INFLAMMATORY BOWEL DISEASE (IBD)

- Crohn's disease (CD) & Ulcerative colitis (UC) are chronic relapsing inflammatory disorders of unknown (idiopathic) origin, collectively known as idiopathic inflammatory bowel disease (IBD), which share many common features.

- IBD result from an abnormal local immune response against the normal flora of the gut & probably against some self antigens, in genetically susceptible individuals.

- CD may affect any portion of the GIT from esophagus to anus, but most often involves the ileum (terminal ileitis);

  50% of cases exhibit noncaseating granulomatous inflammation.

- UC is a nongranulomatous disease limited to the colon.

- CD & UC differ in many respects, including the disease natural history, pathological aspects, treatment & responses to treatment.

- Before considering these diseases separately, the pathogenesis of both CD & UC will be considered.

Etiology & Pathogenesis of both CD & UC

- The normal intestine is in a steady state of "physiologic" inflammation, representing a dynamic balance between

(1) Factors that activate the host immune system, such as luminal microbes, dietary antigens, & endogenous inflammatory stimuli; &

(2) Host defenses that down-regulate inflammation & maintain the integrity of the mucosa

- The search for the causes of loss of this balance in CD & UC has revealed many parallels,

  but the origins of both diseases remain unexplained (thus their designation as idiopathic).

The Genetic Predisposition, Immunologic Factors, & Microbial Factors will be discuss.

►Genetic Predisposition

-There is little doubt that genetic factors are important in the occurrence of IBD.

-First-degree relatives are 3 to 20 times more likely to develop the IBD, & 15% of persons with IBD have affected first-degree relatives.

-In keeping with an underlying immunologic dysfunction, both CD & UC have been linked to specific major histocompatibility complex class II alleles.

-UC has been associated with HLA-DRB1,

-whereas HLA-DR7 & DQ4 alleles are associated with 30% of CD cases in North American white males.

► Immunologic Factors

- It is not known whether the immune responses in IBD are directed against self-antigens of the intestinal epithelium? or to bacterial antigens?

-In both CD & UC, the primary damaging agents appear to be CD4+ cells.

-The inflammatory cytokine TNF may play an important pathogenic role in CD;

this is suggested by the effectiveness of treatment with TNF antagonists in CD.

►Microbial Factors

-The sites affected by IBD-the distal ileum & the colon-are awash {covered by tides} in bacteria.

-While there is no evidence that these diseases are caused by microbes, it is quite likely that microbes provide the antigenic trigger to a fundamentally dysregulated immune system.

-This concept is strengthened by the observations that in murine models, IBD develops in the presence of normal gut flora but not in germ-free mice.

►The Final Common Pathway for the Pathogenesis of IBD is Inflammation,

-which is ultimately, the result of activation of inflammatory cells (neutrophils initially & mononuclear cells later) in the course

, causing mucosal destruction & the intermittent bloody diarrhea that is characteristic of IBD.

- Most current therapeutic interventions act entirely or partly through nonspecific down-regulation of the immune system.

▼ Among diagnostic tests, the most useful is the detection of perinuclear antineutrophil cytoplasmic Abs,

which are present in 75% of persons with UC & only 11% of individuals with CD.

Crohn's Disease (CD)

►GROSSLY

• Site:

In CD there is gross involvement:

- of the small intestine alone in 30% of cases,

- of both small intestine & colon in 40%,

-& of the colon alone in about 30%.

• CD disease may involve :

the mouth, esophagus, stomach, & duodenum,

but these sites are distinctly uncommon.

- Fully developed CD characterized by:

→Classically, sharply limited, & demarcated diseased bowel segments from adjacent uninvolved bowel.

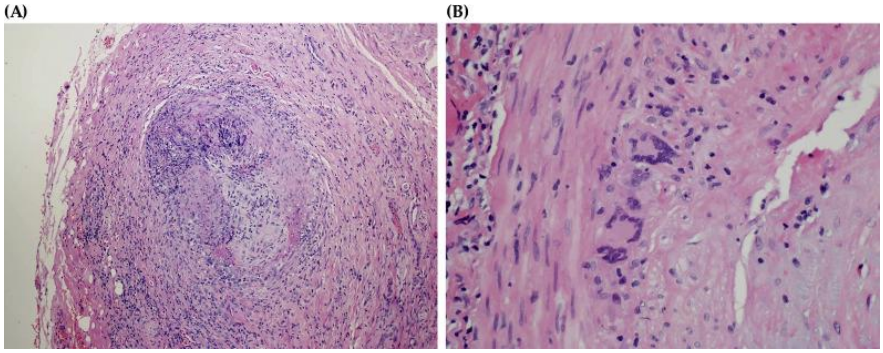
→ Transmural inflammation involving all the bowel wall, with :

-Mucosal damage

-Fissuring (b)

-Fistula formation

-Noncaseating granulomas in 50% of cases, (a)



•The intestinal wall is rubbery & thick,

the result of edema, inflammation, fibrosis, & hypertrophy of the muscularis propria.

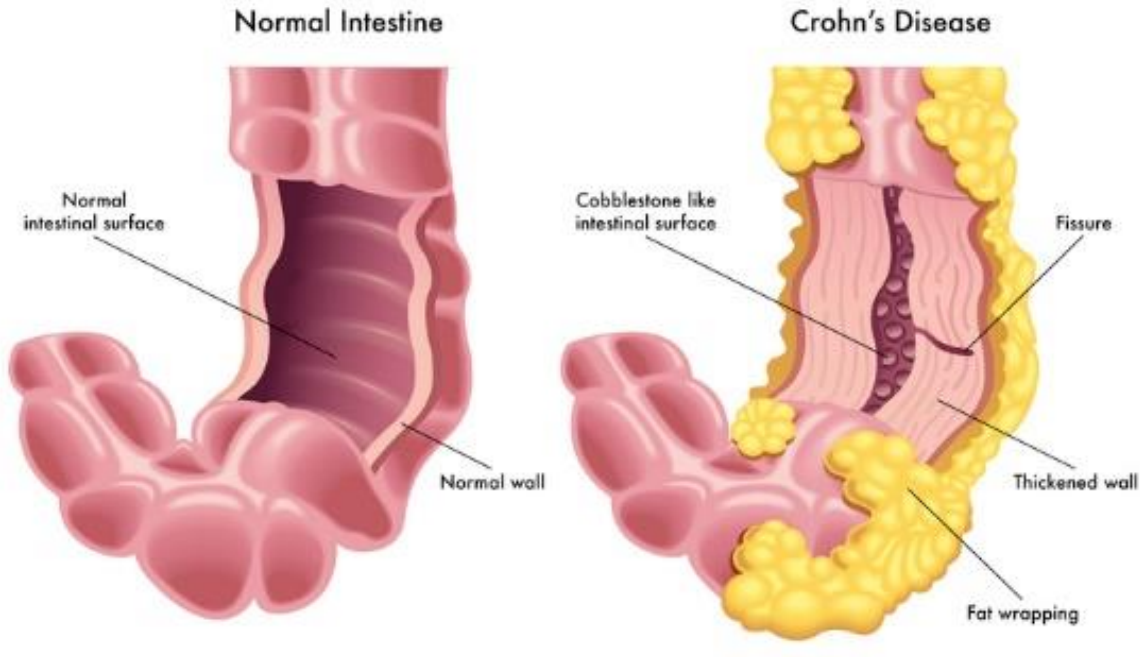
As a result, the lumen is almost always narrowed;

in the small intestine this is seen radiographically as "string sign,"

a thin stream of barium passing through the diseased segment (F4.37).

•In diseased segments, the serosa becomes granular & dull gray & often the mesenteric fat wraps around the bowel surface ("creeping fat“ F15-30).

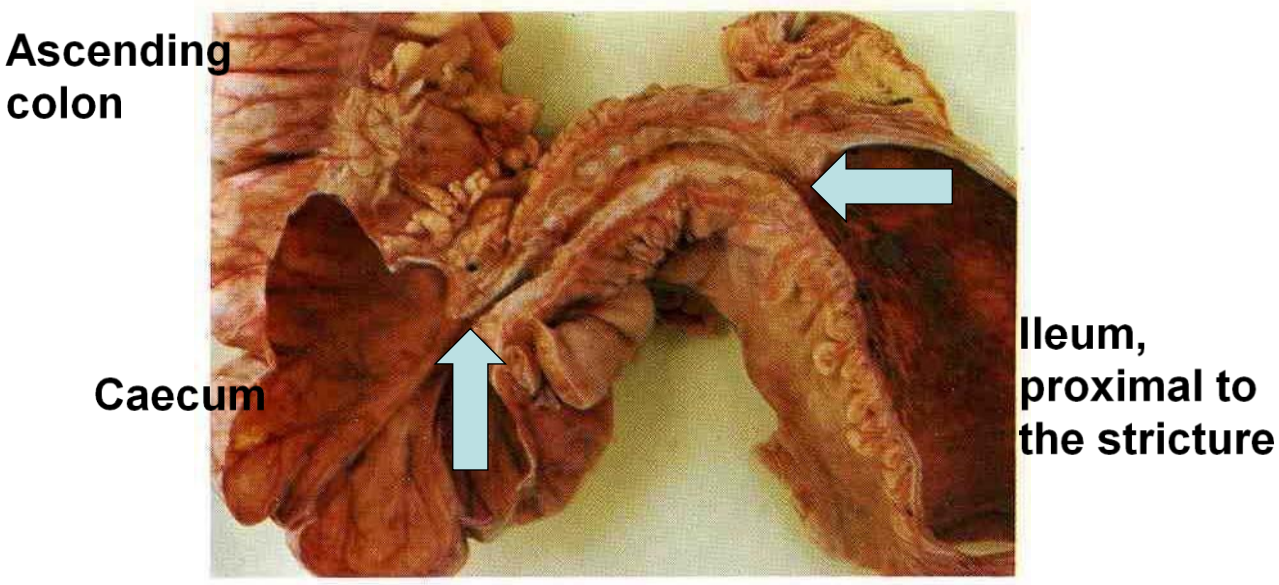
• When several bowel segments are involved, the intervening bowel is essentially normal ("skip" lesions).



Crohn’s disease: ileum.

Long segment of the terminal ileum showing the hose-pipe stricture (string sign on X-ray) which ends suddenly at the ileo-caecal valve (arrows).

The full thickness of the ileal wall shows extensive transmural fibrosis, with extension into the mesentery. There are discrete mucosal ulcers in the dilated ileum proximal to the stricture,



4.37 Crohn’s disease: ileum

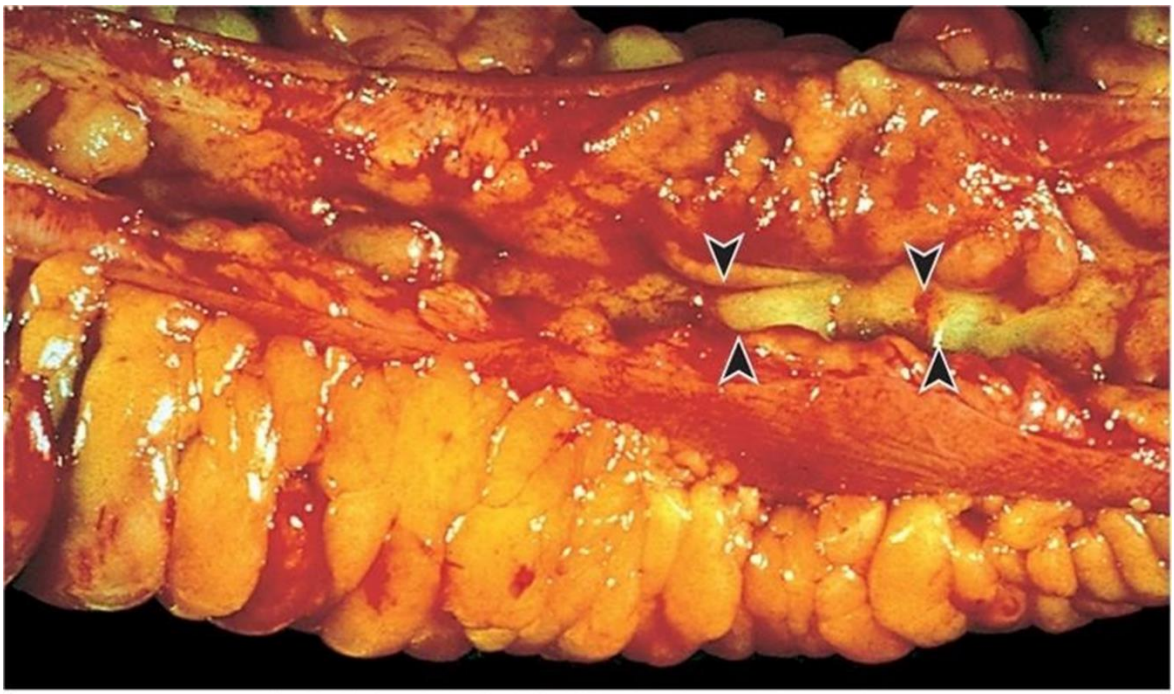
Crohn disease: ileum,

showing

(1) linear ulceration of the mucosal surface (arrowheads),

(2) bowel wall thickening with narrowing of the lumen &

(3) serosal extension of mesenteric fat (“creeping fat”).



- In the intestinal mucosa, early disease shows focal mucosal.....

-ulcers,

resembling aphthous ulcers, edema, & loss of the normal mucosal texture.

Later, ulcers coalesce into long, serpentine linear ulcers, which tend to be oriented along the axis of the bowel (F15-30 & 4.39).

Because the intervening mucosa tends to be relatively spared, it acquires a coarsely textured, cobblestone appearance (F4.40).

-Fissures develop between the folds of the mucosa,

often penetrating deeply through the bowel wall all the way to the

serosa.

This may lead to…

-Adhesions with adjacent loops of bowel.

Further extension of fissures leads to…

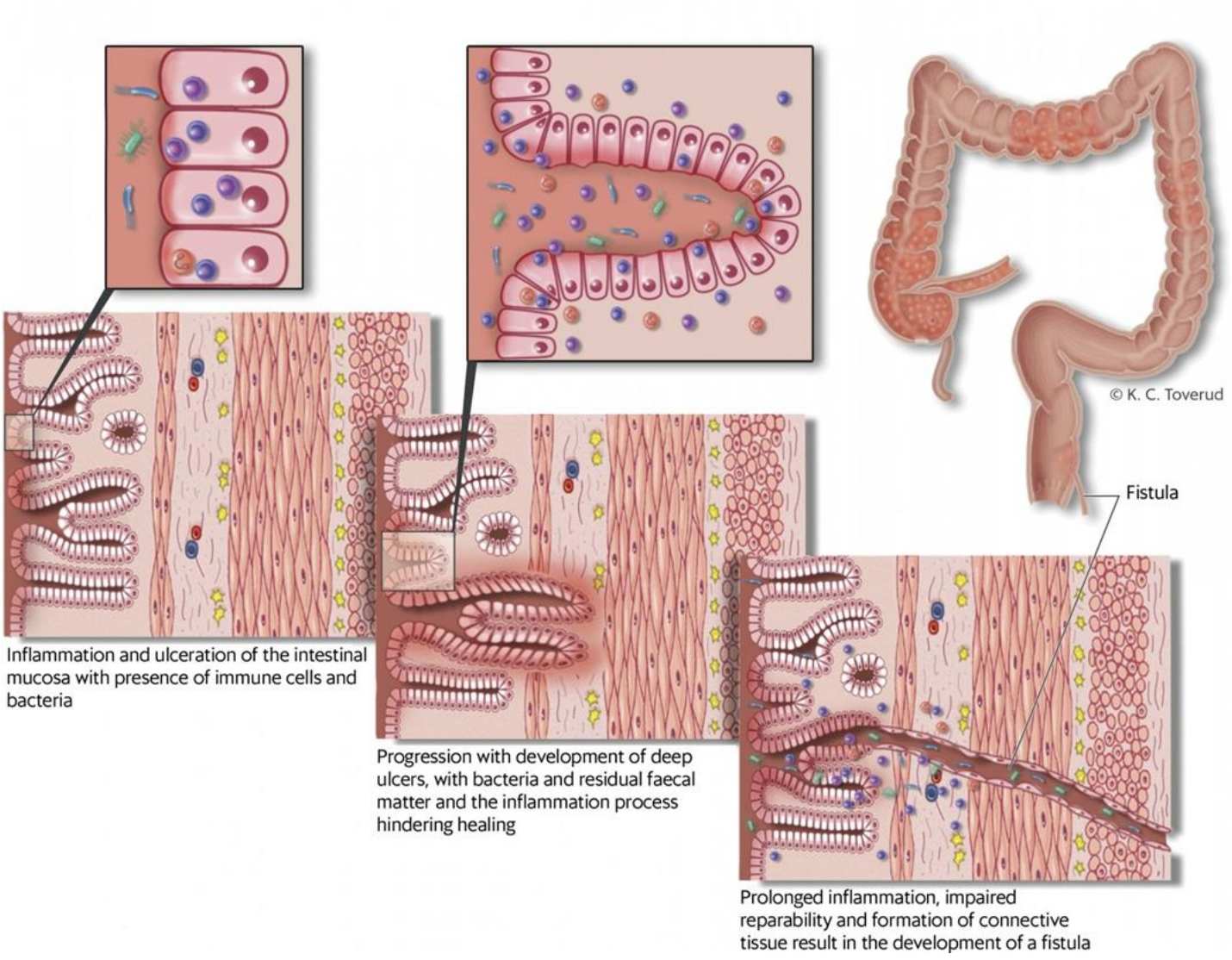
-Fistula

or sinus tract formation to adherent viscera, to the outside skin, or into a blind cavity

to form a localized abscess.

