Pathology

Sheet Slide

number 8

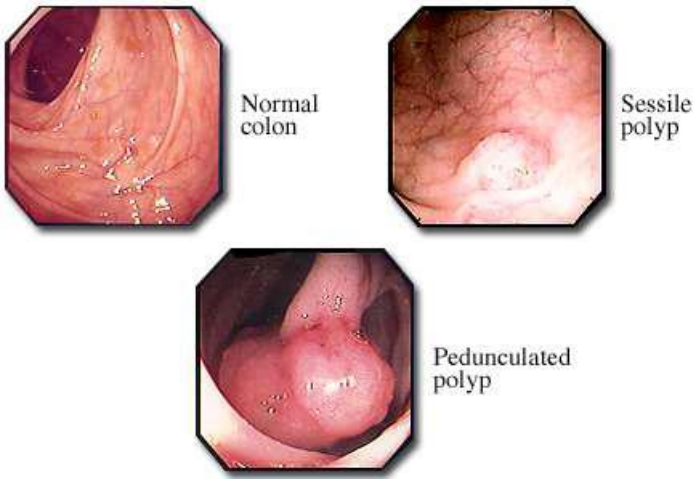
Done by Ola Al-juneidi

Correction Ziad Fraij

Doctor Mazin Al-Salihi

Polyps and Neoplasms of the intestine

Intestinal polyps are most common in the colon. They are divided into two major categories:



1. **Neoplastic polyps.**
2. **Non-neoplastic polyps:**
    a. Hyperplastic polyps.
    b. Inflammatory polyps.
    c. Hamartomatous polyps.

All these polyps could be one of 2 **morphological classes**:

1- Sessile: stuck on the surface of the epithelium (are not separate) and they don't grow into the lumen on a stalk.
2- Pedunculated: polyps with stalks.

*Which of these polyps (sessile or pedunculated) are more likely to cause intussusception?
- Pedunculated polyps because they are the ones that you can tug and cause one of the parts of the upper intestine to herniate and be pulled into the lower part and cause obstruction.

Inflammatory polyps

One example of inflammatory polyps is ***solitary rectal ulcer syndrome:***

It results from abnormal shelf that causes the epithelium to be damaged and scraped every time you evacuate stool which causes inflammation. After all this scraping and inflammation you are going to get a reaction that causes more inflammatory cells to come to the region and this will look like a polyp. When you look at it, you will find that it's purely inflammatory. They are similar to the inflammatory polyps that are found in the nasal tract which are caused by allergy.

Presentation: Patients with this syndrome will present with bleeding, prolapse, pain, and mucus production.

Hamartomatous polyps

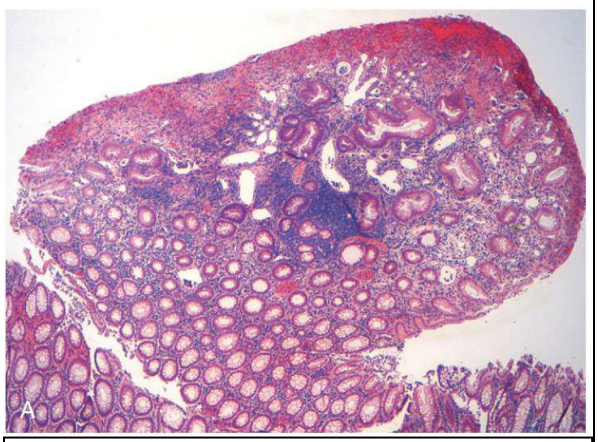
They are developmental problems (abnormal development of tissues) that create bizarre structures.

1) Juvenile Polyps:

- The most common hamartomatous polyps.
- Juvenile means small child.
- As the name implies, a juvenile polyp is typically found in patients less than 5 years of age.
- They either occur singly or multiply. If they occur singly, they are sporadic. I.e. there is no underlying genetic cause. Multiple polyps on the other hand are going to be syndromic; there is a genetic cause. However, if you took a sporadic polyp and a syndromic polyp and look at them under the microscope, you will find exactly the same thing and you won't be able to tell the difference.

- **Morphology:** Under the microscope you will see an ulcerated surface, dilated cystic glands/crypts (they are supposed to look like a circle in a cross section but here they become more dilated), debris, neutrophils, and mucus.

- We worry about these polyps because there is a **risk of adenocarcinoma**.

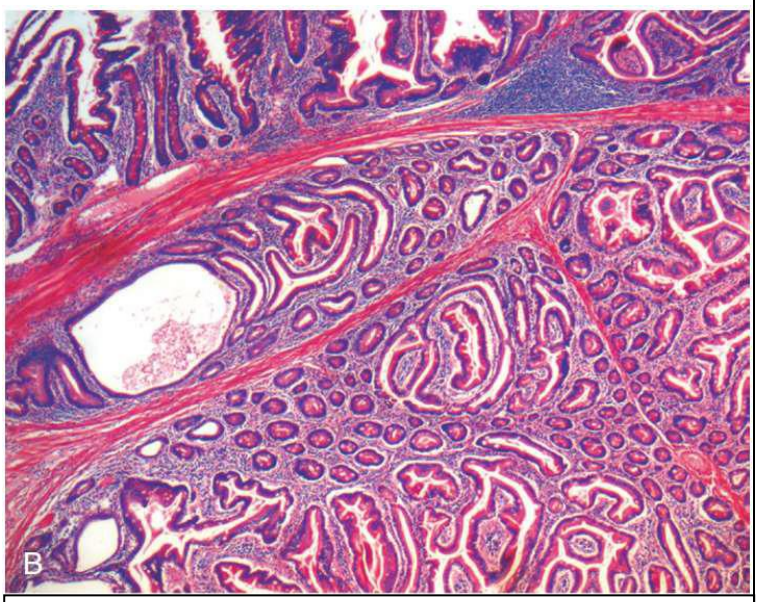


Pedunculated, smooth surfaced, reddish lesions (<3cm)

- The most common **location**: the rectum. Therefore, the **presentation** is a presentation of something in the lower part of the large intestine i.e. bleeding. If it's large and close enough to the anorectal line it will cause prolapse outside the anorectal line.
- **Juvenile polyposis** is an autosomal dominant syndrome. The risk of adenocarcinoma is higher in juvenile polyposis than in sporadic juvenile polyposis. Not because the polyps are different, but because of the sheer number; the more polyps you have, the more likely they will transform (the risk for each individual polyp remains the same).

