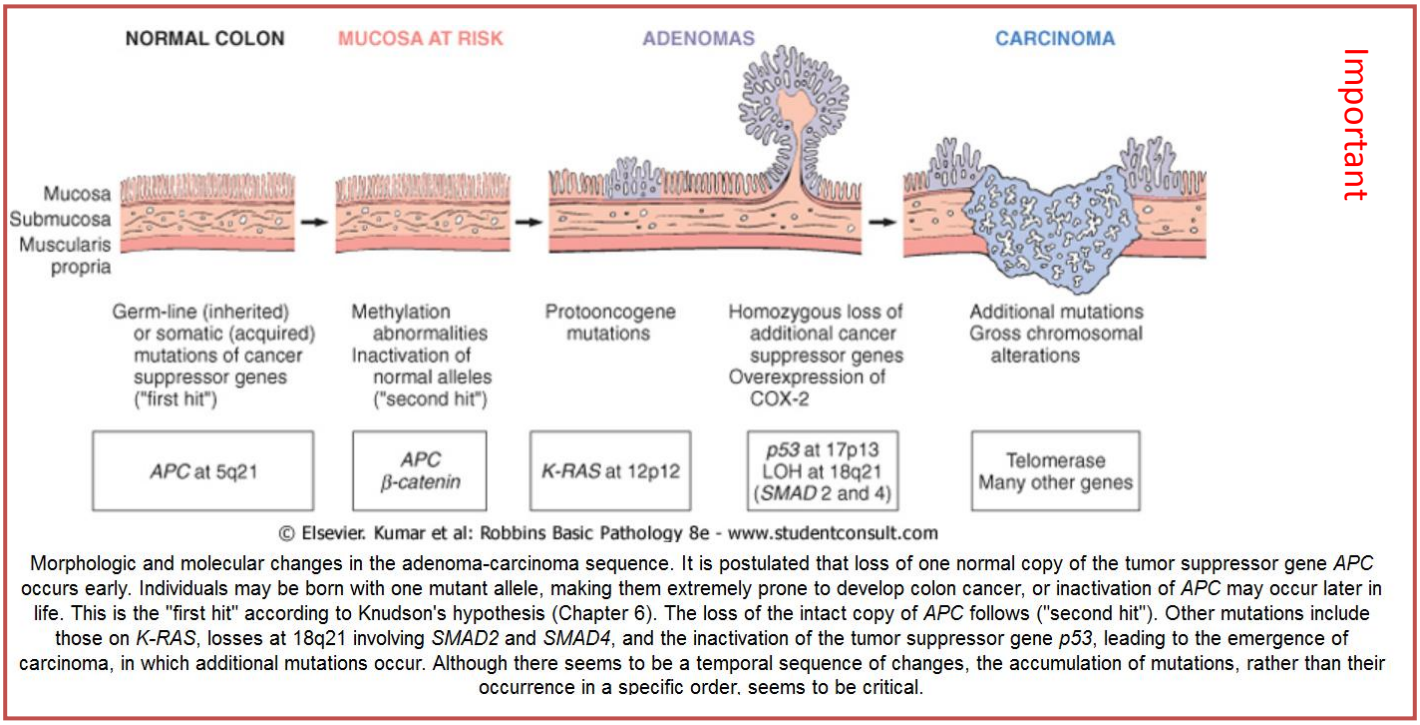
e.g: Familial Adenomatous Polyposis (FAP):

Cause: Hereditary mutation of the APC gene.

Prognosis: affected individuals carry an almost 100% risk of developing colon cancer by age 40 years.

2- The DNA mismatch repair genes pathway

- 10% to 15% of sporadic cases.
- There is accumulation of mutations (as in the APC/B-catenin schema) of one or more of these five DNA mismatch repair genes (MSH2, MSH6, MLH1, PMS1, AND PMS2) → leading to microsatellite instability
- Give rise to the hereditary non polyposis (only one or two polyps) colon carcinoma (HNPCC)



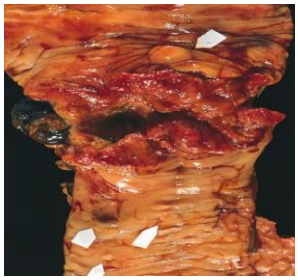
Important

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 develop colon cancer, or inactivation of *APC* may occur later in life. This is the "first hit" according to Knudson's hypothesis (Chapter 6). The loss of the intact copy of *APC* follows ("second hit"). Other mutations include those on *K-RAS*, losses at 18q21 involving *SMAD2* and *SMAD4*, and the inactivation of the tumor suppressor gene *p53*, leading to the emergence of carcinoma, in which additional mutations occur. Although there seems to be a temporal sequence of changes, the accumulation of mutations, rather than their occurrence in a specific order, seems to be critical.