{Summary:

Cobblestone & Ulcers→ Fissures → Adhesions → Sinus → Fistula → Abscess}.



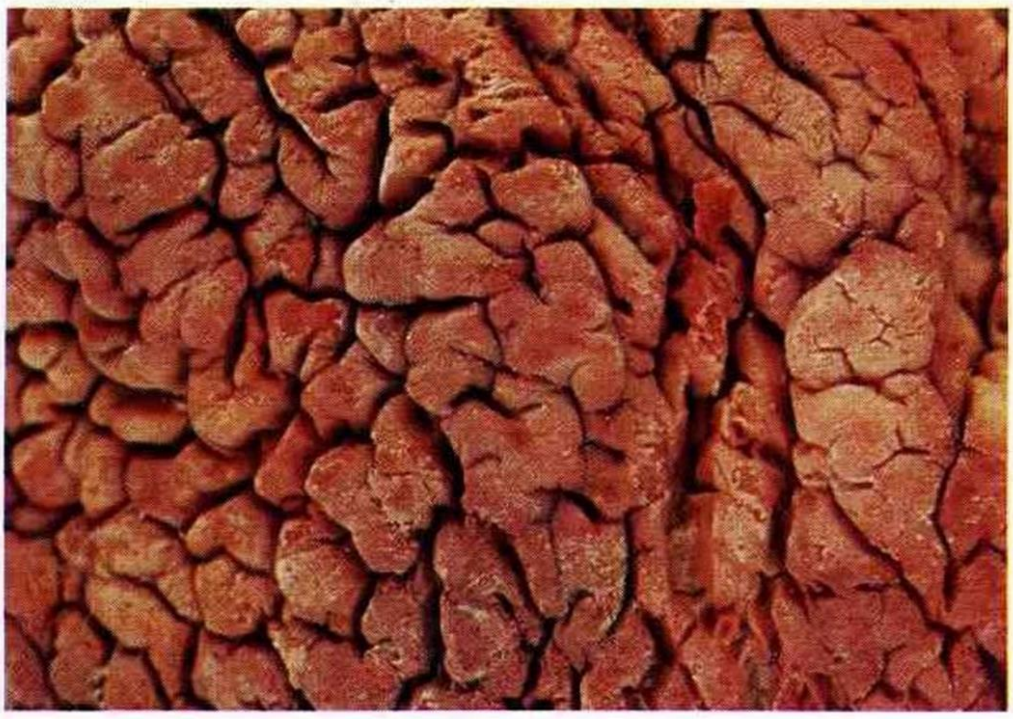
Crohn’s disease: caecum.

-The classic ***cobblestone*** appearance,

- seen in 25% of CD,

- formed by intercommunicating fissures

surrounding by islands of mucosa raised by underlying inflammation & edema.



4.40 Crohn’s disease: caecum

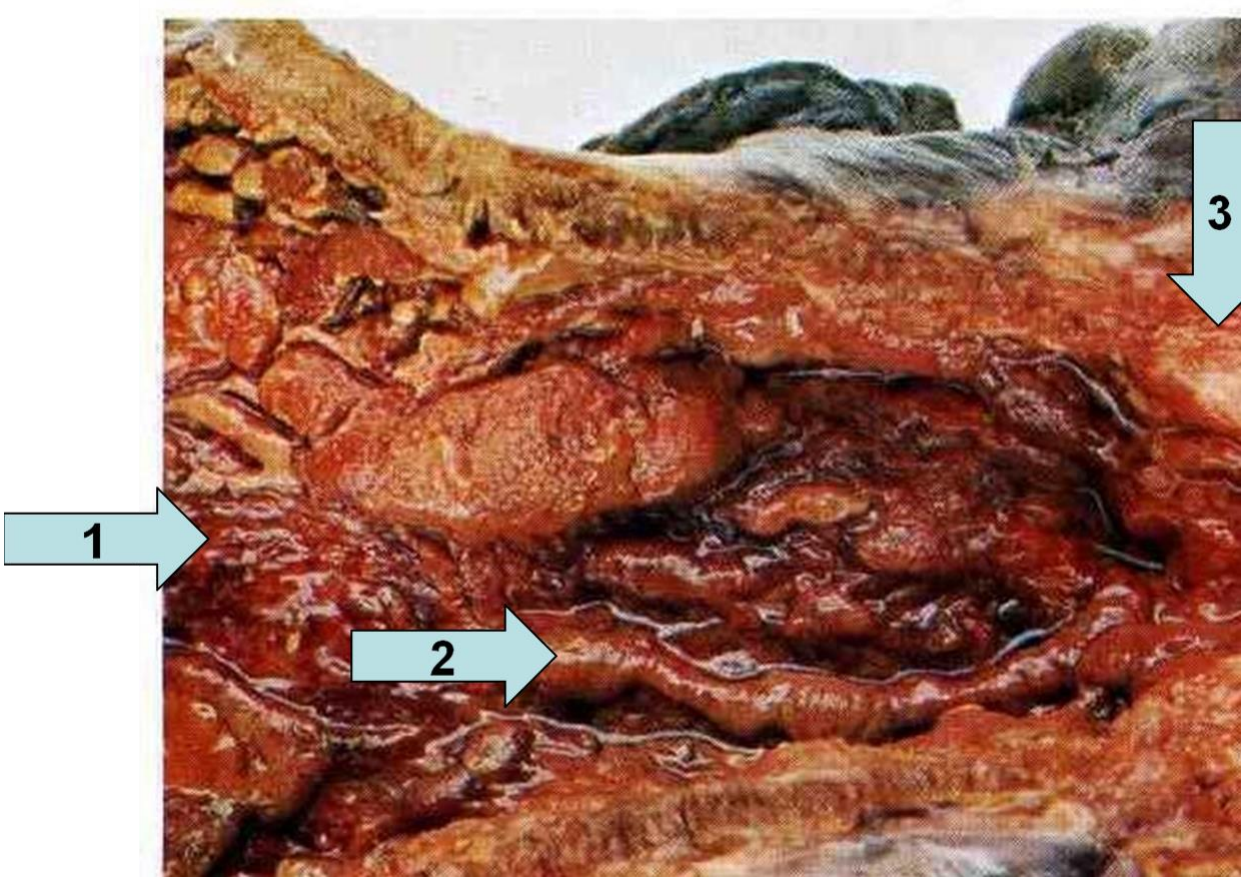
Crohn's disease: ileum.

Three principal features:

(1) irregular ulceration of the mucosa, producing a coarse

(2) cobblestone pattern, &

(3) markedly thickened wall & in the region of the stricture (right) yellowish-white fibrous tissue is evident in the wall.



Histology,

- mucosa show characteristic features (F15-31):

(1) Inflammation, with neutrophilic infiltration into the epithelial layer (cryptitis) & accumulation within crypts to form crypt abscesses;

(2) Ulceration, &

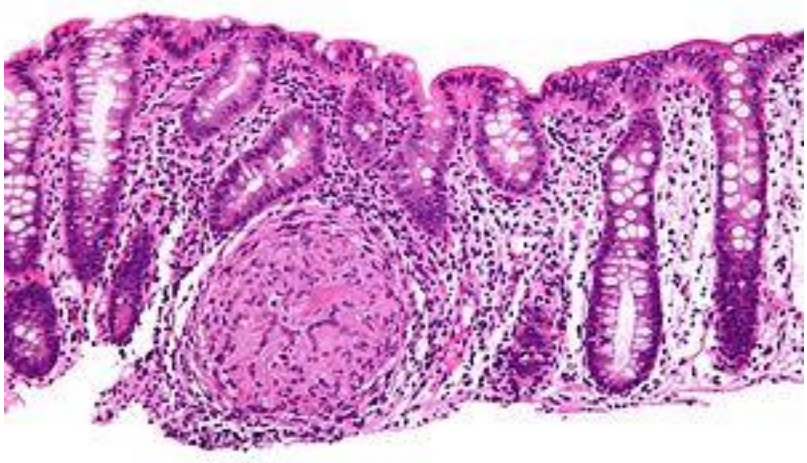
(3) Chronic mucosal damage, distortion & atrophy.

- Granulomas may be present any-where in the GIT, even in individuals with CD limited to one bowel segment.
  However, the absence of granulomas does not exclude the diagnosis of CD.

- In diseased segments, the muscularis mucosae & muscularis propria are usually markedly thickened,

& fibrosis affects all bowel layers (Transmural inflammation).

- Lymphoid aggregates scattered through the full intestinal wall & in the extramural fat are characteristic.



: Crohn disease of the colon,

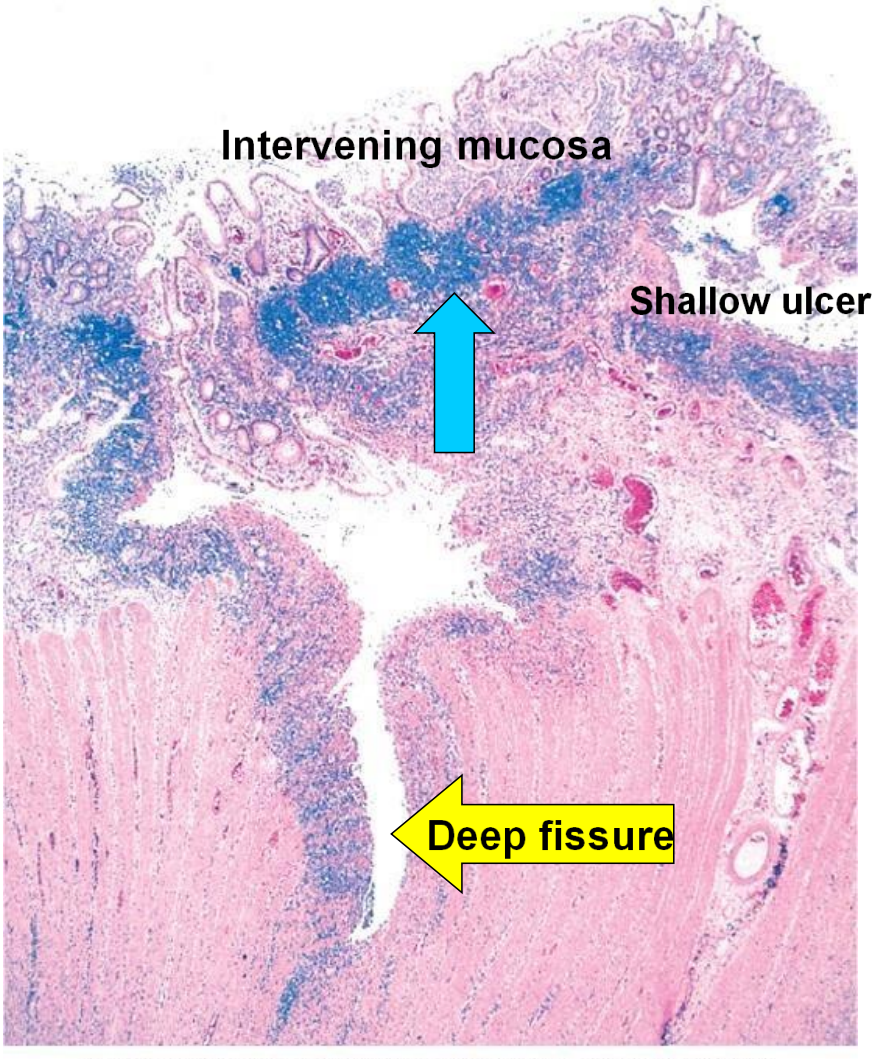
-showing a deep fissure extending into the muscle wall,

-a second, shallow ulcer (upper right), & relative preservation of the intervening mucosa.

- Dense blue patches of cells (lymphocyte aggregates) are present, at the interface between mucosa & submucosa.

-Particularly important in persons with long-standing chronic CD are dysplastic changes appearing in the mucosal epithelial cells.

These may be focal or widespread, tend to increase with time, & predispose to a X 5-6 folds increased risk of carcinoma, particularly of the colon.



►**Clinically,**

the presentation of CD disease is highly variable & unpredictable.

(1) The dominant manifestations are recurrent episodes of diarrhea & crampy abdominal pain.

(2) In most patients, after an initial attack, the manifestations remit either spontaneously or with therapy, but characteristically they are followed by relapses, & intervals between successive attacks grow shorter.

(3) Superimposed on this course are the potential development of malabsorption & some of the extra-intestinal manifestations.

• Active cases of the disease are often accompanied by extra-intestinal complications of immune origin, such as :

-uveitis,

-sacroiliitis,

-migratory polyarthritis,

-erythema nodosum,

- bile duct inflammatory disorders,

- & obstructive uropathy.

► CD may affect any level of the GIT, from mouth to anus,

but most commonly located at the terminal ileum.

- At first, the disease was thought to be limited to the ileum, & that is why it was referred to as "terminal ileitis" or "regional enteritis".

- BUT, CD must be viewed as a systemic inflammatory disease with predominant GIT involvement.

- The debilitating **consequences** of CD include :

(1) Fistula formation to other loops of bowel, urinary bladder, vagina, or perianal skin;

(2) Abdominal abscesses or peritonitis; &

(3) Intestinal stricture or obstruction.

- Rare devastating events are

(I) massive intestinal bleeding,
(II) toxic dilation of the colon, or
(III) ca of the colon or small intestine.

Although the increased risk for ca is significant, it is substantially less than that associated with UC.

Epidemiology

•Worldwide in distribution, CD is much more prevalent in the

US, GB, & Scandinavia than in Central Europe,

& is rare in Asia & Africa.

•The incidence & prevalence of CD has been steadily raising in the US & Western Europe,

with annual incidence in the US of 4 per 100,000 populations (12000 new cases/Year)

• It occurs at any age, from young childhood to advanced age,

but peak incidence is between the 2nd & 3rd decades of life.

• Females are affected slightly more often than males.

• Whites appear to develop the disease 2 to 5 times more often than do nonwhites.

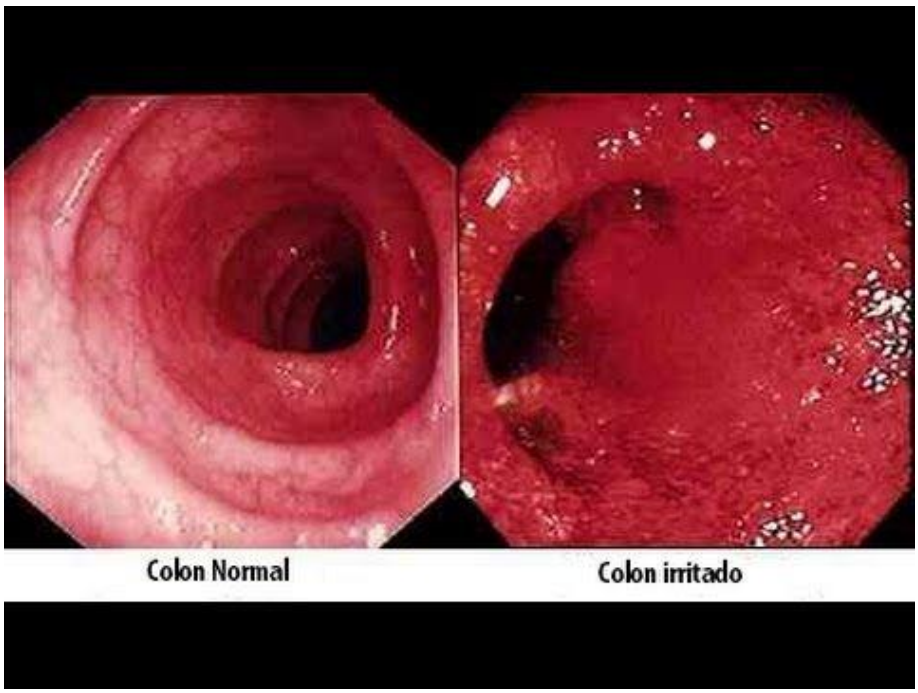
In the US, CD occurs 3 to 5 times more often among Jews than among non-Jews.