2) Peutz-Jeghers Syndrome polyps

- These polyps differ from juvenile polyps in location, age group, and morphology.
- It is an autosomal dominant syndrome.
- **Location:** occur more frequently in the <u>small intestine</u>.



Large, pedunculated with a lobulated contour.

- **Morphology:** Under the microscope, the architecture is very different compared to the juvenile polyps. It is complex glandular architecture with bundles of smooth muscle.If you see bands of smooth muscle, these are not juvenile polyps. Rather, they are Peutz-Jeghers syndrome polyps.

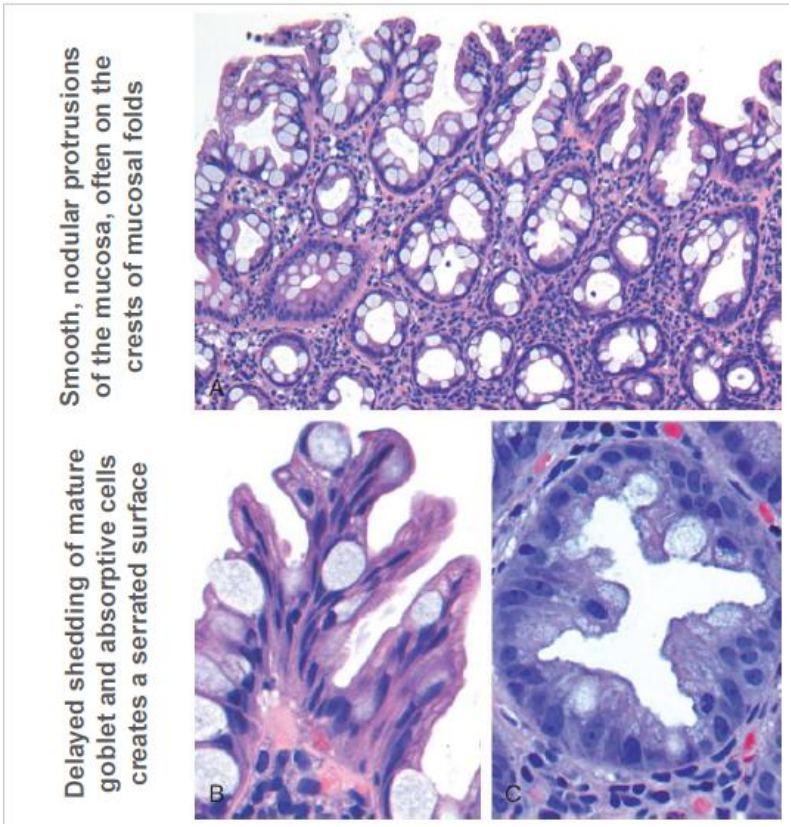
- In this syndrome, there is a serine-threonine kinase 11 (STK11) mutation, also known as liver kinase 1B (LKB1) mutation (the same gene, two different names).

- These could be <u>multiple</u> which are associated with mucocutaneous hyperpigmentation and an increased risk of malignancy. They can also occur outside the GI tract; they occur in the small intestine, stomach, colon as well as the bladder and the lung.

<u>Hyperplastic Polyps</u>

- They are found in elderly patients (60s and 70s).
- Hyperplastic Polyps of the colon are misnamed. They result from a slowing down of the intestine's ability to heal itself. The intestine's epithelium is a labile tissue and it's a steady state population (some cells die off, others take their place). As you get older, your stem cells and the enterocytes get more tired; they can't proliferate at the rate they were proliferating at when you were 20. So as a compensatory mechanism, we stop or at least reduce the rate of shedding. So older cells and more

goblet cells persist in the upper part of the crypts, which results in the serrated appearance (as a serrated knife blade; not straight). This serrated appearance only occurs at the top of the crypts and it doesn't occur all the way to the bottom.



- The reason we are interested in hyperplastic polyps is not because they have a malignant potential (they actually DO NOT have a malignant potential). However, they look under the microscope just like a sessile serrated adenoma. Adenomas in the colon and the intestine have a higher risk of transforming into adenocarcinoma. So you need to recognize the difference between one and the other. **The difference is:** in the sessile serrated adenoma the serration continues all the way to the bottom of the crypt.

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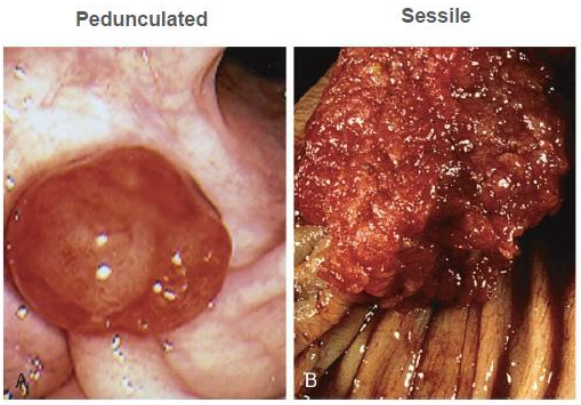
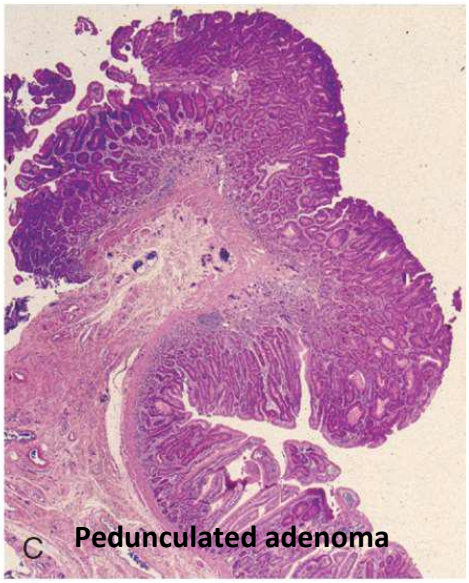
- So the **differential diagnosis** (DDx) of these polyps is a sessile serrated adenoma.
- Hyperplastic polyps are frequently multiple, <0.5cm in size, and localized in the left colon (i.e. the descending colon, the left half of the transverse colon, and the rectum).

