Digestive System

University of Jordan

Faculty of Medicine

Batch of 2013-2019

Medical Committee
The University of Jordan

◯ Slide ● Sheet ◯ Handout ◯ Other

☐ Anatomy ☐ Embryology

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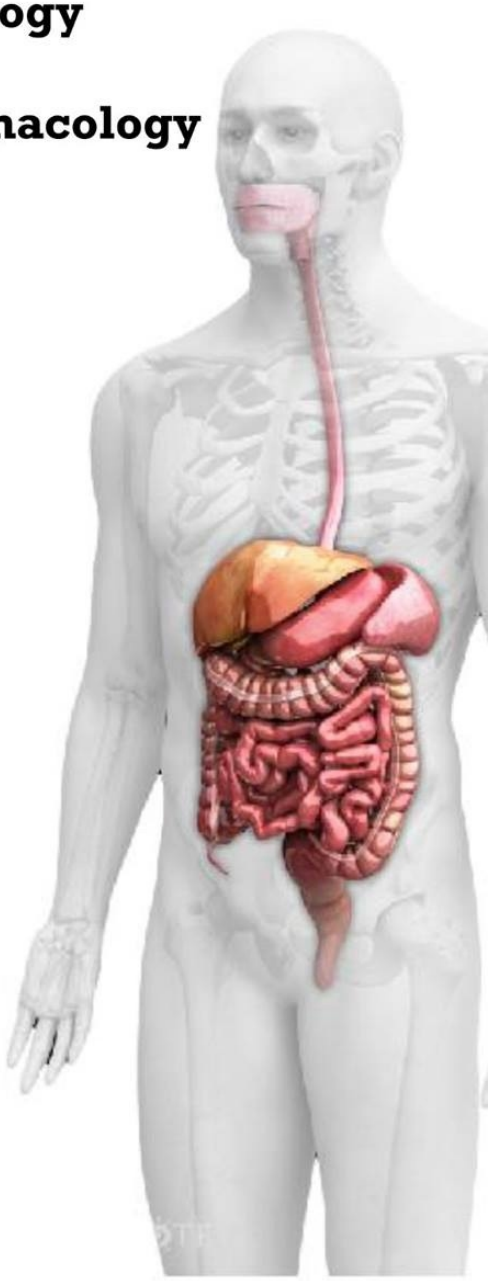

Sheet #: 5

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Date:

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DESIGNED BY: TAMER ALTAMIMI "SMILE"

Small & Large Intestines (cont.)

- Sigmoid Diverticulitis

- **What is diverticulum** ?

It is an outpouching from intestine to the outside due to increased intraluminal pressure

- Generally , there are 2 types of diverticula :

1. The ones that have all 3 layers : mucosa , submucosa , muscularis along with serosa .

2. The ones that have not so much muscular layer , may be even absent .

So , the congenital typically has all 3 layers , that's Mickle's diverticula .They are generally benign with no serious complications .

On the other hand , Sigmoid diverticula aren't so benign , still fairly okay , not disaster ,even if they can lead to medical emergencies like perforation because we're talking about increased pressure .

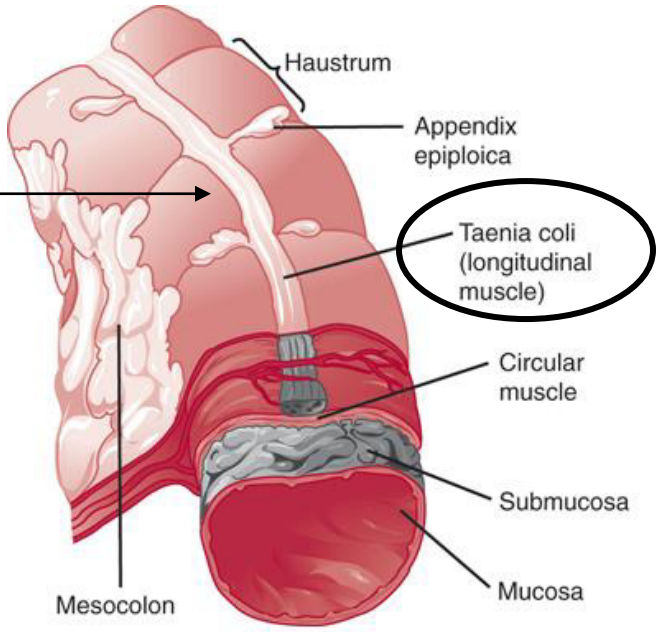
- Now , the whole thing happens because of **the way the bowel is innervated** (The anatomy of the bowel).