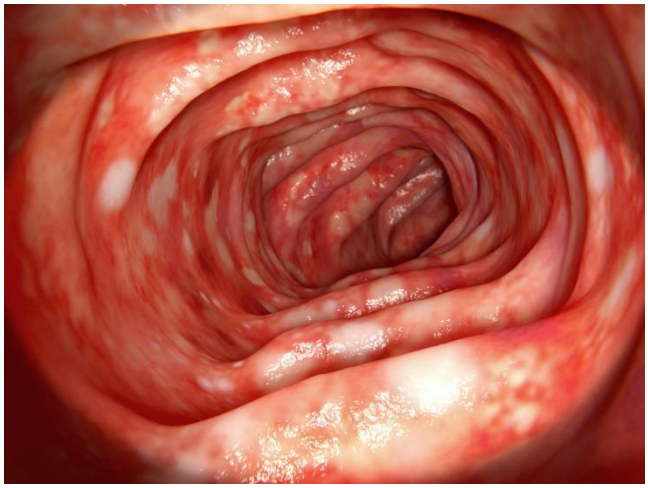
Ulcerative Colitis (UC)

- UC is an inflammatory-ulcerative disease affecting the colon only, which is limited to the mucosa & submucosa, except in the most severe cases.

- Like CD, UC is a systemic disorder associated in some persons with:

  -migratory polyarthritis,
  - sacroiliitis,
  - ankylosing spondylitis,
  - uveitis,
  - erythema nodosum,
  -& hepatic involvement (pericholangitis a & primary sclerosing cholangitis).

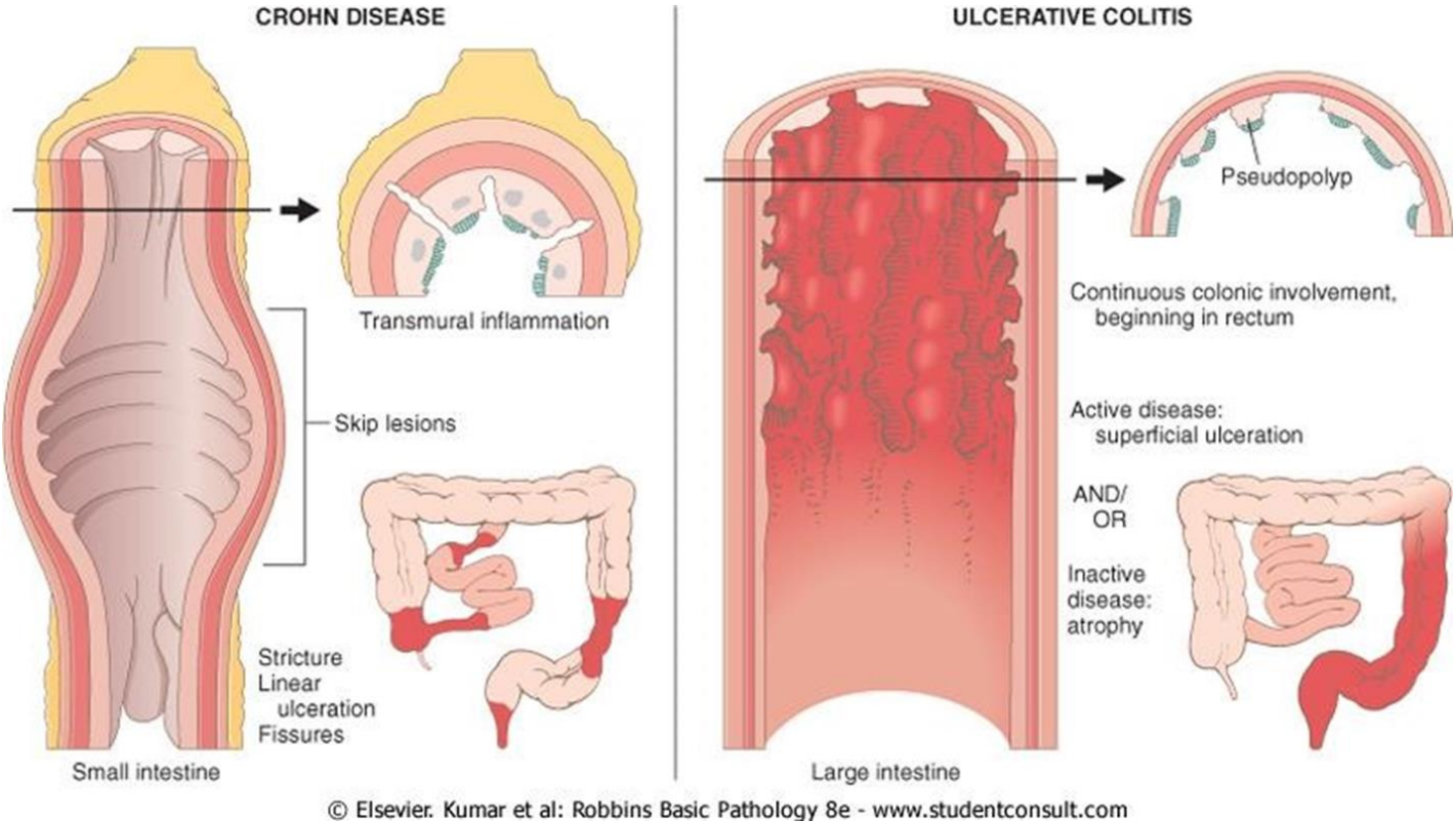




- There are several important differences between UC & CD the most important are:

  In UC:
  1)Superficial colonic mucosal ulcers, rarely extend below the submucosa
  & there is surprisingly little fibrosis, which means …
  Serosal surface is completely normal.
  2)No Mural thickening
  3)No granulomas,
  4)No skip lesions,
  5) there appears to be a High risk of carcinoma development in the colon.

Comparison of the distribution patterns of Crohn disease & ulcerative colitis, & the different conformations of the ulcers & wall thickenings.



►**GROSSLY**,

- UC usually involves:
  - the rectum
  - sigmoid
  - much less frequently involves the entire colon.

- Colonic involvement is continuous from the distal colon, so that skip lesions are not encountered.

- Active UC

  denotes ongoing inflammatory destruction of the mucosa, with gross hyperemia, edema, granularity with friability & easy bleeding,

- In severe UC

  there is extensive & broad-based ulceration of the mucosa in the distal, or the whole colon aligned along its long axis .

  Isolated islands of regenerating mucosa bulge upward to create pseudopolyps

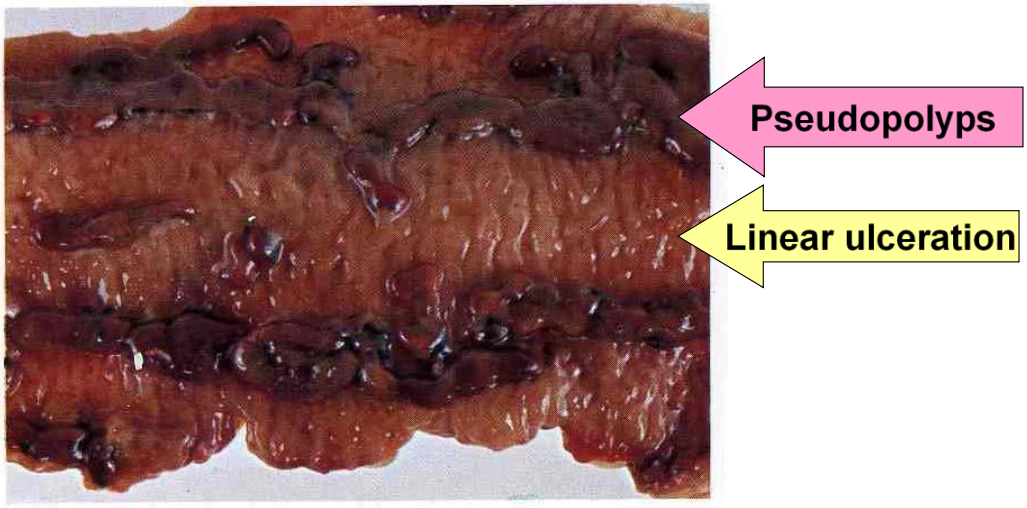
Ulcerative colitis.

Full-thickness linear ulceration followed by

undermining of adjacent intact mucosa

tend to cause the surviving mucosa to project into the lumen as pseudopolyps

("inflammatory polyps" "mucosal tags", which contrast with the pale areas denuded of mucosa).



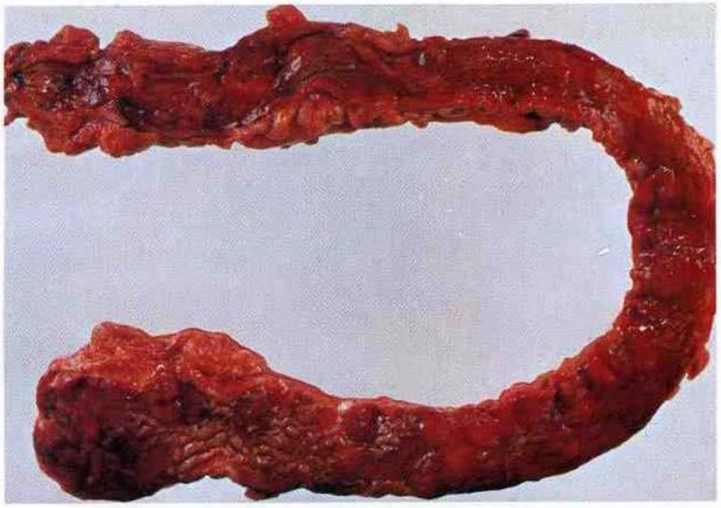
4.59 Ulcerative colitis

- In rare cases, the muscularis propria is so compromised as to permit perforation & pericolonic abscess formation.

- Exposure of the muscularis propria & neural plexus to fecal material also may lead to complete shutdown of neuromuscular function. When this occurs, the colon progressively swells & becomes gangrenous (toxic megacolon).

Ulcerative colitis (Pancolitis).

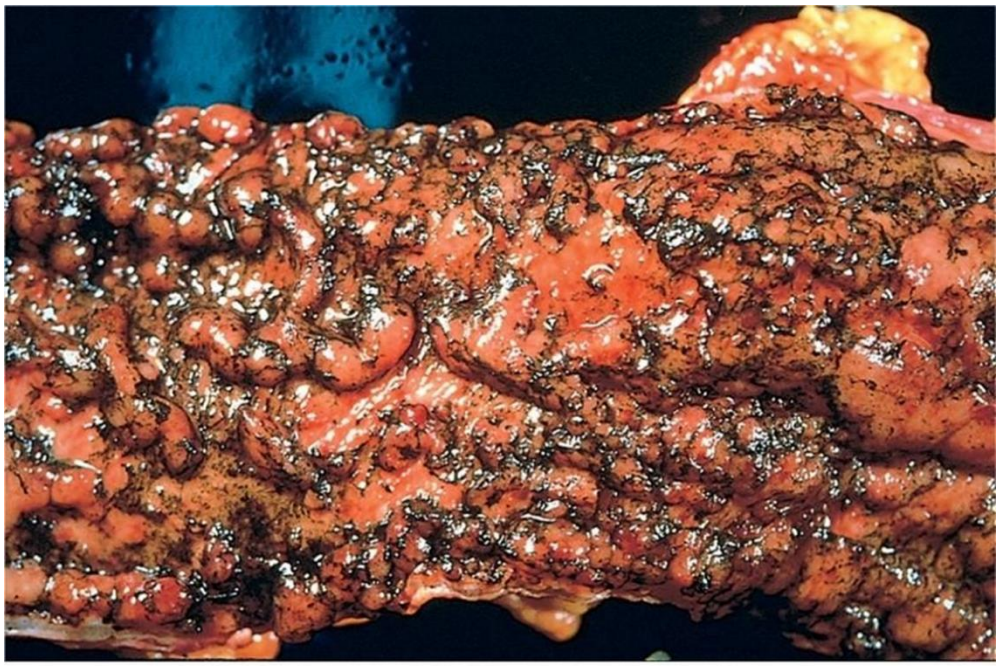
Total colectomy (colon + rectum) specimen showing granular, velvety plum-red (due to intense vascularity) & extensively ulcerated mucosa.



4.58 Ulcerative colitis

There is loss of the normal haustral colonic pattern due to muscular contraction; the length of the colon & rectum is reduced

: Ulcerative colitis.
The pale, irregular regions comprise ulcerations that have in many instances coalesced, leaving virtual islands of residual mucosa.
A tendency towards pseudopolyp formation is already evident.
The darker material is adherent mucus stained by feces.



- The pathologic features of UC are those of
  mucosal inflammation, ulceration, & chronic mucosal damage

- A diffuse, predominantly mononuclear inflammatory infiltrate in the lamina propria is almost universally present,

- Neutrophilic infiltration of the epithelial layer may produce collections of neutrophils in crypt lumina (crypt abscesses),

  which are not specific for UC & may be observed in CD or any active inflammatory colitis.

- Unlike CD, there are no granulomas

- Further destruction of the mucosa leads to outright ulceration, extending into the submucosa.

- With remission of active disease,

  granulation tissue fills in the ulcer craters, followed by regeneration of the mucosal epithelium.

  Submucosal fibrosis & mucosal architectural disarray & progressive mucosal atrophy leads to

  a flattened & attenuated mucosal surface, which remain as residua of healed disease

Ulcerative colitis.

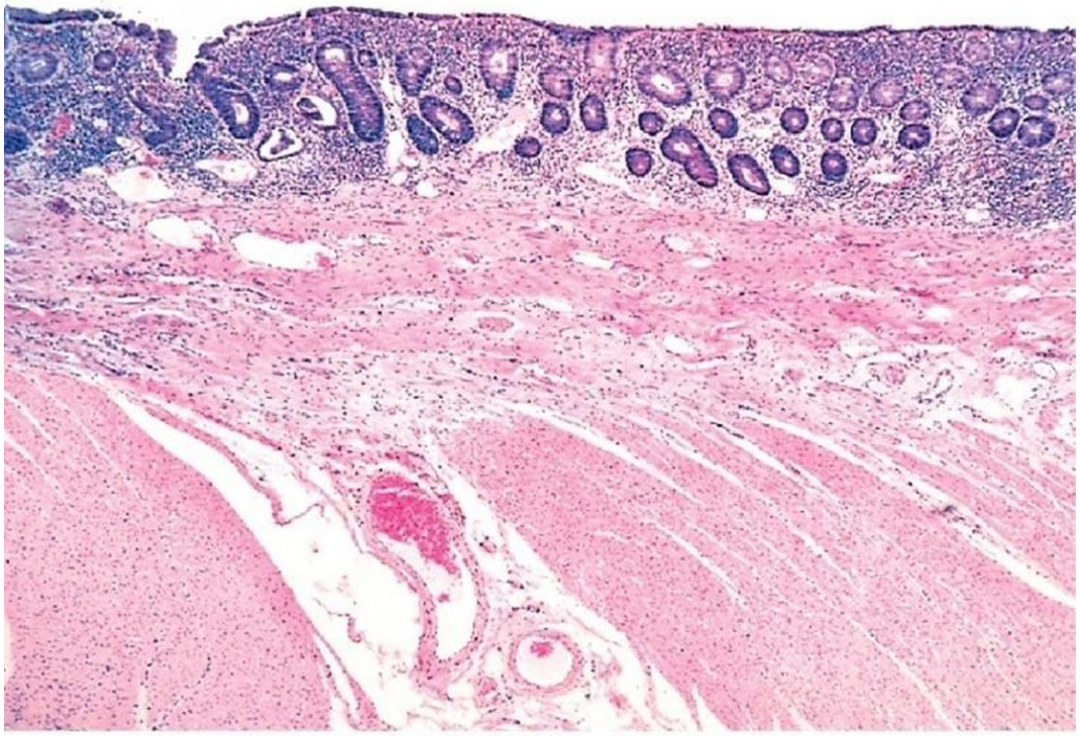
LP micrograph showing

-marked chronic inflammation of the mucosa

-with atrophy of colonic glands,

- moderate submucosal fibrosis,

- & a normal muscle wall



- The most serious complication of UC is
  the development of colon carcinoma.

- Two factors govern the risk:
  -duration of the disease
  -& its anatomic extent.

- It is believed that with 10 years of UC limited to the left colon the risk is minimal,
  & at 20 years the risk is on the order of 2%.

- With pancolitis, the risk of carcinoma is 10% at 20 years
  & 15% to 25% by 30 years.

- Overall, the annual incidence of colon cancer in persons with UC of more than 10 years' duration is 1%.

Clinical Features of UC

- UC is a chronic relapsing disease marked by attacks of bloody mucoid diarrhea that may persist for days, weeks, or months & then subside, only to recur later.

- Presentation is usually insidious, with cramps, tenesmus, & colicky lower abdominal pain that is relieved by defecation.

- Grossly bloody stools are more common with UC than with CD, & the blood loss may be considerable.

- Extra-intestinal manifestations, particularly migratory polyarthritis, are more common with UC than with CD.