Adenomas

- Adenomas, by definition, are epithelial benign tumors of glandular structure or non-glandular structure that have risen from a glandular organ.
- The most common neoplastic growth in the gastrointestinal tract. They give rise to the majority of adenocarcinomas (i.e. most adenocarcinomas arise from adenomas). However, not all adenomas give rise to adenocarcinomas; the majority of adenomas do NOT transform into adenocarcinoma. That's why the incidence of adenomas is a lot higher than the incidence of adenocarcinomas.
- Adenomas can either be sessile (on the surface) or pedunculated (have a fibrous stalk).



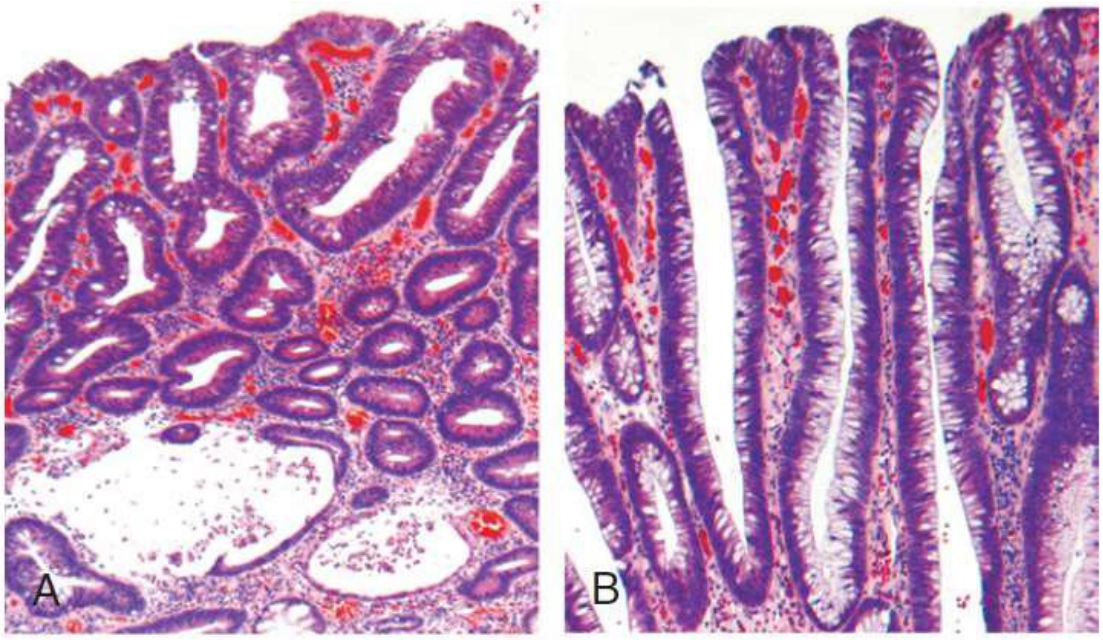
surface texture of both types resemble velvet or a raspberry



Pedunculated adenoma

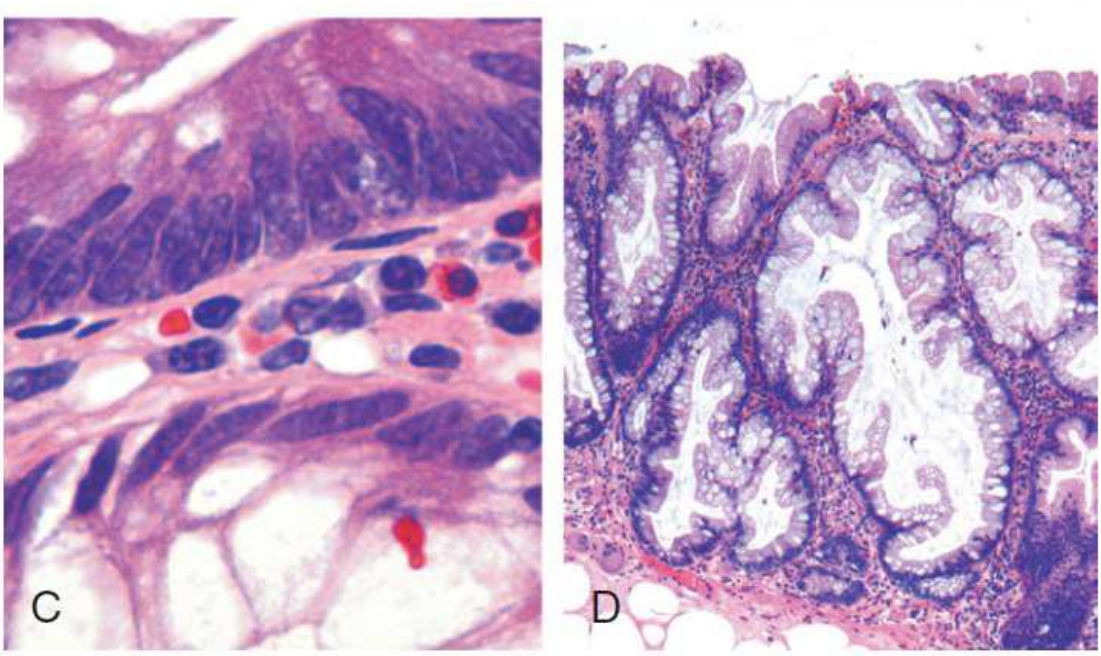
- **Morphology:** When you look at an adenoma that has a fibrous stalk under the microscope, the stalk is typically covered by normal or atrophic tissue and you have hyper-proliferation of epithelial cells on top. If you look closely you may find some inflammatory infiltrate. Depending on how much inflammatory infiltrate there is, you can tell how old or severe it is and how likely it is going to turn into adenocarcinoma (inflammation is related to cancer).
- **The architecture of adenomas:**
    - **Tubular:** full of tubes. It is like you are looking at the crypt in a cross section. (figure A)
    - **Villous:** have slender villi.(figure B)
    - **Tubulovillous:** between tubular and villous.