So , for most of the bowel , we're talking about small intestine . You have the two nerve plexuses and you got innervation that's going through the circular muscle layer , which means that the muscle fibers are separated at that point and you have created a weak point . However , **in small intestine** ,the longitudinal muscle layer can compensate for that defect as towards the nerves go through

.However , in the large intestine , the longitudinal muscles aren't surrounding the whole bowel ; they are actually grouped into 3 lines called the

Taeniae Coli .

- So , this is the longitudinal muscles of the large intestine , only this line (out of the 3 lines around the large intestine) is where the longitudinal muscle is . So , when nerves go through the circular muscle , **they do leave defects** , and if there is an increased pressure inside the large intestine , you can start getting **outpouchings** through these defects .



- This is more common in the **elderly** and it's more common in western societies.

>> The hypothesis is ; it's related to the lack of fibers in the diet , which means that stools are going to be harder and higher intraluminal pressuers are required to expel those stools >> which also means that the outpouchings are going to be more common . It's still a hypothesis .

-In any case , because the nerves go out at regular intervals , the diverticulae that form will **form at regular intervals .**

- For the most part , they're asymptomatic ; however , if they do become symptomatic , it's called **diverticulitis ,**i.e. they have become inflamed , they have become infected . If left untreated and it's a severe inflammation , that could

lead to perforation and peritonitis . However , for the most part , they resolve spontaneously or sometimes after antibiotic therapy .

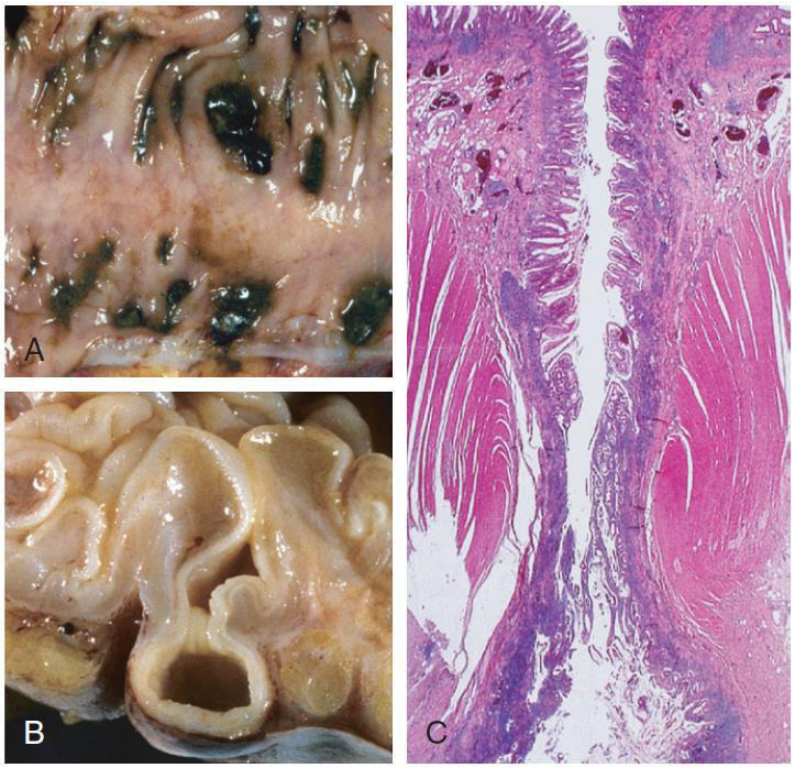
- Looking for the inside of the intestine onto the wall , you can see that the diverticula are mostly forming at regular intervals .

** If you take a cross section , you can see the outpouching to the outside of the intestine .

- It's lined by , for the most part , **atrophic intestinal epithelium** . you can notice that the muscle layer is either very little or often absent .

See there is really nice intestinal mucosa appear (B) and when you look at the diverticula (A) , it's really a mass and you don't have the nice crypts and for most of the part it's atrophic mucosa .