notes: beta-catenin normally functions to regulate cell growth

DNA mismatch repair genes normally check DNA during transcription to repair any abnormal patterns

Colorectal Carcinoma:

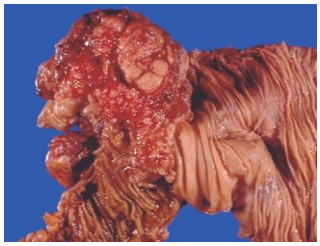


Location: 70% are in the rectum, rectosigmoid and sigmoid colon.
Mainly (50%) in rectosegmoid and rectum

Types: each presents differently

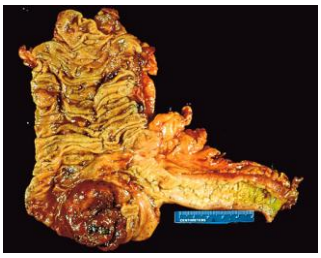
- Left-sided carcinomas:

affects the descending colon
tend to be annular lesions encircling the entire circumference of the lumen and causing narrowing
→ early symptoms of obstruction; severe colic abdominal pain and at later stages abdominal distention.

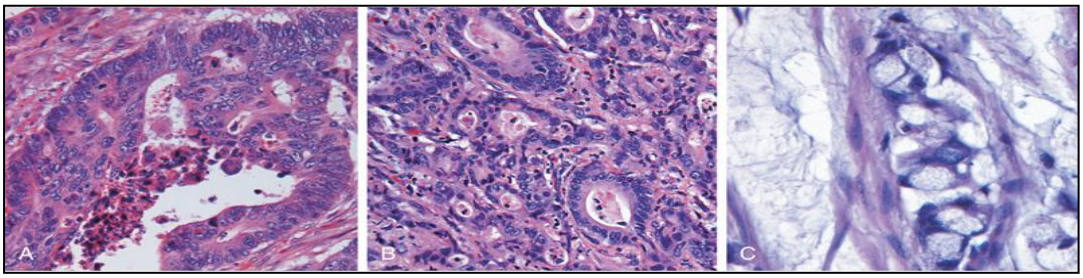


- Right-sided carcinomas:

affects the ascending colon
tend to grow as polypoid, fungating masses.
obstruction is uncommon
Patients usually present with iron deficiency anemia as a result of occult bleeding (tested by fecal occult test)



Morphology:
Mucinous adenocarcinoma secret abundant mucin that may dissect through cleavage planes in the wall.
Mucin is found intracellularly as well as extracellularly in the stroma
Infiltrating malignant glands lined by neoplastic cells



Signs and symptoms:
If located closer to the anus: change in bowel habit, feeling of incomplete defecation, PR bleeding
A (left or right sided) tumor that is large enough to fill the entire lumen of the bowel may cause bowel obstruction but is more common with left-sided.
Right-sided lesions are more likely to bleed.
→ left-sided are detected earlier than right-sided

Tumor marker:
Serum levels of carcinoembryonic antigen (CEA) are related to tumor size and extent of spread.
They are non-specific as they can be elevated in cases of liver cirrhosis or hepatitis. However an increase by over 500 times mainly indicates malignancy.
They are helpful in monitoring for recurrence of tumor after resection.
Staging: by either Duke classification of TNM staging → stage highly correlates to outcome of disease
Prognosis:
Generally, right sided carcinoma has better prognosis than left sided

determined by:

Table 14-8. AJCC Tumor-Node-Metastasis (TNM) Classification of Colorectal Carcinoma

Designation	Description
Tumor	
Tis	In situ dysplasia or intramucosal carcinoma
T1	Tumor invades submucosa
T2	Tumor invades into, but not through, muscularis propria
T3	Tumor invades through muscularis propria
T4	Tumor invades adjacent organs or visceral peritoneum
Regional Lymph Nodes	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis or seeding of abdominal organs

1. degree of invasion

2. involvement of lymph nodes

Table 14-9. AJCC Colorectal Cancer Staging and Survival

Stage*	Tumor-Node-Metastasis (TNM) Criteria			5-Year Survival (%)
	T	N	M	
I	T1, T2	N0	M0	74
II				
IIA	T3	N0	M0	67
IIB	T4	N0	M0	59
III				
IIIA	T1, T2	N1	M0	73
IIIB	T3, T4	N1	M0	46
IIIC	Any T	N2	M0	28
IV	Any T	Any N	M1	6

Prevention:

- Aspirin and other NSAIDs decreases incidence of colorectal adenomas → evidence of some correlation between chronic inflammation and cancer
- Annual fecal occult blood testing: a rough estimate only

Positive indicates occult bleeding which is the classical presentation of right-sided colorectal cancer

However, many false positive results are recorded due to iron supplements or incomplete digestion of meats

- Estrogens and progestin's may reduce colorectal cancer risk
- Dietary alterations: (1) Decrease fat intake to 30% of total caloric intake
  (2) Increase fiber
  (3) Increase intake of fruits and vegetables
- Statins may inhibit growth of colon cancer lines
- Cessation of smoking

Malignant Small Intestinal Neoplasms:

Types in descending order of frequency:

- Carcinoid → most common, arises from neuroendocrine cells
- Adenocarcinomas → arises from epithelial lining
- Lymphomas
- Leiomyosarcomas → very rare

1- Carcinoid Tumors

Definition:

neoplasms arising from neuroendocrine cells found along the length of GIT as well as the respiratory mucosa.