You might read that villous adenomas are more prone to become adenocarcinomas, this is **UNTRUE**. Based on architecture alone, there is no risk difference between tubular and villous adenomas. Size is the most important determining factor of whether adenoma is going to transfer into adenocarcinoma or not. The bigger it is, the more likely it is going to transform. It just happens that villous adenomas grow to a larger size before they are detected. Whereas tubular adenomas, which are typically pedunculated, do not.



- ***Epithelial dysplasia*** is frequently found near or part of the adenoma (it is a separate thing; not the same as adenoma).
    - **Morphology:** It has (just like any dysplasia) different shapes, hyperchromatic nuclei, an epithelium that originally was a single layer and became stratified, etc. So you will see nuclear hyperchromasia, elongation of the nuclei, and stratification under the microscope. (figure C)

- Figure D shows a ***sessile serrated adenoma***. It looks very much like a hyperplastic polyp with one exception: In all hyperplastic polyps the serration stops in the bottom. With sessile serrated adenoma, the serration continues all the way to the bottom of the crypt and it occurs mostly in the right colon.



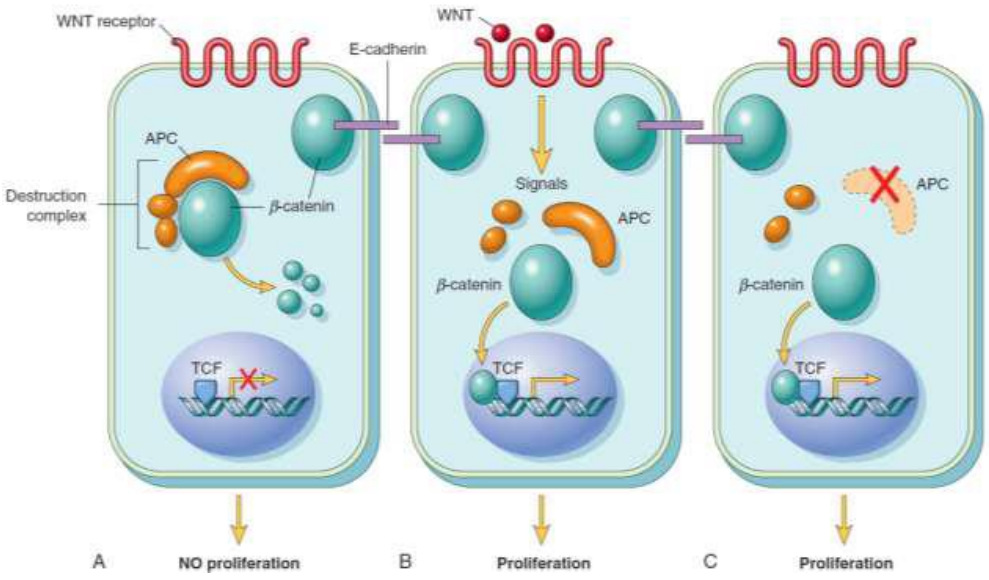
Familial Syndromes

Colonic polyps can occur singly (sporadically) or in multiples. Typically, when you are thinking about multiples (hundreds to thousands) you are thinking about a polyposis syndrome.

1. familial adenomatous polyposis coli (FAP)

- It is the most common polyposis syndrome. It is autosomal dominant.
- These patients generally have left colon predilection.

- The majority of FAP patients have a mutation in APC (adenomatous polyposis coli) gene. APC is part of the β-catenin destruction complex.
  If a cell doesn't receive a signal from the outside (in the form of WNT binding to frizzled receptor), the destruction complex binds to β-catenin destroying it. Therefore, β-catenin can't go into the nucleus and affect transcription.
  If WNT binds to the frizzled receptor, this signals that the complex dissociates. Therefore, β-catenin is safe from destruction and goes into the nucleus along with other transcription factors (e.g. TCF…) turning on transcription of pro-proliferative genes (like cyclin D and MYC).[This also happens when APC is mutated]
  Downregulation of E-cadherin will cause β-catenin to overwhelm the destruction complex resulting in β-catenin going into the nucleus.



- FAP patients can also have a different mutation; not necessarily an APC mutation. They can have a mutation in a base excision repair gene called MUTYH. This also results in hundreds to thousands of adenomatous polyps in the colon. As there are multiple mutations within the gene and multiple genes that can be mutated to produce this disease, you have **variants** of FAP patients that differ in some of the manifestations in the disease:
    - **Gardner syndrome:** Osteomas, desmoids, skin cysts, thyroid, and neoplasia.
    - **Turcot syndrome:** CNS tumors like medulloblastoma (only with APC mutations) and glioblastoma (only with base excision repair mutations).
      [Look at the tables in the book that summarize this]