(C) shows protrusion of the mucosa and submucosa through the muscularis propria .(diverticula)



- If you noticed it's called sigmoid diverticulitis , it's the most common place for diverticula to occur is where the highest pressures are . However , diverticula can occur anywhere in your GIT .

- Inflammatory Bowel Disease [IBD] :

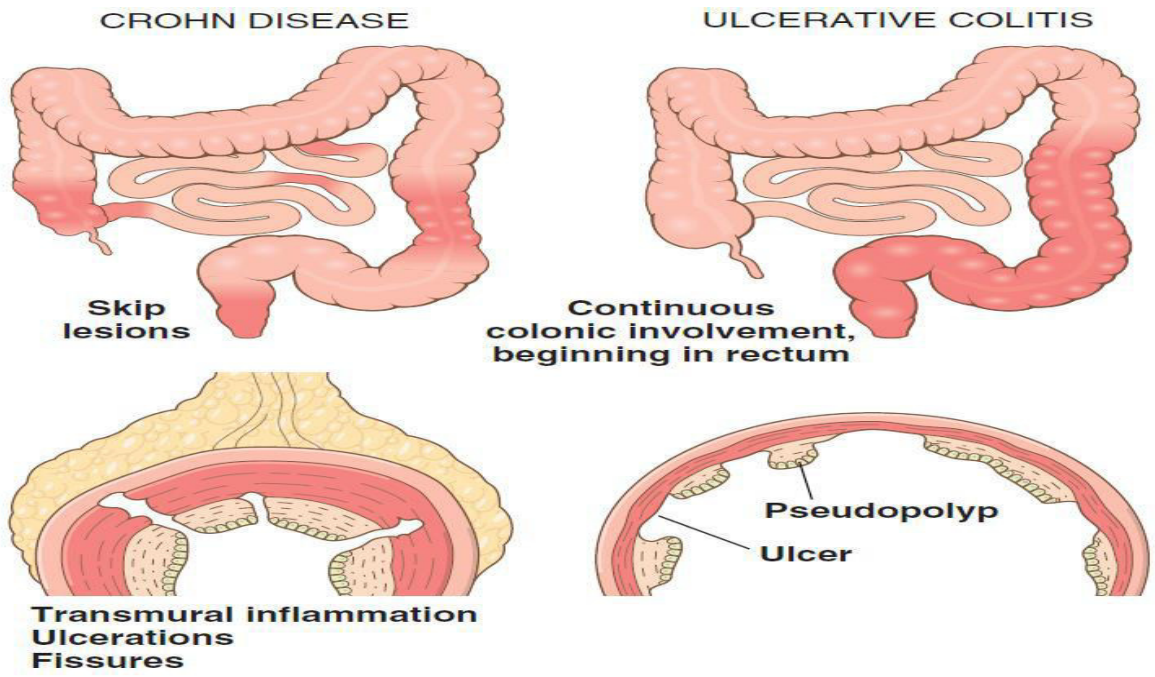
- Chronic inappropriate mucosal immune activation . So , you got immune part and the activation of your immune system is **inappropriate .**

- There are two major forms of this disease :

1) Crohn's disease . 2) Ulcerative Colitis .

- **Crohn's disease :** characterized by having **skip lesions** , which occur all the way through the GIT .
- **Ulcerative Colitis** : typically involves the distal colon . It may involve the whole colon causing **pancolitis**. In severe cases , pancolitis can even involve the ileum and cause what's called **backwash ileitis** .

- The lesions in crohn's disease are more transmural ,i.e. all 3 layers are infected ,whereas it's just mucosa and submucosa that's affected in ulcerative colitis .



- In IBD , the predisposition is **females** (young presentation) . So unfortunately , females this time are at a disadvantage .
Young presentation : we aren't talking elderly (50s - 60s) , but we're talking 30s or may be even 20s !

- There is an increased malignant potential if you have colonic involvement . **If it's crohn's or ulcerative colitis that has colon involvement** , both of them predispose for malignant transformation .

- Malabsorption is more of a problem with crohn's disease because that involves the small intestine while ulcerative colitis rarely involves the small intestine .

Unfortunately , inflammatory bowel disease is on the rise , more and more incidence . So , the **hygiene hypothesis** is that as our food supply becomes more hygienic , less chance of enteritis , less chance of getting bouts نوباتof diarrhea as you are growing up , as your immune system is developing ,i.e.

your gut , which is fairly a large immune organ , needs to learn what's pathogenic and what's not !