- Uncommon but life-threatening complications include:
  -severe diarrhea & electrolyte derangements,
  -massive hemorrhage,
  -severe colonic dilation (toxic megacolon) with potential rupture,
  -perforation & peritonitis.

▼ **Diagnosis** can usually be made by endoscopic examination & biopsy.

- Specific infectious causes must always be ruled out.

Epidemiology

- UC is slightly more common (Double) than CD in the US & Western countries,
  with an incidence of around 7 per 100,000 populations,
  but it is infrequent in Asia & Africa.

- As with CD, the incidence of UC has risen in recent decades.

- In the US it is more common among whites than among nonwhites
- exhibits no particular sex predilection.

- UC may arise at any age
  with a peak incidence between ages 20 & 25 years.

- UC has a familial association;
  20% of persons with the UC have affected relatives.

- Individuals with UC & ankylosing spondylitis have an increased frequency of the HLA-B27 allele,
  but this association is related to the spondylitis & not to UC.

TUMORS OF THE SMALL AND LARGE INTESTINES

- Colorectal cancer is:
  the 1st commonest cancer in Jordanian males & the 2nd in females since 2004.

- In the US, it ranks 2nd to bronchogenic ca among the cancer killers;
  & about 5% of Americans will develop colorectal cancer
  & 40% of them will die from it
  & it represent 70% of all GIT malignancies.

Tumors of the Small & Large Intestines

- **Non-neoplastic Polyps**

Hyperplastic + Hamartomatous {Juvenile} + Peutz-Jeghers + Inflammatory + & Lymphoid polyps.

- **Neoplastic Epithelial Lesions**
  Benign polyps:
  Adenomas

  Malignant polyps:

  Adenocarcinoma (98%) & SCC of the anus

- **Other Tumors**

- Gastrointestinal stromal tumors (GIST),

- Carcinoid tumor

- Lymphoma.

- Several concepts pertaining to terminology must be emphasized:

  NB. Some polypoid lesions may be caused by submucosal or mural tumors.

  However, as with the stomach, the term polyp:

► In the GIT,

-polyp (P) refers to protruding mass arising from the mucosal epithelium.

-P may be sessile, i.e., without a stalk,

-But traction on the mass may create a stalked, so it is pedunculated

-P may be formed as the result of abnormal mucosal inflammation, maturation, or architecture.

- These P are non- neoplastic & do not have malignant potential.

-P that arise as result of epithelial proliferation & dysplasia are termed adenomatous P or adenomas

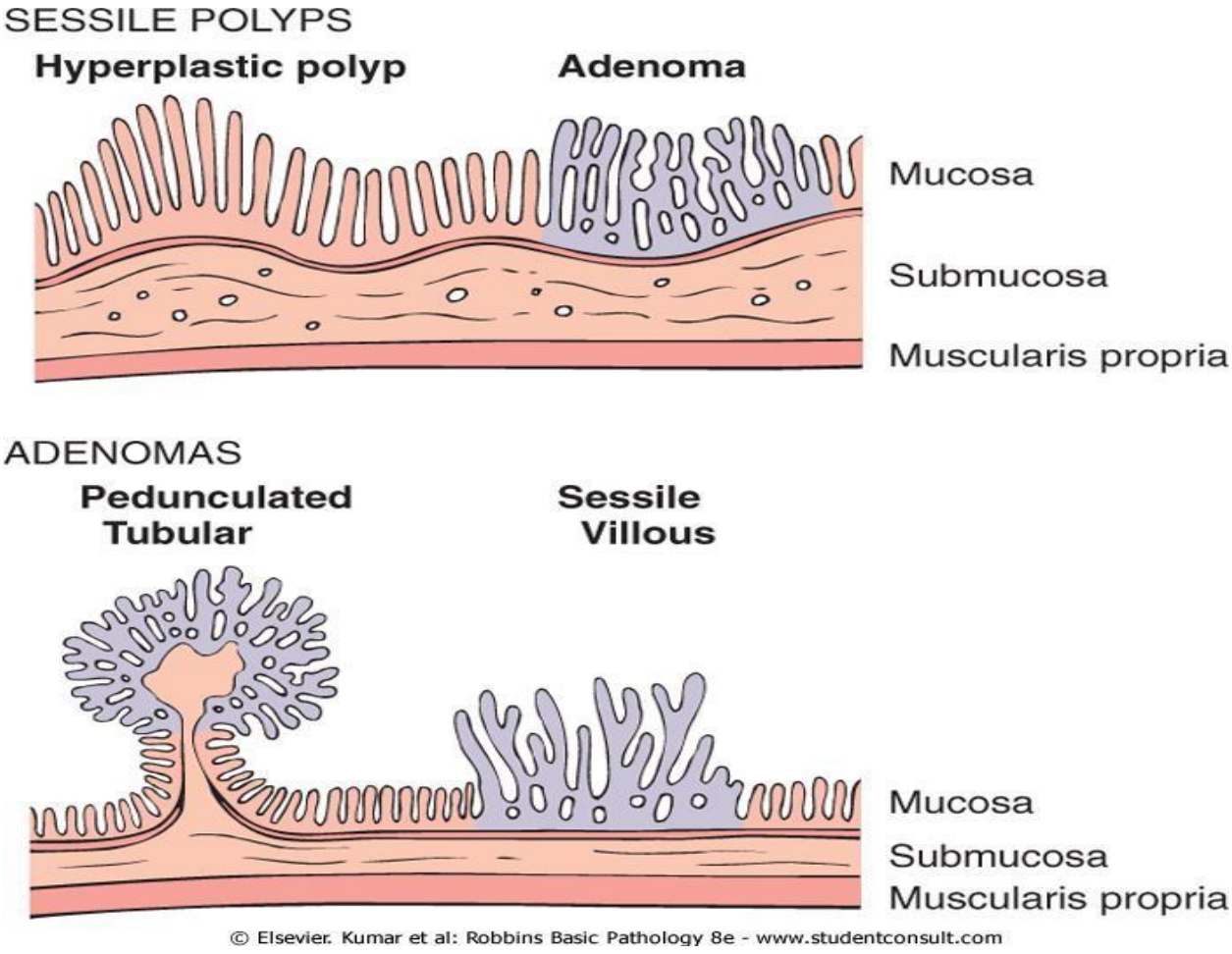
-they are true neoplastic lesions

-they are precursors of carcinoma.

-Hyperplastic P are the most common polyps of the colon & rectum.

-When single, they do not have malignant potential.

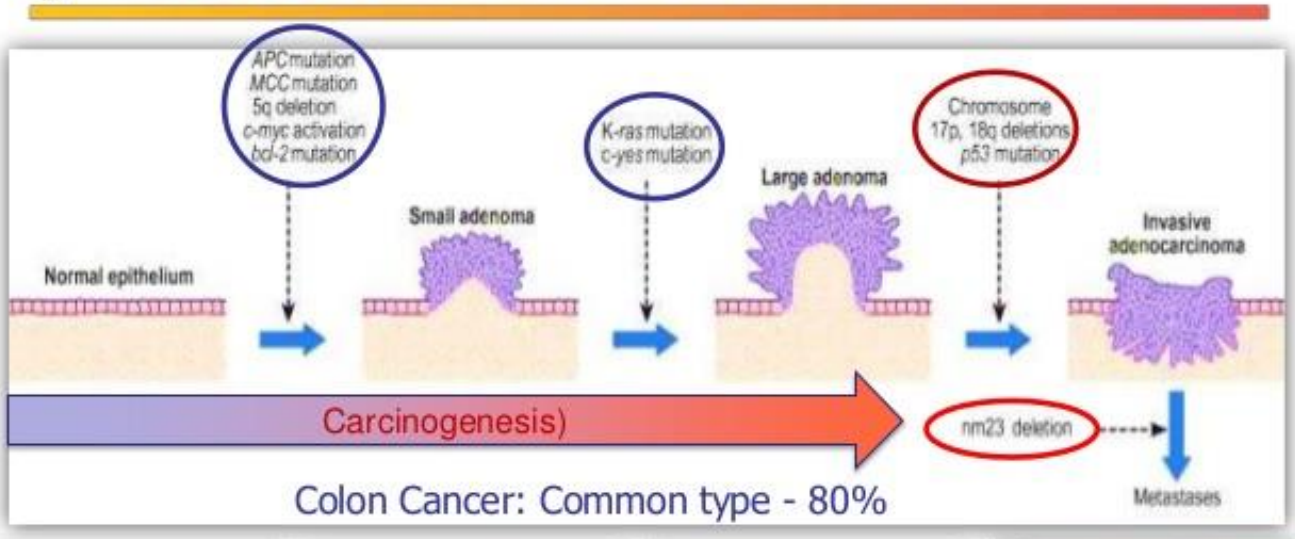
-However, sessile serrated adenoma lesion, which has some similarities with hyperplastic P, may have malignant potential.

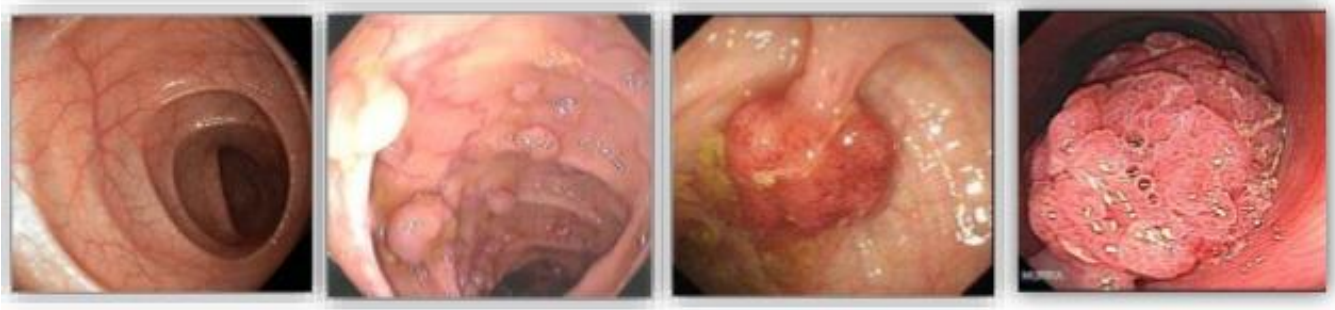


Two forms of sessile polyp (hyperplastic & adenoma)

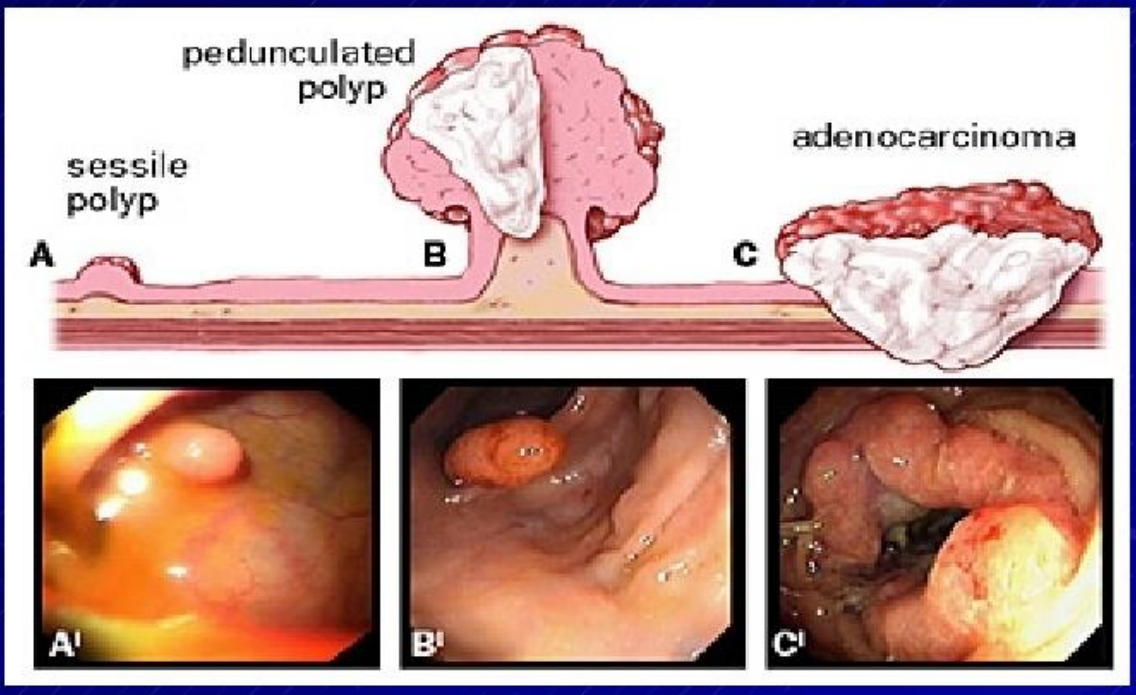
& of two types of adenoma (pedunculated & sessile).

Colon: Normal → Adenoma → Carcinoma





Endoscopic appearance



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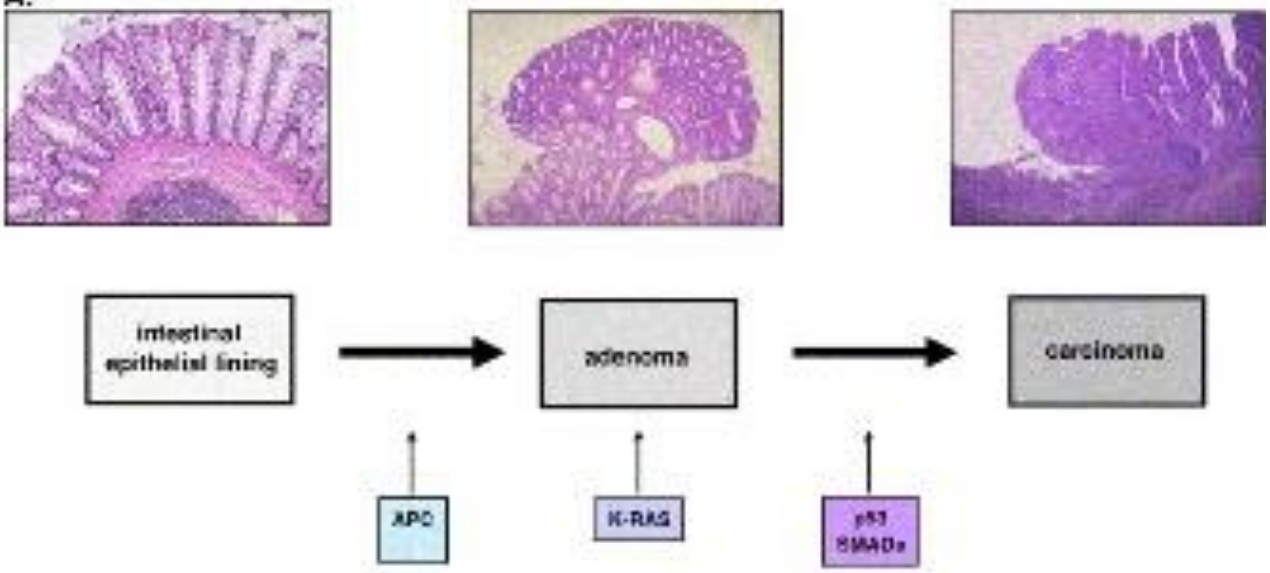
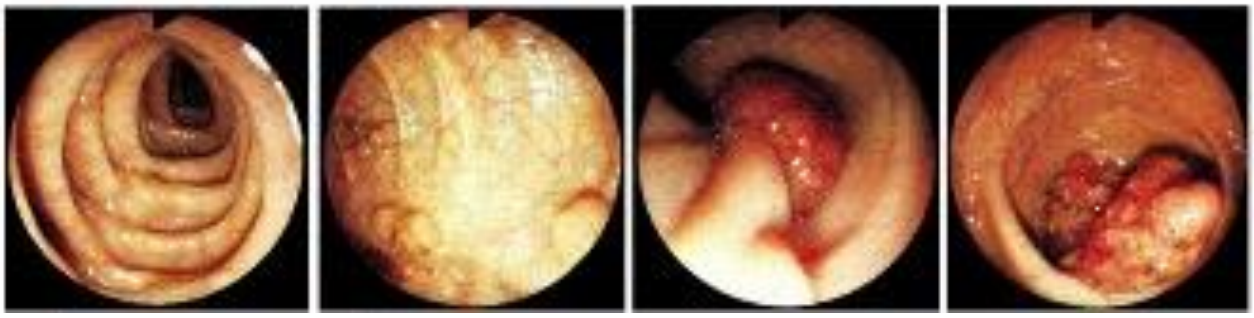

intestinal epithelial lining
adenoma
carcinoma
APC
K-RAS
p53
SMAD4



Non-Neoplastic Polyps

-Majority of intestinal P occurs sporadically, particularly in the colon, &increase in frequency with age.