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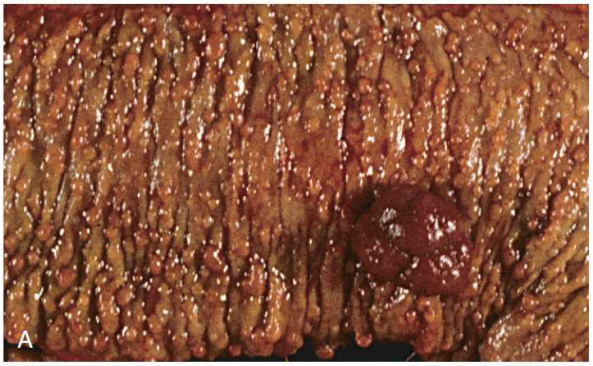
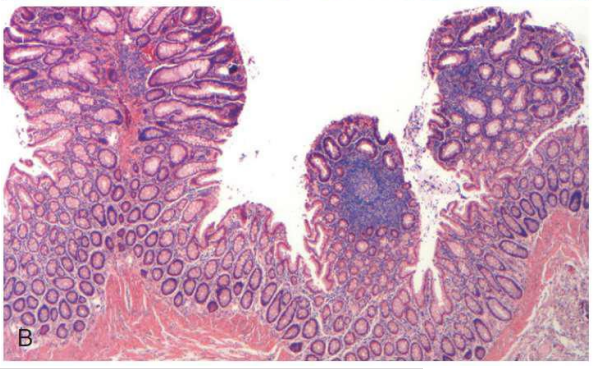


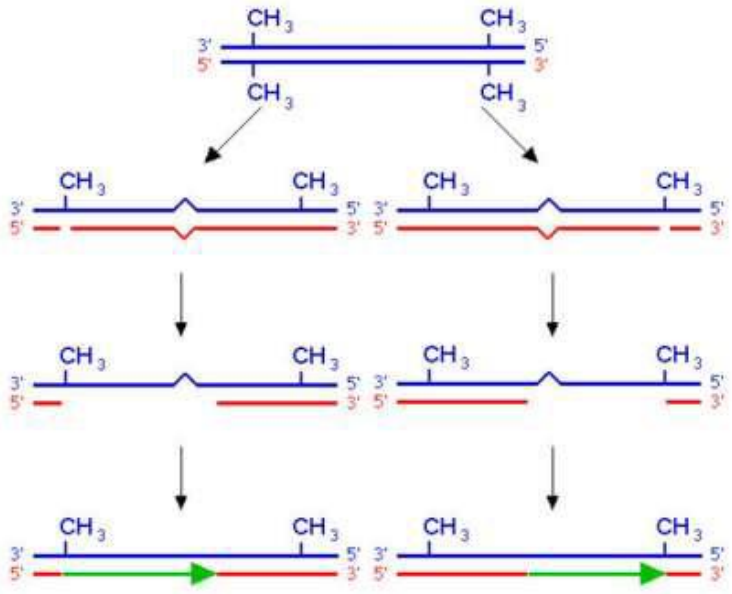
- These patients have hundreds to thousands of adenomatous polyps that are morphologically indistinguishable from sporadic polyps; you can't tell the difference between them under the microscope or even grossly.



- The risk for each polyp to become an adenocarcinoma is the same whether you have one polyp or thousands of polyps. However and because these patients have hundreds to thousands of polyps, addition of all these risks together means that these patients (100% of them with untreated FAP) will have a colon cancer by the time they are 30
- **Treatment:** prophylactic colectomy (you remove the colon). They are put under surveillance, and if you find dysplasia and neoplasia you remove the colon.
- **The difference** between these patients and those with colitis associated adenocarcinoma is:
    - In colitis associated adenocarcinoma: if you find one dysplastic locus, there is a very strong likelihood that a neoplasm is present somewhere else in the colon.
    - In FAP patients: if you find one dysplastic locus, the neoplasm will be near this locus (not somewhere else) unless there is dysplasia there too.

2. Hereditary Nonpolyposis Colorectal Cancer (HNPCC) /Lynch syndrome

- Nonpolyposis → they don't have a lot of pedunculated adenomatous polyps.
- It is also autosomal dominant; you have to lose the second copy of the gene for the disease to happen.
- In this syndrome there is a mutation in a DNA mismatch repair gene mostly MSH2 or MLH1. Mismatch repair is active when the cells proliferate. Whenever you copy DNA, one strand is going to be methylated and the other won't. If there is a mismatch between the two strands, the products of these mismatch repair genes will read and repair. They are also responsible for maintaining the



microsatellites which are repeated sequences in various parts of the genome and are the basis of the DNA fingerprint. So these patients could get away with murder because their DNA fingerprint will change form one time to the next.

- There are characteristic mutations that result from this mutator phonotype which are: TGFβ type II receptors and BAX mutations. These two genes have actually got microsatellites in their promoter region and this microsatellite instability may affect the transcription of TGFβ type II receptors and BAX.
  Early on (before cells become independent of growth factors) TGFβ pathway is anti-proliferative throughout the tumor duration. However, later on its effect on proliferation becomes irrelevant because the tumor has become independent. The other effects become more relevant, which are epithelial to mesenchymal transition, immune evasion, angiogenesis, and fibrosis.
  When you turn off the production of BAX, you turn off apoptosis (another hallmark of cancer).
- These patients (unlike those with APC mutations) have a right colon predilection at a younger age.

Adenocarcinoma

- The most common cancer in the GI tract.
- Adenocarcinomas can arise from one of two distinct **pathways**:
  1. **The APC-WNT-β-catenin pathway** through pedunculated polyps
  2. **HNPCC microsatellite instability pathway** which sometimes goes through sessile serrated adenomas or doesn't.
- The peak incidences of adenocarcinoma are people in their 60s and 70s.
- It is an example of a multifactorial disease; there are genetic and environmental factors. Diet has a lot to do with adenocarcinoma. If you do not have a good diet (low in fiber, high in fat and refined sugars), you are at a higher risk for adenocarcinoma. So people who live in developed countries (Europe, USA) are at a higher risk for getting adenocarcinoma.