- Remember if we are talking cell member wise , you are only 10% human , that means that 90% of cells in your body are bacteria and the vast majority of those bacteria are nonpathogenic ; however , if while your immune system is developing and while you are growing up , your immune system doesn't see any pathogenic bacteria in the gut , it will not learn what's harmful and what's not in some cases with some cases and genetic predisposition , which means because our diet is becoming cleaner and cleaner , incidence of IBD - which is an *inappropriate activation towards these bacteria that are normal in our gut , is increasing & increasing* .

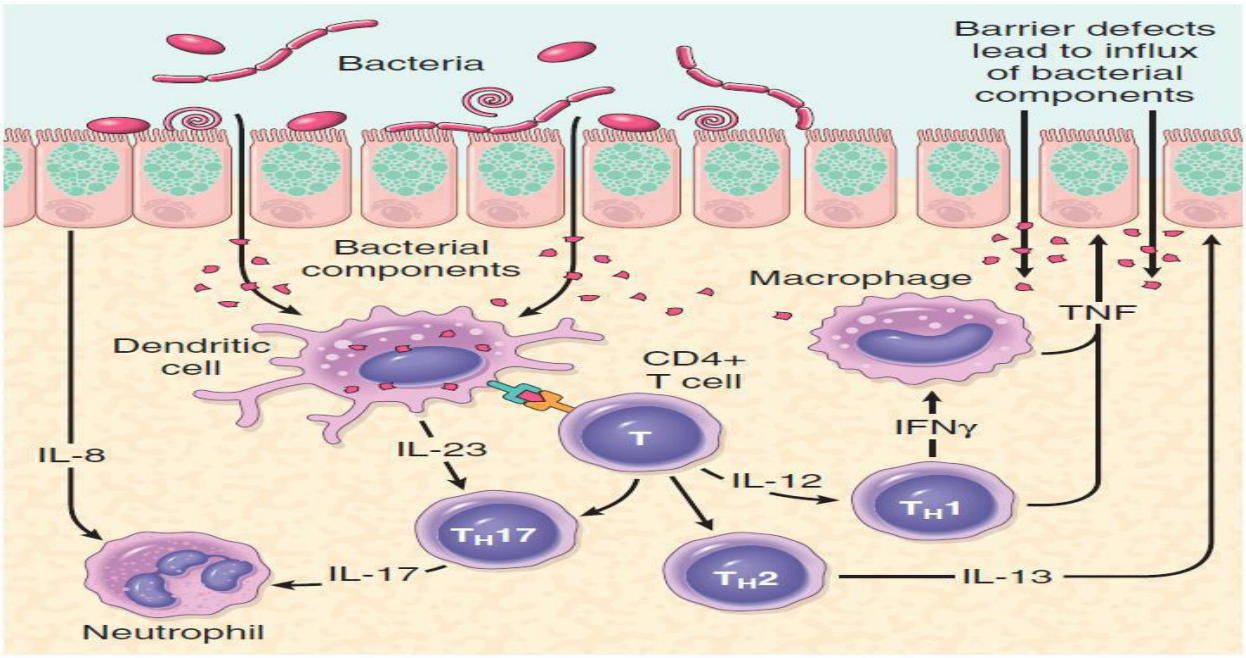
** A student asked : so should we humans be exposed to food poisoning ?
Apparently , yes . As you are growing up , nobody generally dies from a minor bout of enterocolitis , it's something you get trained for ,your gut trains to recognize what is pathogenic & what's not . It's kind of the same hypothesis with allergies , for example , if you have an allergy towards something and you keep giving yourself small doses of the allergen , your body builds a tolerance , it recognizes that this isn't something that is pathogenic .

- The pathogenesis is three things:
1- Your aberrant host interaction with intestinal bacteria .
2- Intestinal epithelial dysfunction makes it worse .
3- Aberrant mucosal immune response .

- The mainstay الدعامة الأساسية of therapy is immune suppression and immune-modulation . It's not ideal but that's what is working right now

because we don't have fully understood the pathogenesis of IBD , we understand some parts of it ,but not all.