-Non-neoplastic P represent about 90% of all epithelial P in the large intestine

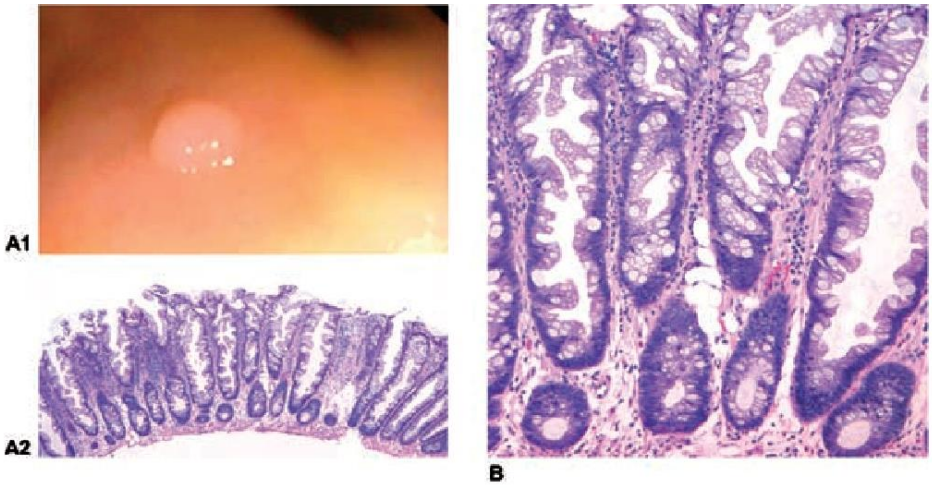
- are found in more than 50% of persons older than 60y.

Hyperplastic polyps

- Are the commonest non-neoplastic P of the colon & rectum.
- Are small (<5 mm in□),
  -nipple-like,
  - hemispherical,
  -smooth protrusions of the mucosa,
- 50% found in the rectosigmoid area.
- May occur singly, but are more often multiple.

Histology

- they contain abundant crypts lined by well-differentiated goblet or absorptive epithelial cells,
  separated by a scant lamina propria.



- Vast majority of hyperplastic polyps have no malignant potential.
- BUT some, either solitary or multiple ("hyperplastic polyposis") so-called sessile serrated adenomas, which are located on the right side of the colon, may be precursors of colorectal ca.
- These P show microsatellite instability & can give rise to ca by the mismatch repair pathway.

Juvenile (Rectal) polyps

- Are essentially hamartomatous proliferations of the lamina propria, enclosing widely spaced, dilated cystic glands.

• Occur mostly in children younger than 5 years old, but also may be in found in adults of any age.

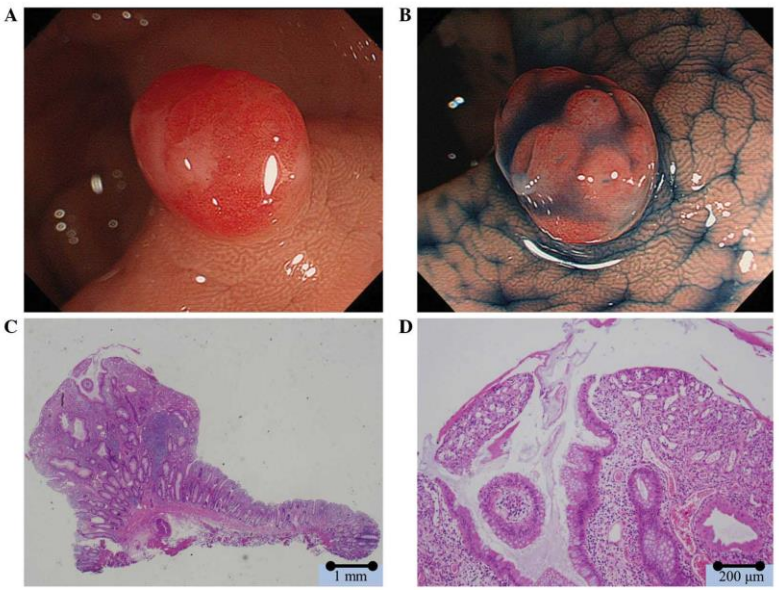
• Occur singly, in the rectum, 1-3 cm in ?;

rounded, smooth, or slightly lobulated & sometimes pedunculated.

• May cause rectal bleeding &

• May become twisted on their stalks (torsion) to undergo painful infarction.

• Because they are hamartomatous, they have no malignant potential.



Adenomas

- Adenomas are neoplastic P that range from small pedunculated to large sessile tumors.
- Prevalence of colonic adenomas

  is 20% -30% before age 40,

  rising to 50% after age 60.

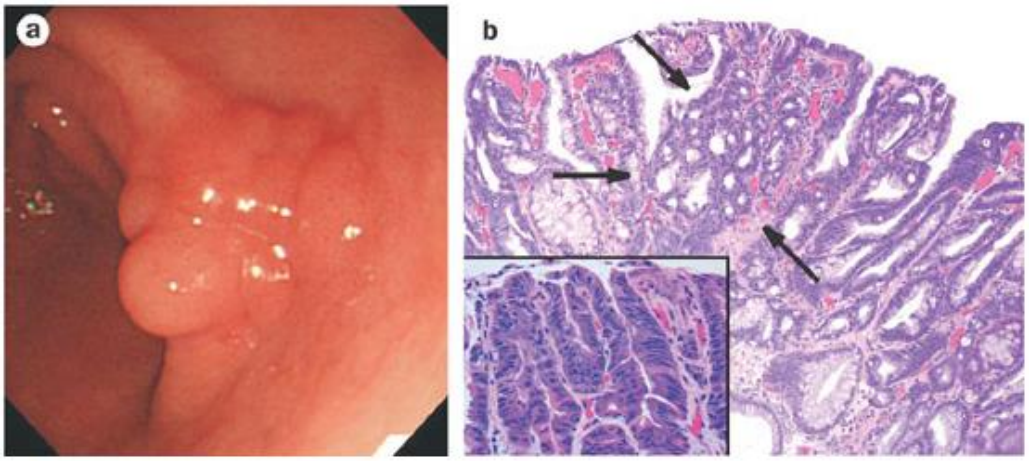
- M/F ratio is 1:1
- All adenomatous lesions arise as a result of epithelial proliferation & dysplasia,
  which may range from mild to so severe as to represent transformation to carcinoma.

▼There is a well-defined familial predisposition to sporadic adenomas,

accounting for about a X4 fold greater risk for adenomas among first-degree relatives,

& also a X4 fold greater risk of colorectal ca in any person with adenomas.

- There is strong evidence that most sporadic invasive colorectal adenocarcinomas arise in preexisting adenomatous lesions.



- The 4 subtypes of adenomatous P base on their epithelial architecture are:

►Tubular adenomas, 90%;

-mostly small & pedunculated; showing tubular glands, recapitulating mucosal topology,

►Villous adenomas,1%

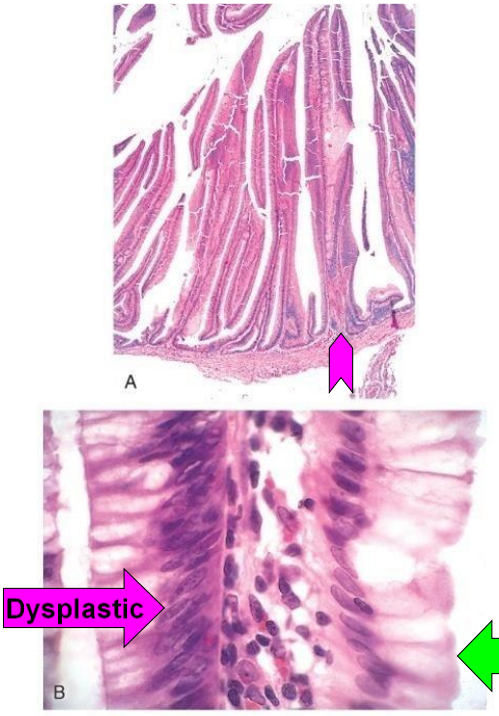
- villous projections, tend to be large & sessile

►Tubulovillous adenomas, 5% -10%

- a mixture of the above,

►Sessile serrated adenomas

- serrated epithelium lining the crypts.



F15-37: **A**, **Sessile villous adenoma,** with villous (finger-like) architecture. Each frond is lined by dysplastic epithelium.

B, Portion of a villous frond with **dysplastic** columnar epithelium on the **left** & **normal** colonic columnar epithelium on the **right.**

- The malignant risk with an adenomatous P is correlated with

3 interdependent features

- polyp size,

- histologic architecture,

- severity of epithelial dysplasia

as follows:

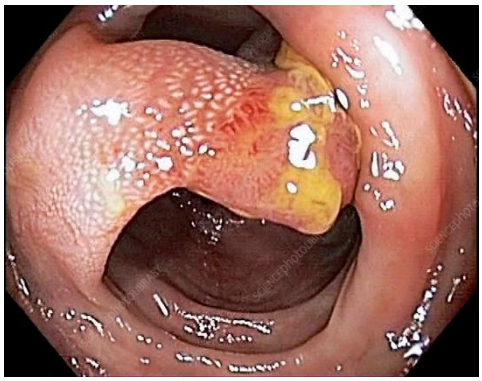
- Cancer is rare in tubular adenomas smaller than 1 cm in .

- Cancer risk is high (approaching 40%) in sessile villous adenomas larger than 4 cm in.

- Severe dysplasia, is often found in villous areas.

- Among these variables, maximum diameter (F4-67) is the chief determinant of the risk of an adenoma's harboring ca.

Tubular adenomas



- May arise anywhere in the colon, however,

  50% are found in the rectosigmoid area.

- 50% of tubular adenomas are single,
  in the other 50%, two or more are present.

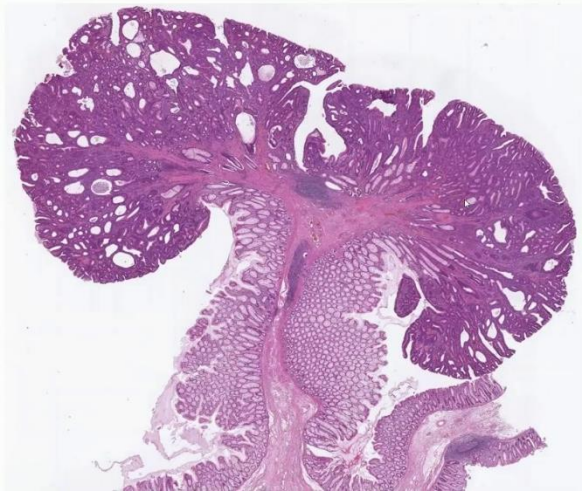
Small tubular adenomas are sessile,

while Larger ones are pedunculated; having stalk & with raspberry-like heads.

Histology,

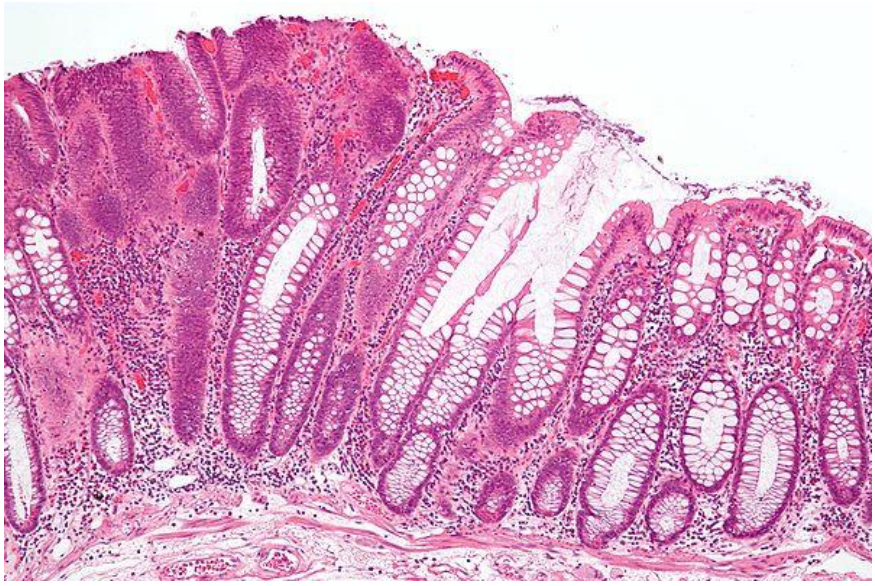
- the stalk of tubular adenomas is covered by normal colonic mucosa, but the head is composed of neoplastic epithelium, forming branching glands lined by hyperchromatic, tall cells, which may/may not show mucin secretion (F15-36B).

- In the clearly benign lesion, the branching glands are well separated by lamina propria, & the level of dysplasia or cytologic atypia is slight.



- However, all degrees of dysplasia may be encountered, ranging up to cancer confined to the mucosa (intramucosal carcinoma) or invasive carcinoma extending into the submucosa of the stalk.

- A frequent finding in any adenoma is superficial erosion of the epithelium, the result of mechanical trauma.



►**Clinically,**

the smaller adenomas are usually asymptomatic, until such time that occult bleeding (much more frequently from villous adenomas) leads to clinically significant anemia

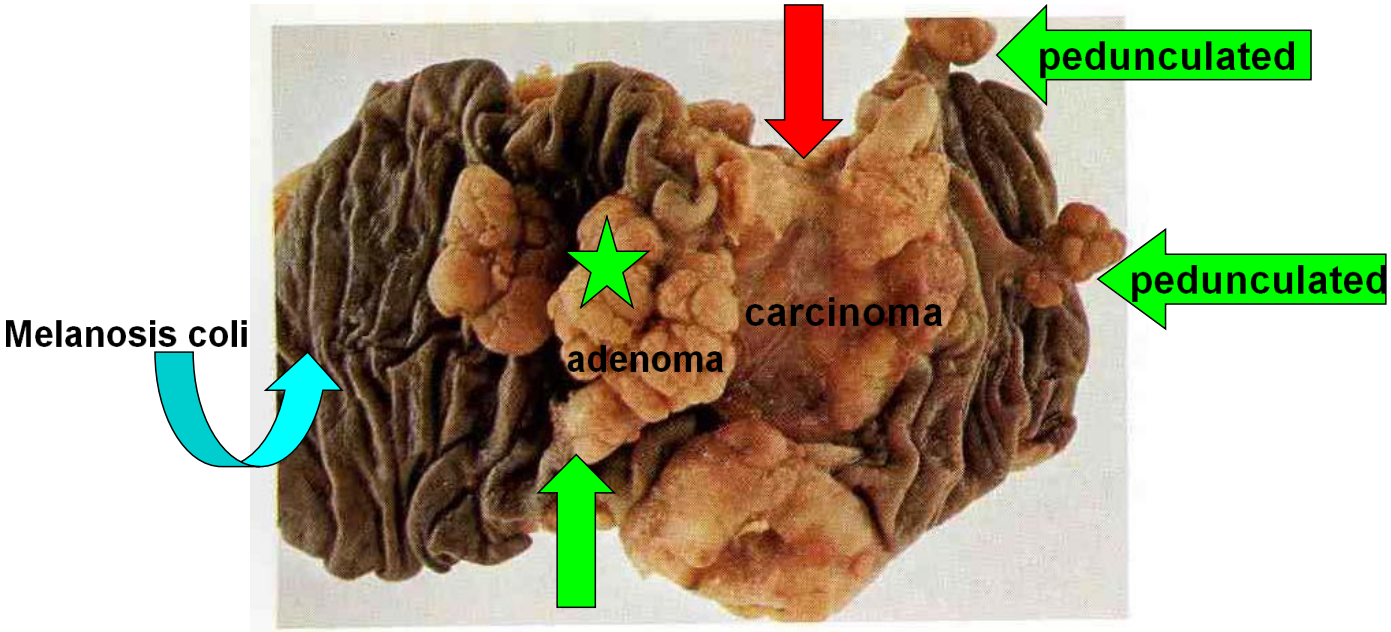
Papillary (Tubular) adenoma & carcinoma: colon.

Note

(1) Complete circumferential ulcerating ca is present (right centre) in direct continuity with large sessile adenoma to its left,

(2) there are two small pedunculated polypoidal adenomas (right & above right).

NB. The dark color of the colonic mucosa is due to melanosis coli.