While those who live in Africa have a very low rate of colorectal adenocarcinoma. People in Japan originally had a low rate of adenocarcinoma, but as they are adopting a western lifestyle more and more the risk of adenocarcinoma is increasing.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are protective; they reduce prostaglandins. WHY? When COX2 is overexpressed, adenocarcinoma progresses faster because prostaglandins produced by it can transactivate the EGF receptor and turn on pro-proliferative pathways downstream. COX2 alone will NOT produce a tumor. However, once a tumor is established and COX2 is overexpressed, this will lead to a faster progression and a bigger tumor with more metastasis.
  **NSAIDs are *not* protective against the occurrence of adenocarcinoma. They actually stop the *progression* of it. So they may prevent adenomas from turning into adenocarcinomas (the transformation has already occurred). Alone, COX2 over-expression is insufficient to create a tumor.
- COX2 is over-expressed in 90% of all adenocarcinomas.
- The older you are, the more likely a tumor has occurred (the Peak incidence 60-70yrs). So the medical recommendation is that when you are 50 and above you should go for a screening colonoscopy once every year or every two years based on your risk factors. If you are a part of a family that has an increased incidence above the general population of adenocarcinoma in the colon, you will go into screening earlier.

Side note:

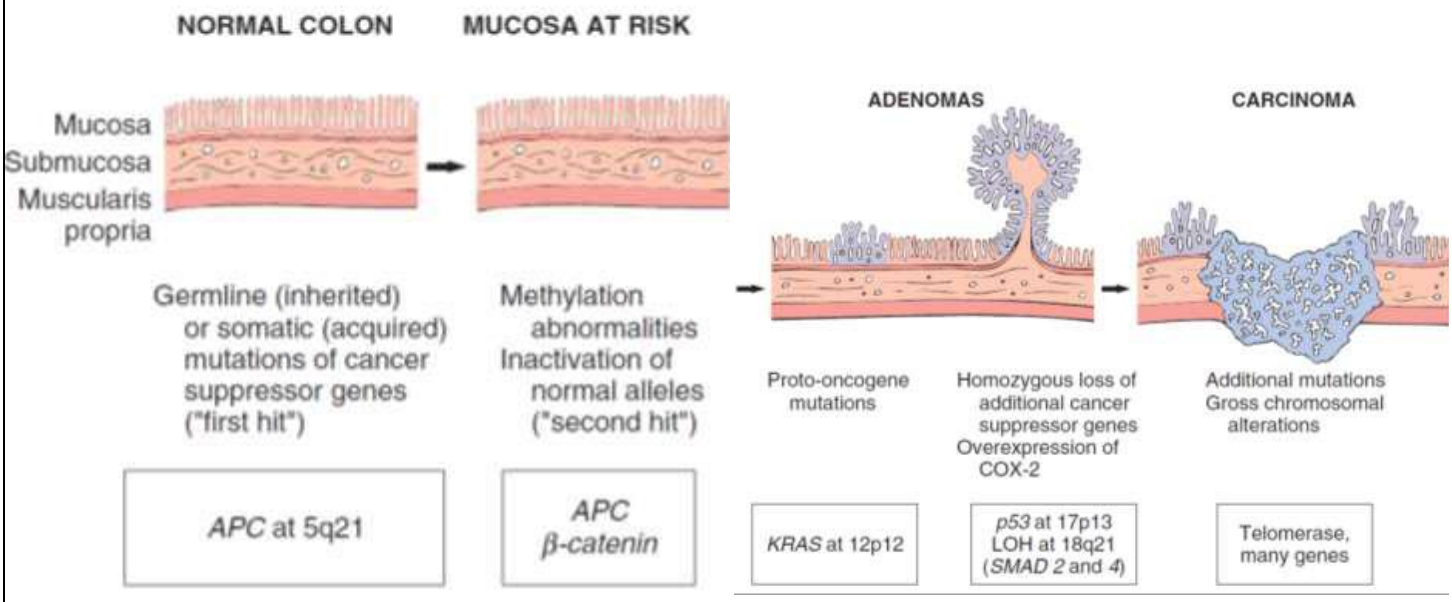
Generally, when doctors find a polyp after colonoscopy, they will remove it and send it off for histopathologic examination. The patient will continue screening throughout his lifetime.

1. The APC-WNT-β-catenin pathway:

- The adenoma-carcinoma sequence of this pathway is characteristic of the vast majority of sporadic colon cancer.
- 80% of all colorectal carcinomas have an APC mutation whether they are sporadic or inherited.

- When you lose the first APC gene (by inheritance or sporadically), nothing happens until you lose the second (by deletion, epigenetic silencing or others). Only then you get the beginning of a tumor.
- The second hit (losing the second allele) can be in the same pathway or outside the same pathway, which results in the same thing (i.e. a pit in the pathway that results in a functional nullification of the second allele of APC).

  RAS (a G protein) is one of the oncogenes that can be mutated turning on PI3 kinase pathway and the other proliferative pathways downstream, and this turns on proliferation by overexpressing MYC. You can also have P53 mutations and TGF-β pathway mutations (remember SMAD; one of the transduction molecules in TGF-β pathway). Once you have lost p53, you have gone into genomic instability. The BFB cycle (breakage-fusion-bridge cycle) starts and the only way to stop it is either by mitotic catastrophe or turning telomerase on. So, at the late stage of the carcinoma, you also have telomerase along with other genes that are upregulated or mutated (depending on their pro- or anti-tumorigenic activity).