Location: 60 to 80% appendix and terminal ileum.
10 to 20% rectum.
May also occur in the esophagus and pancreas

Age group:

the peak incidence is in the sixth decade, but they may appear at any age.

Incidence:

- They compose less than 2% of colorectal malignancies (majority is adenocarcinoma)
- almost half of small intestinal malignant tumors (most common)

Behavior:

Mainly they act as benign tumors in that they are localized

Aggressive behavior correlates with:

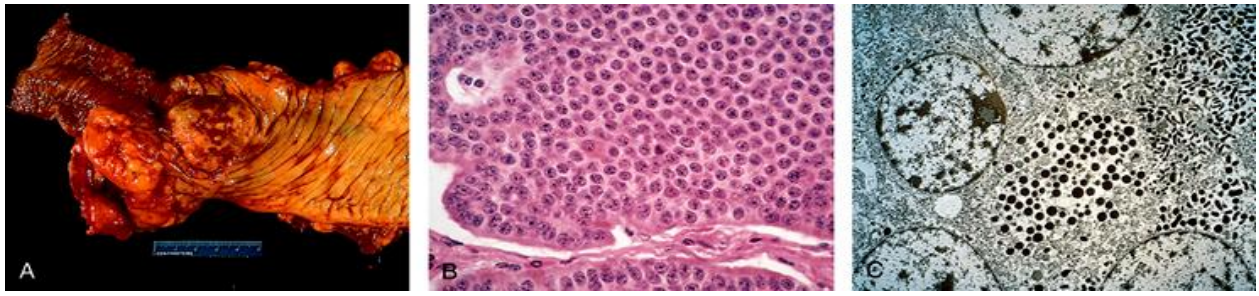
- The site of origin: in appendiceal or rectal carcinoids are usually benign and rarely metastasis
  Ileal, gastric and colonic carcinoids are usually aggressive
- the depth of local penetration
- the size of the tumor

Appendiceal and rectal carcinoids infrequently metastasize (local invasion), even though they may show extensive local spread.

90% of ileal, gastric, and colonic carcinoids that have penetrated halfway through the muscle wall have spread to lymph nodes and distant sites at the time of diagnosis, especially those larger than 2 cm in diameter.

Morphology:

• A solid, yellow-tan appearance
• The cells are monotonously similar (coin-like, having a scant, pink granular cytoplasm and a round-to-oval stippled nucleus) → do not show many features of malignancy
• Ultrastructral features: neurosecretory granules (electron dense bodies) in the cytoplasm (produce active peptide)



Note: similar appearance to melanoma except in melanoma the calls are larger and appear more oval

Clinical features:

• Asymptomatic (especially in the appendix → most oftenly discovered after appendectomy)
• May cause obstruction, intussusception or bleeding.
• May elaborate hormones: Zollinger-Ellison (gastrin hypersecretion → peptic ulcer), Cushing's carcinoid or other syndromes such as carcinoid syndrome.

Intussusception is a process in which a segment of intestine invaginates into the adjacent intestinal segment's lumen, causing bowel obstruction. As the polyp is pushed by the food it entrs the next segment pulling the underlying segment with it. This leads to decreased blood flow → ischemia -> ulceration and eventually bleeding in severe cases.

Carcinoid syndrome:

Incidence: 1% of carcinoid tumor & in 20% of those of widespread metastasis
The syndrome is classically associated with ileal carcinoids with hepatic metastases.

Cause: excessive production of serotonin

N.B: normally serotonin is degraded in the liver to an inactive form. However, in patients with hepatic dysfunction as a result of metastases, serotonin will reach the blood circulation causing most of the symptoms below.

Symptoms:

- paroxymal flushing
- episodes of asthma-like wheezing
- right-sided heart failure
- attacks of watery diarrhea
- abdominal pain

2- Lymphoma:

Types:

• most often low-grade lymphomas arising in mucosal-associated lymphoid tissue (MALT) lymphoma associated with H.Pylori infection → continuous stimulation of the lymphocytes in the mucosa
• high-grade non-Hodgkin's lymphomas of B cell type.
• t-cell lymphoma associated with celiac disease.