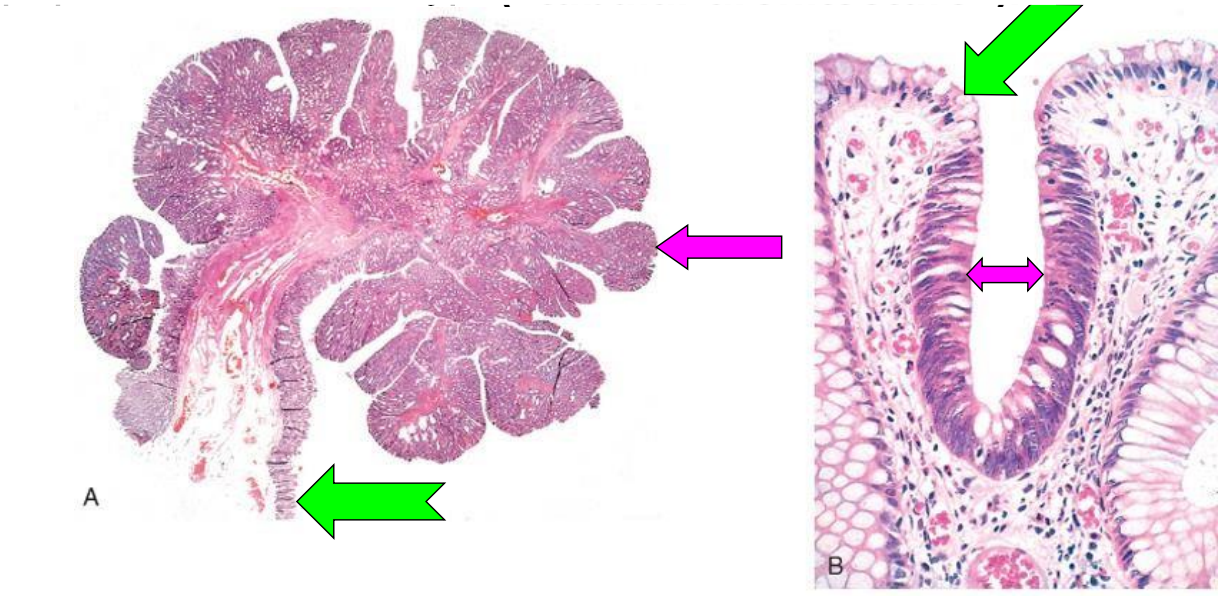
4.67 Carcinoma and papillary adenoma: colon

A, Pedunculated adenoma showing a fibrovascular stalk covered by normal colonic mucosa

& a head contains abundant dysplastic epithelial glands-hence the blue color.

B, A small focus of adenomatous epithelium in an otherwise normal (mucin-secreting, clear) colonic mucosa,

showing how the dysplastic columnar epithelium (stained deeply blue) can populate a colonic crypt ("tubular architecture").



Villous adenomas (1%)

- are larger, tend to occur in older persons,
- most commonly in the rectum & rectosigmoid, but they may be located elsewhere,
- are sessile, up to 10 cm in □, cauliflower-like masses projecting above the surrounding mucosa (F4.66).

: Villous adenoma: rectum. Large (10 cm in □), sessile projecting tumor, with shaggy surface made up of numerous thin finger-like processes.

Q: what are the effects & complications of this adenoma?

4.66 Villous papilloma: rectum

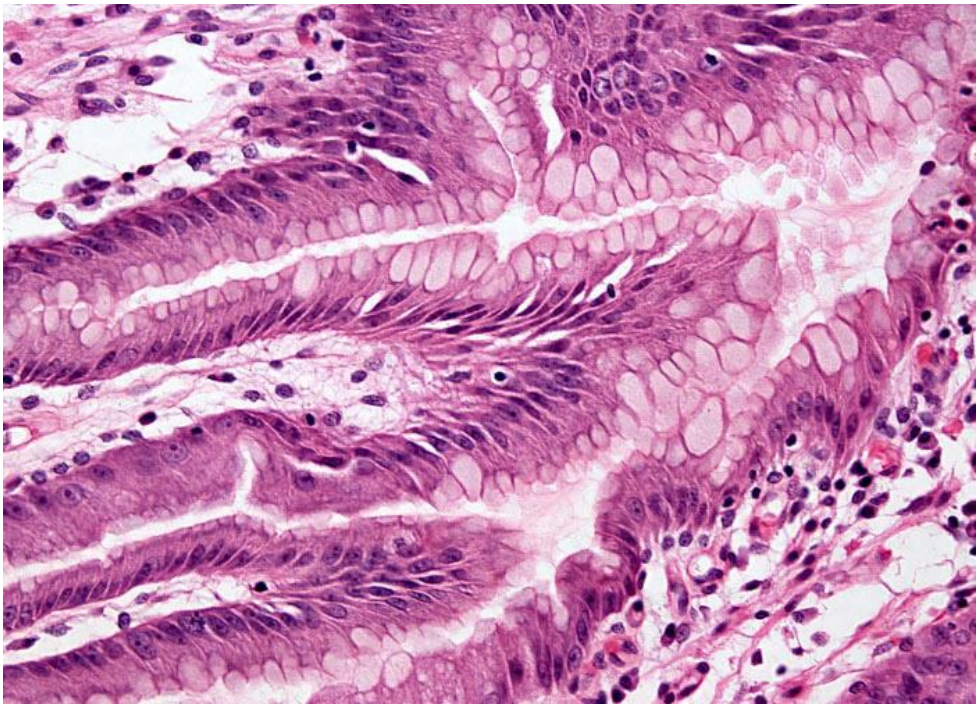
Histology

- there is frond-like (finger-like) villiform projections of the mucosa covered by dysplastic, piled-up, columnar epithelium

- . All degrees of dysplasia may be encountered,

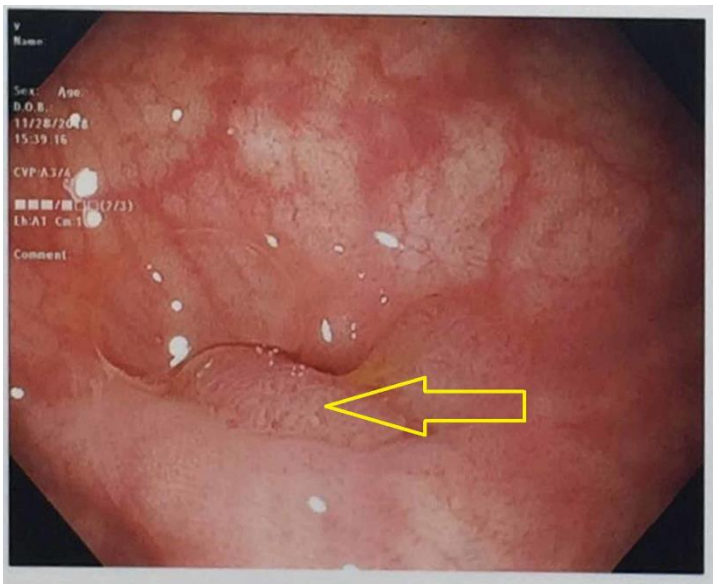
- invasive carcinoma is found in as many as 40% of these lesions, the frequency being correlated with the size of the P.

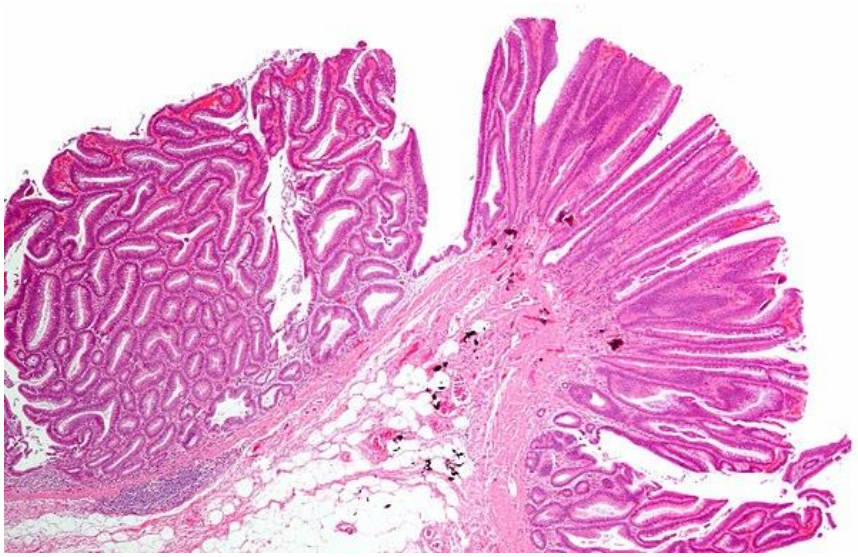
- Villous adenomas may secrete sufficient amounts of mucoid material rich in protein & potassium to produce hypoproteinemia or hypokalemia.



Tubulovillous adenomas (5-10%)

- are composed of mix tubular & villous areas
- . They are intermediate between the tubular & the villous lesions in their frequency of, been pedunculated or sessile, their size, the degree of dysplasia, & the risk of harboring intramucosal or invasive carcinoma.

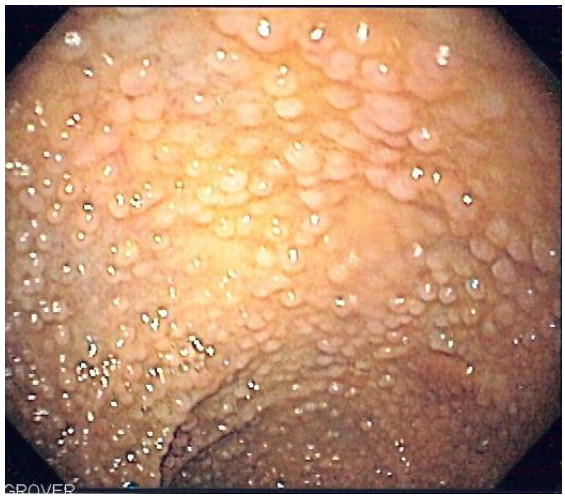




- All adenomas, are to be considered potentially malignant; therefore, prompt & adequate excision is mandated.

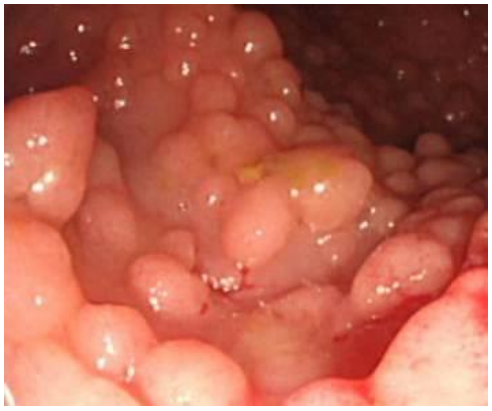
Familial Polyposis Syndromes

The importance of this uncommon, autosomal dominant disorders, called familial polyposis syndromes, lies in the propensity (tendency) for malignant transformation.



▼ Familial adenomatous polyposis (FAP)

- individuals typically develop 500 to 2500 {a minimum of 100 is required for the diagnosis} colonic adenomas that carpet the mucosal surface (F15-38);



- Multiple adenomas may also be present elsewhere in the GIT, including almost a 100% lifetime incidence of duodenal adenomas.

- Most polyps are tubular adenomas;
- an occasional P have villous features.

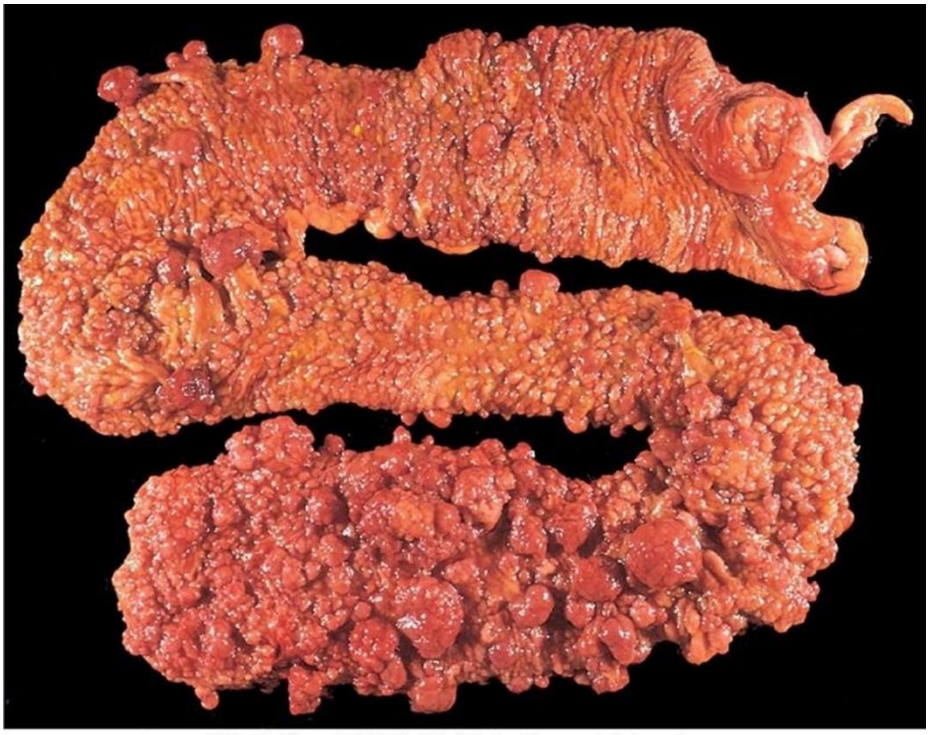
- Polyps usually become evident in adolescence or early adulthood.

- The risk of colonic cancer is virtually 100% by midlife, unless a prophylactic colectomy is performed.

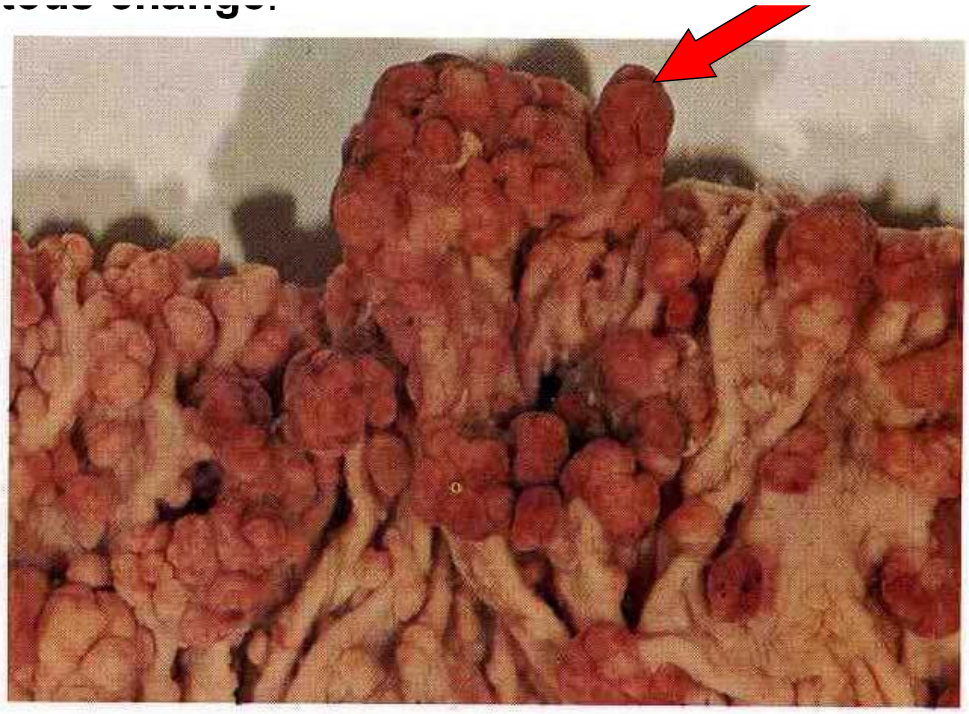
► The genetic defect underlying FAP has been localized to the APC gene on chromosome 5q21.

- Gardner syndrome & the much rarer Turcot syndrome share the same genetic defect as FAP.
- These syndromes differ from FAP with respect to the occurrence of extraintestinal tumors in the latter two: osteomas, gliomas, & soft tissue tumors, to name a few.