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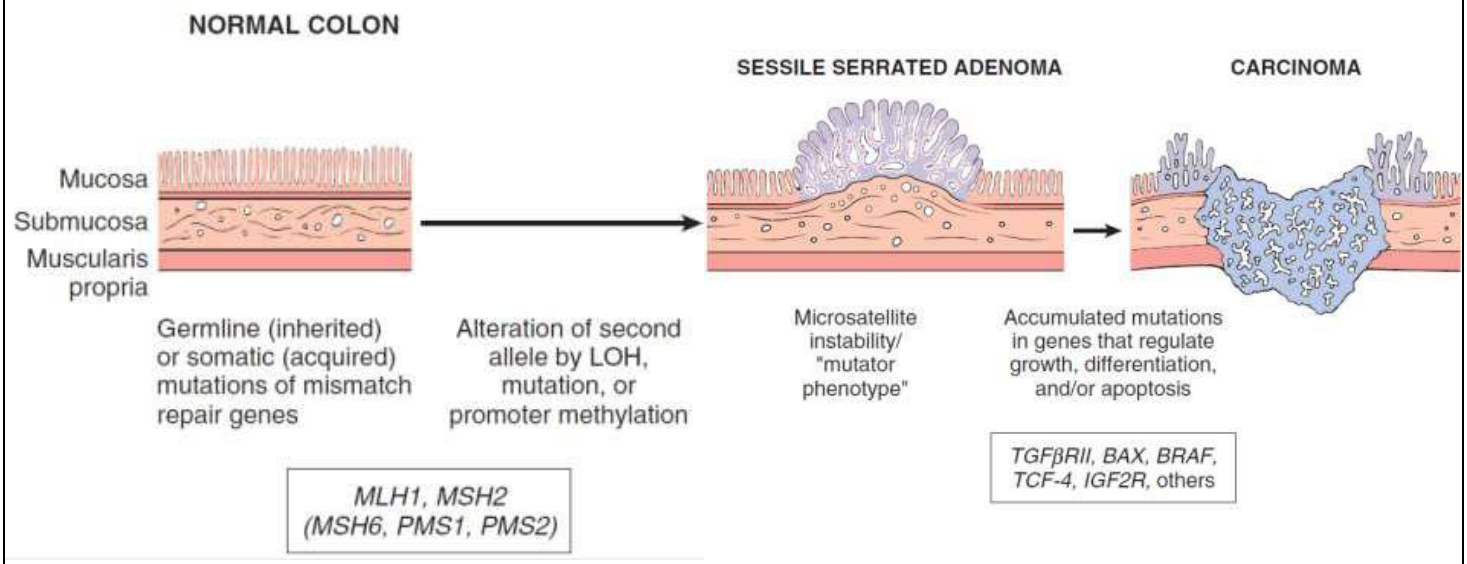
2. HNPCC microsatellite instability pathway/The DNA mismatch repair pathway:

- Here there is a mutation within the mismatch repair genes after you have inherited or lost the first gene in your lifetime. Then you have signature mutations in TGF-β receptors, BAX, RAF, TCF-4 (it is downstream of β-catenin), and IGF (insulin-like growth factor) receptor, but NOT p53. You will not find p53 or RAS mutations in the microsatellite instability pathway whether sporadic or inherited.



Morphology of adenocarcinomas:

- It is very different between right-sided and left-sided adenocarcinoma:
  - → Right-sided adenocarcinomas: grow as masses into the lumen, away from the epithelial surface. So they are called ***exophytic tumors***. This means they are less likely to cause an obstruction by growing all the way around (they extend along one wall of the cecum).
  - → Left-sided adenocarcinomas: are called ***"napkin ring" tumors*** because they grow all the way around in the wall of the distal colon. They can get big and thick enough to cause obstruction.

  They both (right and left-sided) stimulate a <u>desmoplastic reaction</u> because the same cytokines and growth factors that are used for repair and chronic inflammation are now being produced in the tumor microenvironment. So, they are stimulating fibroblasts to proliferate

and deposit ECM. This means these tumors are going to be easy to palpate as solid masses, not because of the tumor cells themselves but because of the accompanying fibroblastic reaction.

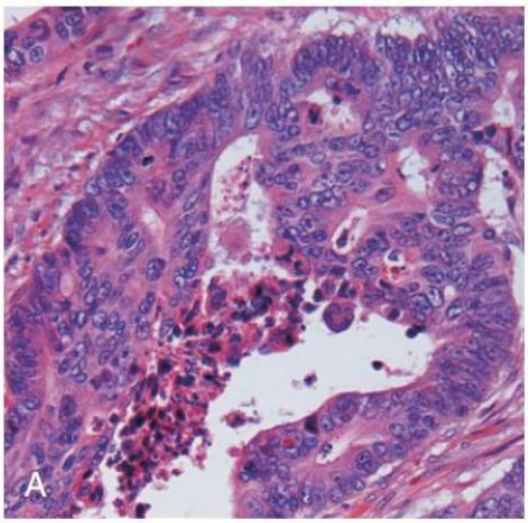
- Unfortunately, obstruction or a solid mass that you can palpate in abdominal examination are both late presenting signs of adenocarcinoma.

- **Clinical Features:**

  → The typical presentation of a right-sided tumor is fatigue, tiredness, weakness due to irondeficiency anemia. These, unfortunately, are non-specific symptoms. If you get an elderly patient (6^{th} or 7^{th} decade or above) with irondeficiency anemia, a gastrointestinal tumor should be at the very top of your differential diagnosis. 9% of iron deficiency anemia above 60 years of age in the western society are gastrointestinal tumor related. It's not a big percentage, but the consequence is severe. Once you exclude a gastrointestinal tumor, work on the patient for everything else.

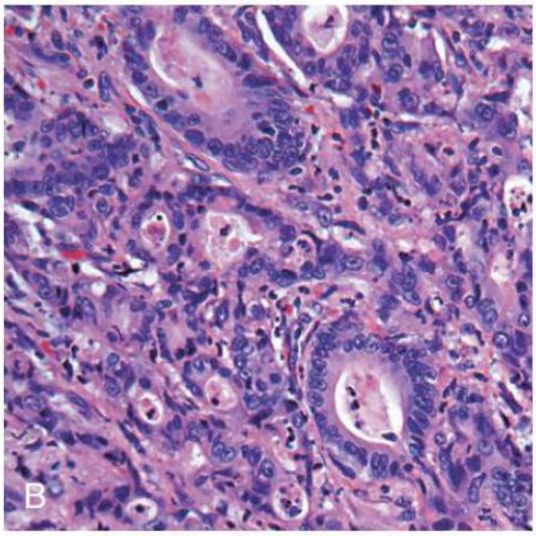
  → Left-sided colon tumors are more likely to present with obstruction, constipation, changes in bowel habits, cramping and potentially bleeding. These are also late presenting signs, which is why people who are 50 years of age and older should undergo a screening program (colonoscopy) once a year to check if they have polyps, are dysplastic, or have neoplasia.