- That is a composite of both crohn's and ulcerative colitis, they don't exist all of them in both . But , for the most part , you'll notice that it's very similar pathogenesis to celiac disease , it's just the offending agent is different >> In this case, it's **not gliadin but it it's <u>your normal intestinal bacteria</u> .**
  So, there is an inappropriate response to these normal bacterial component which there shouldn't be . There's a CD4 T-helper immune activation that activates macrophages in this case and neutrophils rather than activating CD8 cells .



- What is the genetics of it ??

- There is an increased risk if you have a family member with IBD , more so for crohn's than ulcerative colitis .

**For Crohn's , concordance rates for twins (we're talking about identical twins ,i.e. monozygotic twins) are about 50% , it's only about 16% for ulcerative colitis .

Concordance rates for twins means : if one twin has it , the likelihood of the other twin having it , That's typically how we know initially if this disease is genetically related or not .

**So , *it seems that crohn's is more of an inherited problem whereas ulcerative colitis is more than an acquired problem .*

- There are 3 different protein products[NOD2 , ATG16L1 , & IRGM] and all of them related to ***detection and response to intracellular bacteria*** .So, these 3 proteins all sense and react to intracellular bacteria .Therefore , whenever you absorb some of these bacteria ;your macrophages some kind of clean the place up , do they respond to the dendritic cells , when these are antigen-presenting cells in this case, receive these bacterial components , do they respond or not ? They shouldn't .
- So ,regarding abnormalities in these , we aren't talking mutations , we are just talking *polymorphisms whether they are more or less active* .

- These polymorphisms are associated with crohn's disease not ulcerative colitis , which kind of lends to the fact that it seems that crohn's disease is more genetically related than ulcerative colitis . But still we don't know exactly what these genes are doing in IBD .All of them (protein products) are responsible for the reaction to intracellular bacterial product and the last two(ATG16L1 & IRGM) are actually related to **autophagy** .

So , again if you ingested something and now you are going to break down whatever you are ingesting along with some cellular components , well , those will be presented to outside and stimulate the T-cell response . Unfortunately , what is not supposed to happen is *presentation of these foreign bacterial products to T-cells* , but what happens is they're presented to T-cells! and you know that CD4 T-cells produce various cytokines and these cytokines will move the T-cell development to one or another way .

- You have T-helper cells type [1 , 2 , and 17], and depending on which helper cell is produced , do we recruit more neutrophils , do we stimulate tissue macrophages ?
It turns out that TH1 & TH17 development is associated with *Crohn's disease* .

- Interleukin -23 receptor polymorphisms seem to be protective in crohn's and ulcerative colitis .
- **Interleukin -23** is responsible for stimulation and development of T-cells towards TH17 (T-helper type 17) which also stimulates neutrophils .

- The reason why the doctor is coming back to neutrophils(although we took that in inflammation chapter last semester) is that one of the criteria of how severe the disease is , is how many neutrophils have come to the area .

- TH2 development is more associated with ulcerative colitis and increased interleukin -13 which is responsible for some of the damage in **ulcerative colitis** , that means if you have high levels of IL-13 , you are more likely to affect the junction of the epithelia , allowing further bacterial products to come in .

- Finally , interleukin-10 is one of the anti-inflammatory interleukins .So, polymorphisms of IL-10 and IL-10 receptors are associated with ulcerative colitis . Hence , if you don't have that anti-inflammatory response from IL-10 , you are more likely to inappropriately activate your immune system .

** **Polymorphisms that reduce IL-10 or blunt receptor response to IL-10 are associated with ulcerative colitis .**

Epithelial Defects :

-There's a defect in the epithelial tight junctions and these defects are associated with crohn's disease . Some paneth's cell granules that are abnormal are also associated with crohn's disease ,and these granules that are anti-bacterial can affect the composition of your intestinal bacteria .

- So , what about your intestinal bacteria ?

Your intestinal bacteria vary a lot from one person to the next . What did you eat when you are growing up .

The current theories for intestinal bacteria are depending on the composition of your intestinal bacteria . Also , there are wide ranges of diseases that can be affected ,for e.g., obesity , inflammatory bowel disease , celiac disease ...etc

- So , what is so special about your intestinal bacteria ??