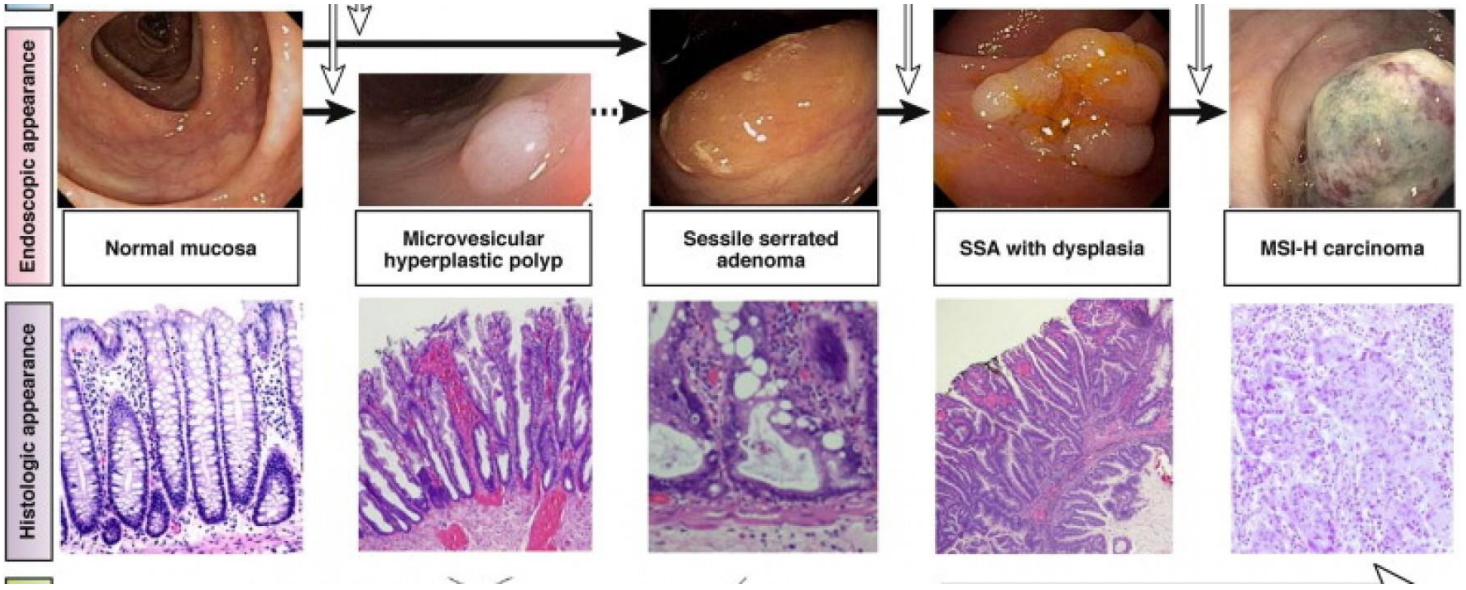
Familial adenomatous polyposis. The surface is carpeted by innumerable (thousands) polypoid adenomas



Familial Adenomatous Polyposis: Colon. The colonic mucosa is covered with large number of polypoid adenomas. The large pedunculated polyp (top center, arrow) has undergone carcinomatous change.

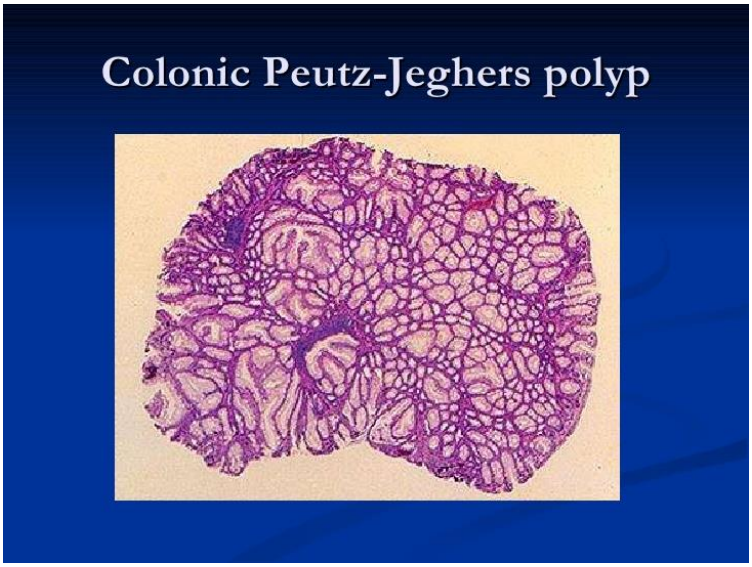


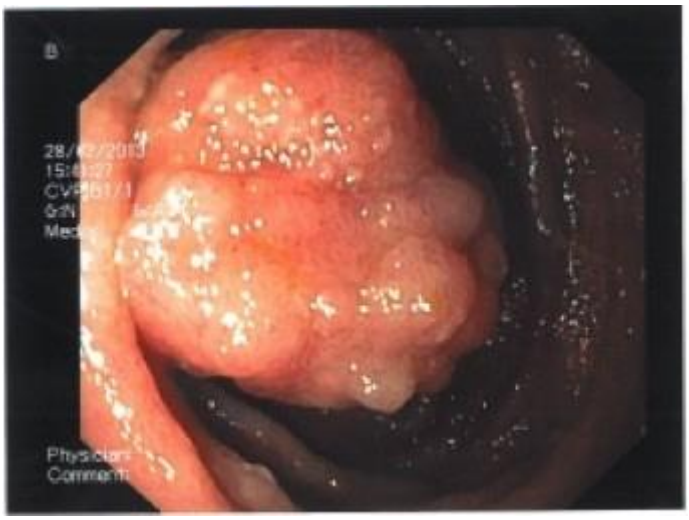
4.64 Familial adenomatous polyposis: colon

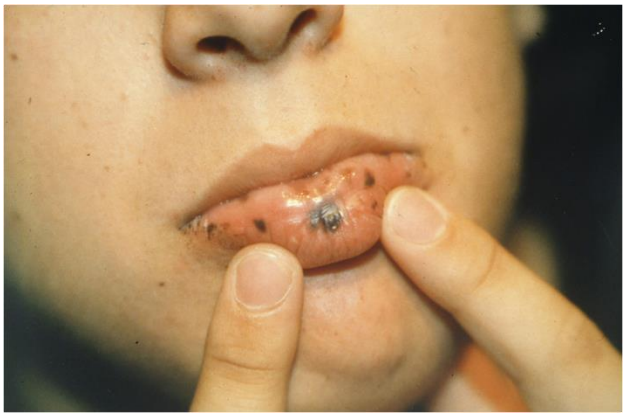


▼Peutz-Jeghers polyps

- are uncommon hamartomatous polyps that occur as part of the rare autosomal dominant PeutzJeghers syndrome,
- characterized in addition by melanotic mucosal & cutaneous pigmentation.
- (This syndrome is caused by germ-line mutations in the LKB1 gene, which encodes a serine threonine kinase).







▼ Cowden syndrome

- is also characterized by hamartomatous polyps in the GIT & by an increased risk of tumors of the thyroid, breast, uterus, & skin.

- This syndrome is caused by germ-line mutations in the PTEN (phosphatase & tensin homologue) tumor suppressor gene.

  - Peutz-Jeghers & Cowden syndromes, like the other familial polyposis syndromes, are associated with an increased risk of both intestinal & extraintestinal malignancies.

Colorectal Carcinoma (Ca)

- Colorectal cancer is the 1st commonest cancer in Jordanian males & the 2nd in females since 2004.

- Adenocarcinomas comprise 98% of all colonic cancers (2% SCCa anal channal).

▼ It represent prime challenges to the medical profession, because they almost always arise in adenomatous polyps that are generally curable by resection .

Morphology of colorectal ca:

• Site:

25% @ cecum & ascending colon,

25% @ descending colon & proximal sigmoid;

25% @ distal sigmoid & rectum.

25% @ remainder are scattered elsewhere

•Most often ca occur singly & have frequently obliterated their adenomatous origins.

When multiple carcinomas are present, they are often at widely separated from each other.

Grossly,

•ca in the proximal {cecum & ascending colon} tend to grow as polypoid, exophytic masses (F15-41). Obstruction is uncommon.

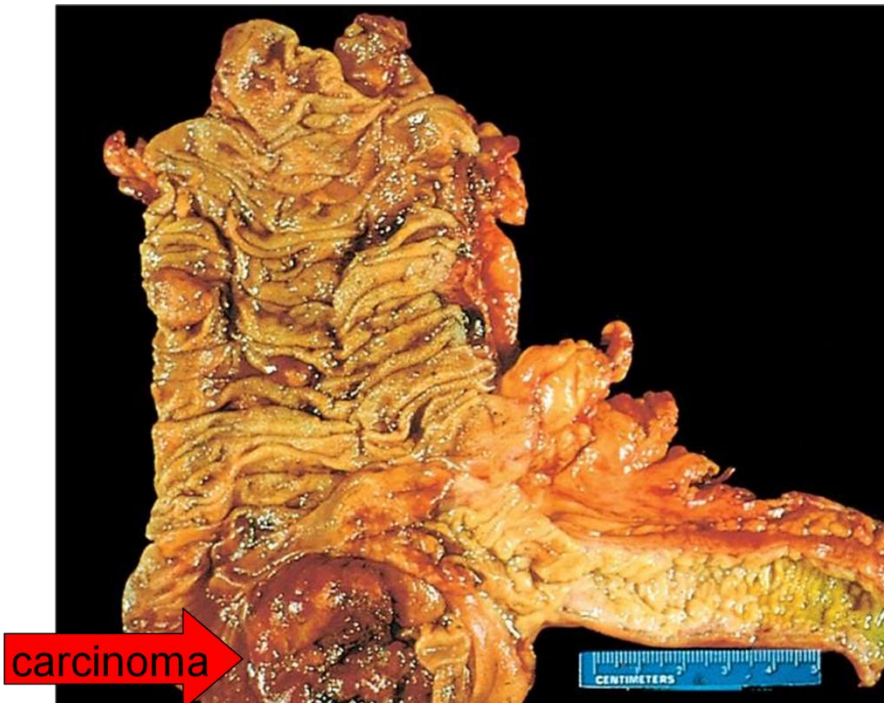
•Distal colon ca tend to be annular stenosing , encircling lesions that produce so-called napkin-ring constrictions of the bowel & narrowing of the lumen ; the margins of the ulcerating napkin ring are classically heaped up.

Some ca are ulcerative

•With time, all colorectal carcinomas directly penetrate bowel wall & appearing as firm masses on the serosa.

Carcinoma of the cecum.

The exophytic carcinoma projects into the lumen but has not cause obstruction

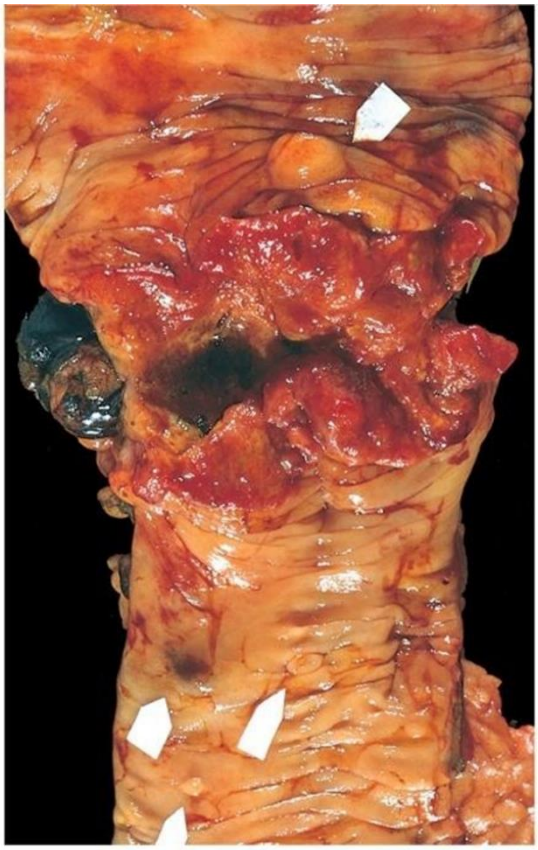


Annular stenosing carcinoma: colon.

A slowly growing, ulcerating T which spread circumferentially. around the wall.

The considerable fibrous tissue stroma of the T {visible on the cut surface of the T & adjacent serosa (arrows)} subsequently contract, narrows & constricts the lumen.

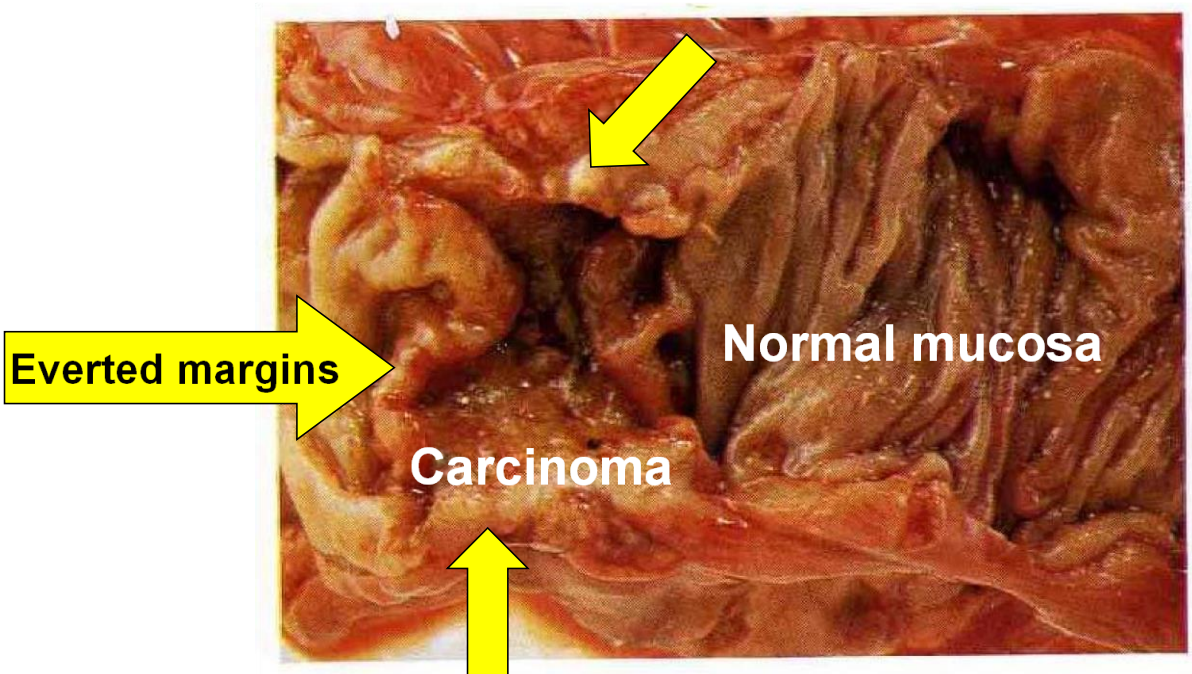
T margins are everted & its base is necrotic



Carcinoma of the descending colon

This circumferential tumor has heaped-up edges & an ulcerated central portion.

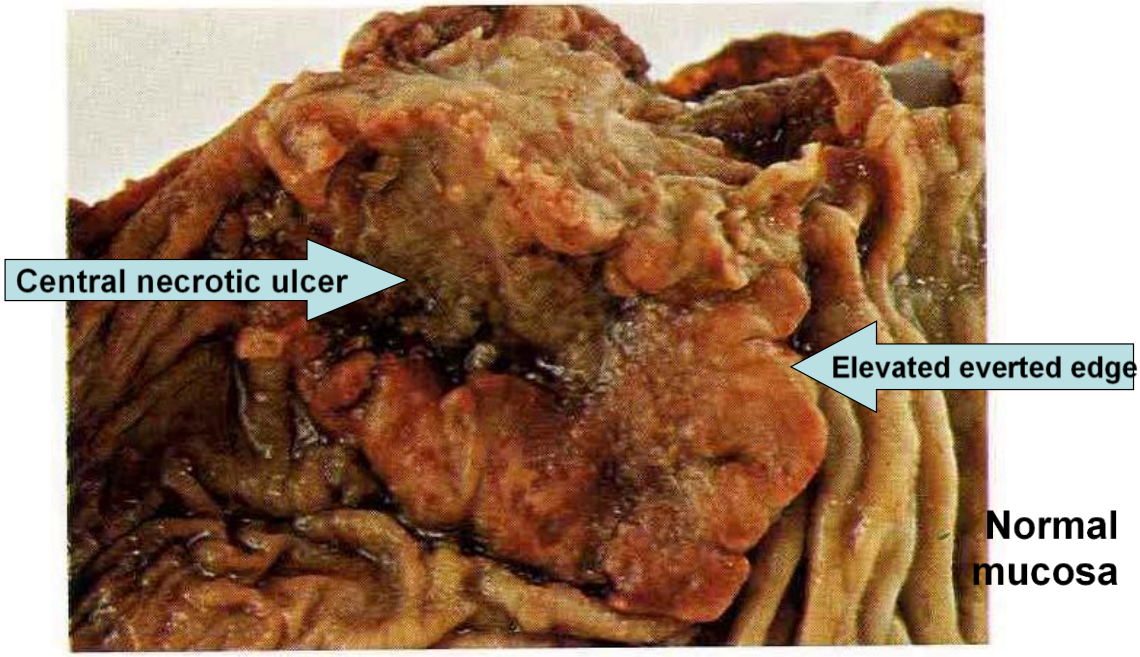
The arrows identify separate mucosal polyps



4.71 Carcinoma: colon

Carcinoma: rectum.