- **Under the microscope**, you will find the same effects that you saw in dysplasia; nuclear elongation, hyperchromasia, and stratification.
  Additionally, if it is a *well differentiated adenocarcinoma* you can still identify a crypt and you will find debris, nuclear infiltration, dead cells (necrosis) inside the crypt because they are growing beyond their blood supply.



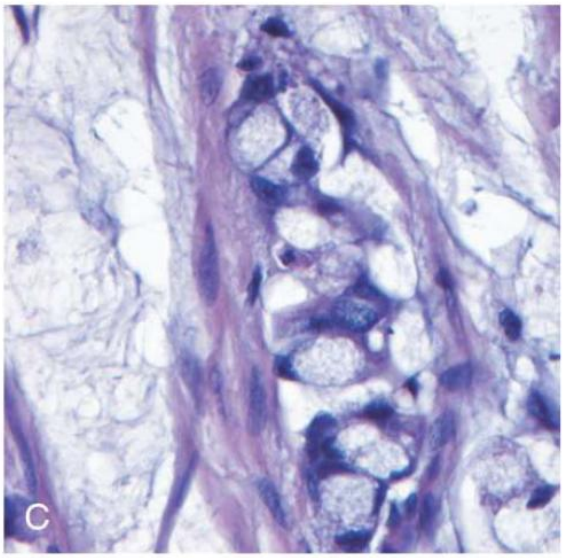
Well-differentiated adenocarcinoma

If it's not well differentiated, you may find some nests trying to be glandular structures. But for the most part it looks nothing like the original colon tissue i.e. it is a *poorly differentiated adenocarcinoma*. You will also find infiltrating inflammatory cells.



Poorly differentiated adenocarcinoma

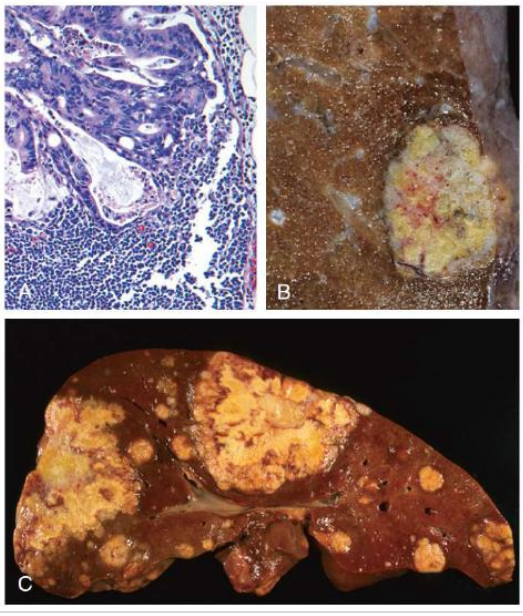
- One subtype of colonic adenocarcinoma is ***mucinous adenocarcinoma*** (it can also be found in stomach adenocarcinomas). These cells have a signet ring appearance.
  It is particularly aggressive, mucin-producing, hard-to-treat, very fast progressing tumor; it has poor prognosis.



Mucinous adenocarcinoma

Prognosis

- The prognosis of the patient depends on how big the tumor is, how far it has invaded, how many lymph nodes it has metastasized to (figure A) and whether it has metastasized to the lung(figure B) or the liver (figure C).



- The most common location of metastasis is the liver. **WHY?** Because the portal circulation goes to the liver.
  *How can it metastasize to the lung?
  → There is a portosystemic anastomosis at the end of the rectum, so the tumor cells can directly drain into the systemic circulation and metastasize to the lung. There are other ways for this to happen.

  Carcinoid tumors will only manifest with systemic manifestations once they metastasize with the exception of rectal carcinoids because of that portosystemic shunt where the chemicals they produce can go directly to the systemic circulation and cause the effect of carcinoid.

Grading & Staging

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

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

There are 2 classification systems:

1. Tumor-Node-Metastasis classification:
   a. Tumor→ small, medium, or big tumor (T1-4).
   b. Lymph nodes→ more lymph nodes (N1) or no lymph nodes (N0)
   c. Metastasis→ metastasis (M1) or no Metastasis (M0)

2. The American joint committee on cancer (AJCC): four stages:
   Stage1: small tumor
   Stage2: big tumor
   Stage3: big or small tumor with lymph nodes
   Stage4: any size tumor with metastasis

The later the patient presents (no screening) → the bigger the tumor is, the more metastasis there is, the more lymph nodes are involved → poor prognosis and the least likelihood of survival. That doesn't mean you don't try; you still do.

The appendix

Acute appendicitis

Whether you think of it as a reservoir of immune cells in the intestine or a vestigial organ that has no function, it can do a lot of damage. If you block the appendix (a blind sac) with a hardened part of feces or less likely a gall stone, this results in increased pressure and more inflammation. Bacteria may be also involved. You can also get suppuration from the neutrophils that are there and involvement of all the layers. If at a point it bursts, you end up with suppurative peritonitis. So you want to catch it before it bursts.

Presentation of acute appendicitis: these patients will present with fever, loss of appetite, and pain around the umbilicus that then localizes to the right iliac fossa. This point is called Mcburney's point which two thirds of the way between the umbilicus and the superior iliac crest. When you press at this point, the patient will be in severe pain. Another sign is called Rovsing's sign: if you press in the *left* iliac fossa and then take your hand away quickly, the patient will also be in pain. This is called *rebound tenderness*.

Why do we worry about acute appendicitis?

- Because of its differential diagnosis. It is common but there are other things that look like acute appendicitis and you should never miss. ***Ischemic bowel disease*** is at the top of the list. [go back to the previous lectures and check it out]

Carcinoid tumor of the appendix

It is a common tumor of the appendix. [Dr.Heyam already covered this]

The End