Location:

• May occur in any part of the intestine.
• The ileocecal region as well as the jaws are the favored site for Burkitt's lymphoma.

Questions from the male doctor:

A 68-year-old woman presents with intermittent constipation, weight loss, and a swollen abdomen. She has had two previous polypectomies: one showed a tubular adenoma and the other was a tubulovillous adenoma. Colonoscopy is performed and this gives good visualization of the colon round to the transverse colon only; no lesions are seen. Double-contrast barium enema shows an irregular stricture with shouldered edges approximately 4 cm long in the ascending colon. A tumor is diagnosed and surgery is advised. The tumor is resected and is found to have invaded through the thickness of the bowel wall, but is completely excised. Three of 15 lymph nodes identified contained metastatic tumor, but the 'high tie' node is free of disease.

1. What is the most likely diagnosis with this presentation?
2. What stage is this tumor and what is the prognosis?
3. What is the association between adenoma and carcinoma?
4. Where is the metastatic spread most likely?

•1. The most likely diagnosis is colorectal adenocarcinoma.
•2. This is a Dukes' C carcinoma (T3, N1, M0; stage IIIB) provided no distant metastases are located on staging scanning. Tumors in the right colon tend to present later than those of the distal colon because the bowel contents are more fluid, and so obstruction occurs later. There is about 30% 5-year survival with this type of disease.
•3. There is much evidence to suggest that most carcinomas of the colon arise in pre-existing adenomas (adenoma–carcinoma sequence). Patients with familial adenomatous polyposis (FAP) have a very high risk of developing colorectal carcinomas.
•4. Colorectal carcinomas metastasize mainly to regional lymph nodes and liver, less commonly developing other systemic metastases such as brain, bone and lung.

A 6-year-old boy has been brought to outpatients by his mother because he has abdominal pain after some meals. This has been getting increasingly frequent and it sounds, from his description, somewhat colicky in nature. You discover that he has always had very smelly, loose, pale bulky stools, which his parents have put down to the fact that he likes milk. On examination, he is pale, underweight, and of short stature. His abdomen is mildly distended.

1. What are the important differential diagnoses on presentation?
2. Blood tests reveal a mild macrocytic anemia with Howell–Jolly bodies. There is a low level of vitamin B12, and folate is at the lower end of normal. Autoantibody screens reveal a positive reaction to antigliadin antibodies. Do these tests help to narrow down the diagnosis?
3. A duodenal biopsy shows villous atrophy with increased intraepithelial and lamina proprial lymphocytes. What is the final diagnosis?
4. What treatment options are available?

52 y/o female presented with fatigue and weakness. She experienced 6 kg wt loss in a 6 six months

CBC .....Hg 7.5 g/dl, hematocrit 26 %

Serum ferritin 8 ng/dl

Iron deficiency anaimia

Rx oral iron treatment

Underlying cause?

•Menestrual period …….normal

•Stool and urine analysis……blood in the stool

•Colonoscopy …….ascending colon 6 cm mass

•Biopsy ……..adenocarcinoma

•CT scan ……no liver nodule

Familial polyposis coli is characterized by?

a. Autosomal recessive pattern of inheritance
b. Multiple hamartomatous polyps throughout the colon
c. 100% risk of carcinoma
d. An association with fibromatosis and multiple osteomas
e. An association with tumors of the central nervous system

The answer is c.

Although most colonic polyps occur sporadically, there are several conditions in which colonic polyposis is familial and sometimes associated with extraintestinal abnormalities. Familial polyposis coli is usually transmitted as an autosomal dominant condition and is characterized by multiple adenomatous colonic polyps, with a minimum of 100 polyps necessary for diagnosis. As with sporadic adenomatous polyps, there is a risk of malignancy, and this increases to 100% within 30 years of diagnosis. Panproctocolectomy is therefore usually recommended.

Gardner's syndrome is the association of colonic polyposis with multiple osteomas, fibromatosis, and cutaneous cysts. The association of colonic polyposis with central nervous system tumors is known as Turcot's syndrome.

Additional Questions:

What is the most common type of polyp in children?

a. Hyperplastic polyps
b. Juvenile (hamartomatous) polyps
c. Inflammatory pseudopolyps
d. Adenomatous polyps

Serum levels of carcinoembryonic antigen (CEA):

a. Are markers for colorectal cancer
b. Mainly used to monitor recurrence of malignancy after resection
c. Are non-specific markers
d. All of the above

What are the two most common sights for carcinoid tumors?

a. The ileum and jaw
b. The pancreas and appendix
c. The ileum and appendix
d. The ileum and rectum

Which of these is true about mucosal-associated lymphoid tissue (MALT) lymphoma?

a. It is a high-grade tumor
b. It attacks the jaws most frequently
c. Associated with H.pylori infection
d. Associated with celiac disease

Answers:

b, d, c, c