Large, flat, slightly raised tumor with central ulcer, showing elevated & everted edge

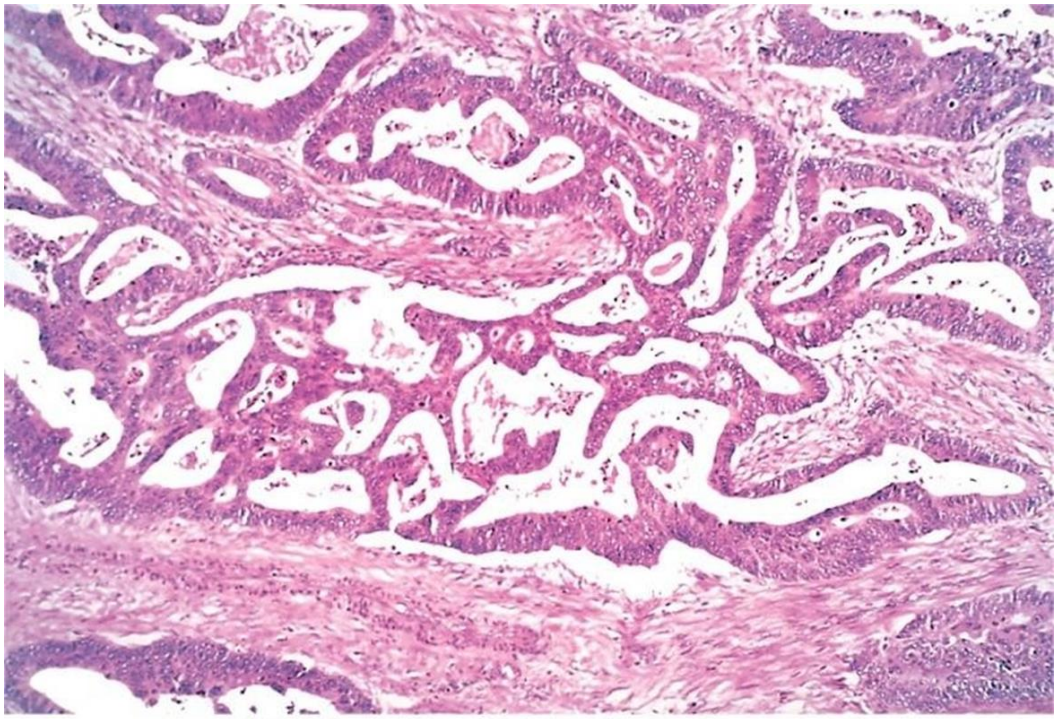


4.72 Carcinoma: rectum

Histology,

- all are adenocarcinomas, range from well-differentiated (F15-43) to undifferentiated, frankly anaplastic masses.
- Many tumors produce mucin, which is secreted into the gland lumina; or into the interstitium of the gut wall where it dissect through it, facilitating the extension of cancer & worsen the prognosis.
- Cancers of the anal zone are predominantly SCCa.

Invasive adenocarcinoma of colon, with infiltration of the muscular wall by malignant glands



►**Clinically**,

- colorectal ca remain asymptomatic for years; symptoms develop insidiously & late.

- Cecal & right colonic ca most often present with fatigue, weakness, & iron deficiency anemia.

- Left-sided ca may produce occult bleeding, changes in bowel habit, or crampy left lower quadrant discomfort

® Rule: Although anemia in females may arise from gynecologic causes, the rule is: iron deficiency anemia in an older man means GIT cancer until proved otherwise

- All colorectal carcinomas invade & spread directly into adjacent structures & by metastasis through the lymphatics & BV.

- In order of preference, the favored sites for metastasis are
  -the regional LN
  -liver
  -lungs,
  -&bones.

- Generally, the ca spreads beyond curative surgery in 25% to 30% of patients.
  The challenge is to discover the neoplasm when curative resection is possible.

- Ca of the anal region are locally invasive & metastasize to regional LN & distant sites.
- Almost 80% of cancers of the anal canal are SCCa.

Diagnosis of colorectal T rely on:

digital per-rectal (PR) examination

+ fecal testing for occult blood loss

+ endoscope

+ confirmatory biopsy for diagnosis,

& Barium enema

- CT & other X-ray studies are used to assess metastatic spread.

- Serum markers for T, such as elevated blood levels of CEA, are of little diagnostic value, because they reach significant levels only after the cancer has achieved advanced stage.

- Because APC mutations occur early in most colon cancers, molecular detection of APC mutations in epithelial cells, isolated from stools, is being evaluated as a diagnostic test (400$).

- The single most important prognostic indicator of colorectal ca is the tumor stage (TNM) at the time of diagnosis

Pathogenesis

- It is now believed that there are two pathogenetically distinct pathways for the development of colon cancer,

(A) APC/β-catenin pathway (or adenoma-carcinoma sequence), &

(B) Mismatch repair (or microsatellite instability) pathway.

- Both of these pathways involve the stepwise accumulation of multiple mutations,

but the genes involved & the mechanisms by which the mutations accumulate are different.

►(A) The first pathway, variously called the adenomacarcinoma sequence, the APC/β-catenin pathway, or the chromosome instability pathway,

- is characterized by :

chromosomal instability associated with stepwise accumulation of mutations in a number of oncogenes & tumor suppressor genes.

- The molecular evolution of colon cancer along this pathway occurs through a series of morphologically identifiable stages (F15-39

- Initially, there is localized epithelial proliferation,

followed by formation of small adenomas,

progressively enlarge & to be more dysplastic,

& ultimately develop invasive ca.

- Such adenoma-carcinoma sequence, accounts for about 80% of sporadic colon tumors.

- The genetic correlates of this pathway are as follows:

(I) Loss of the APC tumor suppressor gene, present in 60% to 80% of sporadic colonic ca.

This is believed to be the earliest event in the formation of adenomas.

Recall that in the FAP & Gardner syndromes, germ-line mutations in the APC gene give rise to hundreds of adenomas that progress to form ca.

(II) Mutation of K-RAS.

Seen in 10% of adenomas less than 1 cm,

in 50% of adenomas larger than 1 cm,

& in 50% of ca.

(III) 18q21 deletion.

Loss of a putative cancer suppressor gene on 18q21 has been found in 60% to 70% of colon cancers.

Three genes have been mapped to this chromosome location:

DCC (deleted in colon carcinoma), SMAD2, & SMAD4

(IV) Loss of p53.

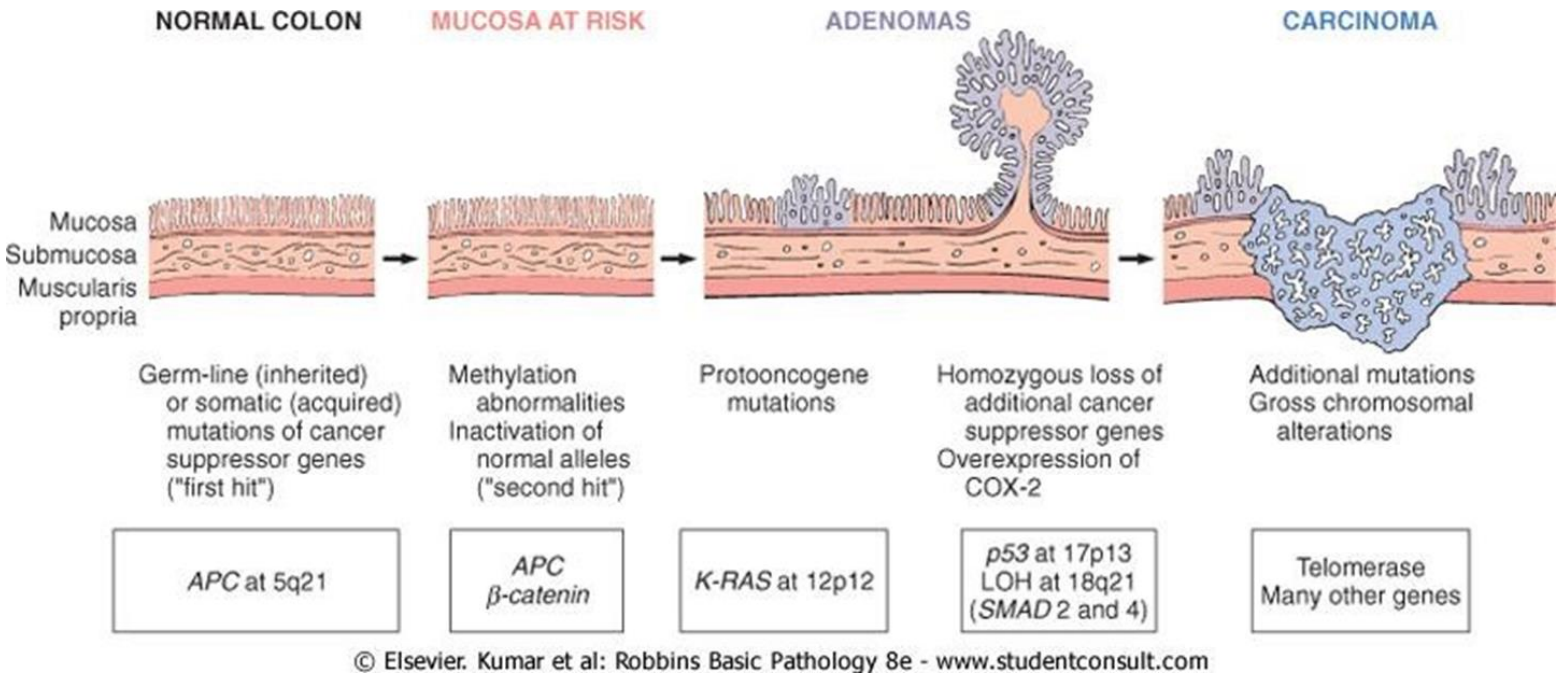
Loss of this tumor suppressor gene is noted in 70% to 80% of colon cancers,

yet similar losses are infrequent in adenomas,

suggesting that mutations in p53 occur late in colorectal carcinogenesis.

(V) Alterations in the methylation level of tumor suppressor genes

occur in the development of colorectal tumors in the adenoma-carcinoma pathway.



► (B) The second pathway of colorectal carcinogenesis is characterized by genetic lesions in DNA mismatch repair genes .

- It is involved in 10% to 15% of sporadic cases.

As in the APC/β-catenin schema, there is accumulation of mutations, but the involved genes are different.

- There may be no detectable antecedent lesions, or the tumors may develop from sessile serrated adenomas.

- Defective DNA repair caused by inactivation of DNA mismatch repair genes is the fundamental & the most likely initiating event in colorectal cancers that follow this path.

- Inherited mutations in one of five DNA mismatch repair genes - MSH2,

-MSH6,

-MLH1,

-PMS1,

-PMS2)

give rise to the hereditary nonpolyposis colon carcinoma (HNPCC).

- Loss of DNA mismatch repair genes leads to a hypermutable state in which simple repetitive DNA sequences, called microsatellites, are unstable during DNA replication, giving rise to widespread alterations in these repeats.

- The resulting Micro Satellite Instability (MSI) is the molecular signature of defective DNA mismatch repair,

& hence this pathway is often referred to as the MSI pathway.

- Sessile serrated adenomas located on the right side of the colon display MSI & may be precancerous.

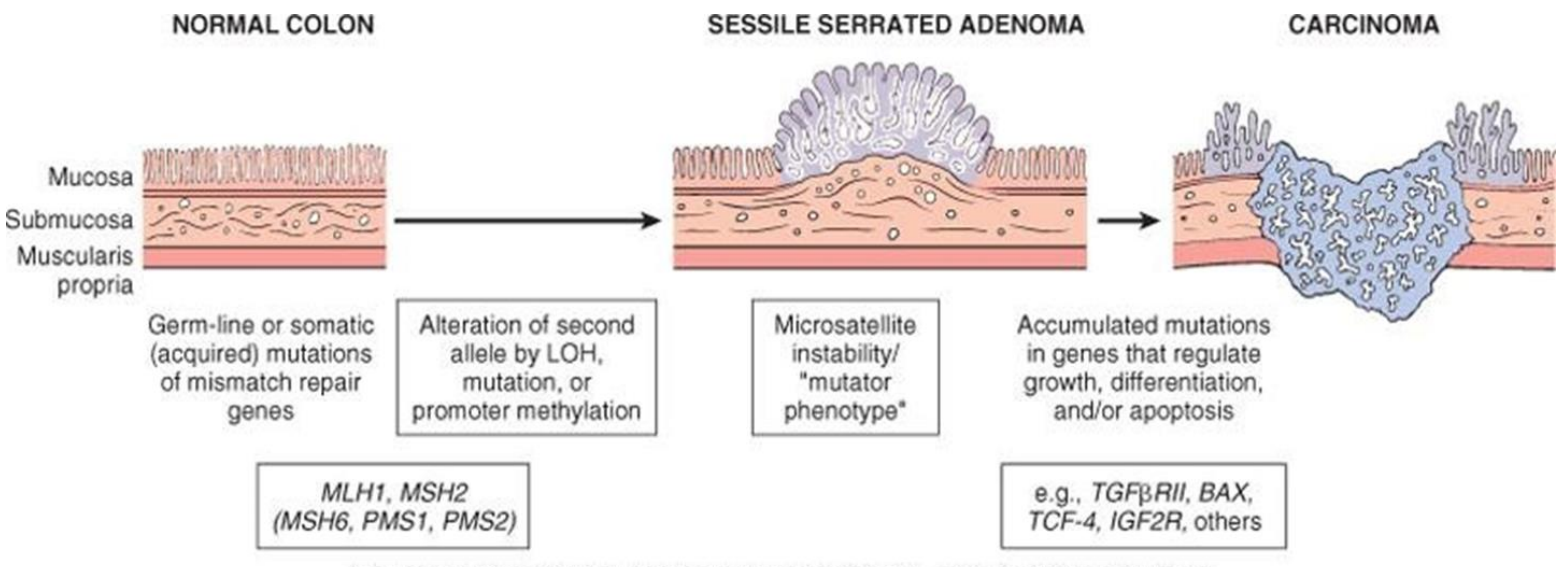
- Fully developed T that arise via the mismatch repair pathway do show some distinctive morphologic features, including :

-proximal (Rt) colonic location,

- mucinous histology,

-& infiltration by lymphocytes.

- Generally, these T have a better prognosis than do stage matched tumors that arise by the APC/β-catenin pathway



Epidemiology

- Peak incidence for colorectal ca is 60 to 70 years of age; fewer than 20% of cases occur before the age of 50 years.

- M/F ratio is 1.2:1.

- Adenomas are the presumed precursor lesion for most of the tumors;

- The frequency of colorectal cancer arises de novo from flat colonic mucosa remains undefined, but appears to be low.

- Both genetic & environmental influences contribute to the development of colorectal ca.

  ► When colorectal cancer is found in a young person,

  (1) preexisting ulcerative colitis or

  (2) one of the polyposis syndromes must be suspected.

  (3) individuals with hereditary nonpolyposis colorectal cancer syndrome {HNPCC, also known as Lynch syndrome, also at risk of developing other tumors, such as cholangiocarcinomas}, caused by germ-line mutations of DNA mismatch repair genes,

  are at a high risk of developing colorectal cancers.

- Colorectal ca has a worldwide distribution,

with the highest incidence rates in the US, Canada, Australia, New Zealand, Denmark, Sweden, & other developed countries.

▼ Its incidence is substantially lower, up to 30-fold less, in India, Africa, & South America.

►Environmental influences, particularly dietary practices, are implicated in the striking geographic variation in incidence. The dietary factors receiving the most attention are a:

(1) Low contents of unabsorbable vegetable fiber &

(2) High contents of refined carbohydrates,

(3) High fat content (as from meat), &

(4) Decreased intake of protective micronutrients such as vitamins A, C, & E.

- It is theorized that:

reduced fiber content leads to:

- decrease stool bulk,

-& fecal retention in the bowel,

-& an altered bacterial flora of the intestine.

- Potentially toxic oxidative byproducts of carbohydrate degradation by bacteria are therefore present in higher concentrations in the stool & are held in contact with the colonic mucosa for longer periods of time.

• Moreover, high fat intake enhances the synthesis of cholesterol & bile acids by the liver,

which in turn may be converted into potential carcinogens by intestinal bacteria.

- Refined diets also contain less of vitamins A, C, & E,
  which may act as oxygen radical scavengers.

- Intriguing as these scenarios are, they remain unproven!

- Epidemiologic studies suggest that use of aspirin & other NSAIDs exerts a protective effect against colon cancer.

- In the Nurses' Health Study, women who used 4 to 6 tablets of aspirin daily for 10 years or more had a decreased incidence of colon ca

- The development of ca from adenomatous lesions is documented by the following general observations:

-Populations that have a high prevalence of adenomas have a high prevalence of colorectal ca, & vice versa.

-The distribution of adenomas within the colorectum is more or less comparable to that of colorectal ca.

-The peak incidence of adenomatous polyps antedates by some years the peak for colorectal cancer.

-When invasive ca is identified at an early stage, surrounding adenomatous tissue is often present

- The risk of cancer is directly related to the number of adenomas, & hence the virtual certainty (100%) of cancer in persons with Familial Polyposis Syndromes.

- Programs that carefully follow persons for the development of adenomas, & remove all that are identified reduce the incidence of colorectal cancer.