From the previous lecture ,for e.g you know that in case of *lactose intolerant* , your intestinal bacteria will break down disaccharides .Also, as part of the hepatobiliary circulation , intestinal bacteria deconjugate some of the bilirubin that can be reabsorbed and so on and so forth .

- You carry 10^{12} microorganisms/mL of fecal material in the colon . Half of the weight of your fecal material is ***bacteria*** and if you actually count the number of cells on average , you are 90% bacteria !Remember that prokaryotes are considerably smaller than eukaryotes .That's why we're talking on a cell number basis , not cell volume or weight .

- The other thing is that some trials are using Metronidazole to alter the bacteria in the gut , these trials were successful in maintaining remission in crohn's disease خففوا من المرض. So, that further confirms that there's something related to the composition of the bacteria in your intestine that will push you towards development of ulcerative colitis or crohn's disease (specifically we are talking about crohn's) .

>> So , if we put all of that together , you have bacteria in your gut , and some parts of bacterial broken down by-products can get passed your epithelium , they activate inappropriately dendritic cells (antigen-presenting cells in this case) and these antigen-presenting cells will stimulate CD4 T-cells and depending on which interleukins are produced , they will develop into the different TH1 , TH2 or TH17 . Depending also on if we are talking about crohn's disease or ulcerative colitis and that can also stimulate macrophages , &the cytokines can directly damage the epithelium , that can also stimulate neutrophils as well . Neutrophils can also directly damage the epithelium . So, now you have more epithelial defect >> More epithelial defect means that more bacterial products coming in , more activation ,and again you've started a vicious circle, a self-sustaining cycle حلقة مفرغة.

- There are differences between crohn's and ulcerative colitis other than where they happen and how deep they go .

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❖ Crohn's Disease :

- The most common sites for crohn's disease are the ***terminal ileum , iliocecal valve , and cecum .***
- Has skip lesions .

** The lesions don't necessarily have to be continuous , so there could be a lesion , then normal tissue , then another lesion elsewhere and so on .

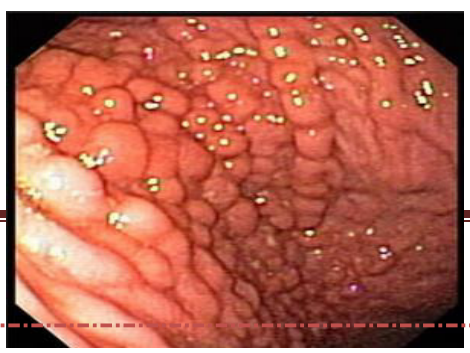
- Strictures التضيقاتare very common in crohn's disease . So , remember if you have an inflammatory condition , you could induce fibrosis , strictures ,and intestinal obstruction .
- Strictures can be surgically resected if they cause a major intestinal obstruction problem ;however, they very frequently recur at the site of the surgery .

-The cobblestone appearance occurs because the very first lesions which we call them " aphis ulcer or aphthous ulcer" , deep ulcer in the intestine, happen in different locations , but they eventually coalesce تلتئم to become these serpentine ulcers that go through the intestine .

>> That leaves areas of normal tissue around it .

** Cobblestone : stone bricks that are connected to each other by a cement substance , I mean there is a space between the bricks .

That is the cobblestone appearance seen in Crohn's disease, there are Serpentine Ulcers that move around normal pits of mucosal tissue .



Cobblestone

- Additionally , the wall is frequently thickened because we're talking about a fibrosing inflammatory reaction .
- Because the whole wall is involved , there are frequent fissures (very deep) , perforations (you go inside the whole layer) and fistula .

** **Fistula** : inappropriate connection of one part of the bowel to another part or from the GIT to other tracts like the urinary tract or to the genitourinary tract for e.g.

So, these are common in crohn's disease , not so much in **ulcerative colitis**

- Crohn's disease also stimulates serosal fat to surround the inflammatory area , this may be the last ditch effort trying to plug up holes, you don't know!! But this is what's called ***creeping fat*** .

You know that , around the intestines , you've got these epiploicae of fat (little fat sacs) and the fatter you are , the bigger they are . These in crohn's disease start migrating towards the inflammatory area and it looks like the fat is creeping along the wall of the intestine .

So , the thickening that happens is causing edema , inflammation , fibrosis , and sometimes hypertrophy of the muscularis propria as well .

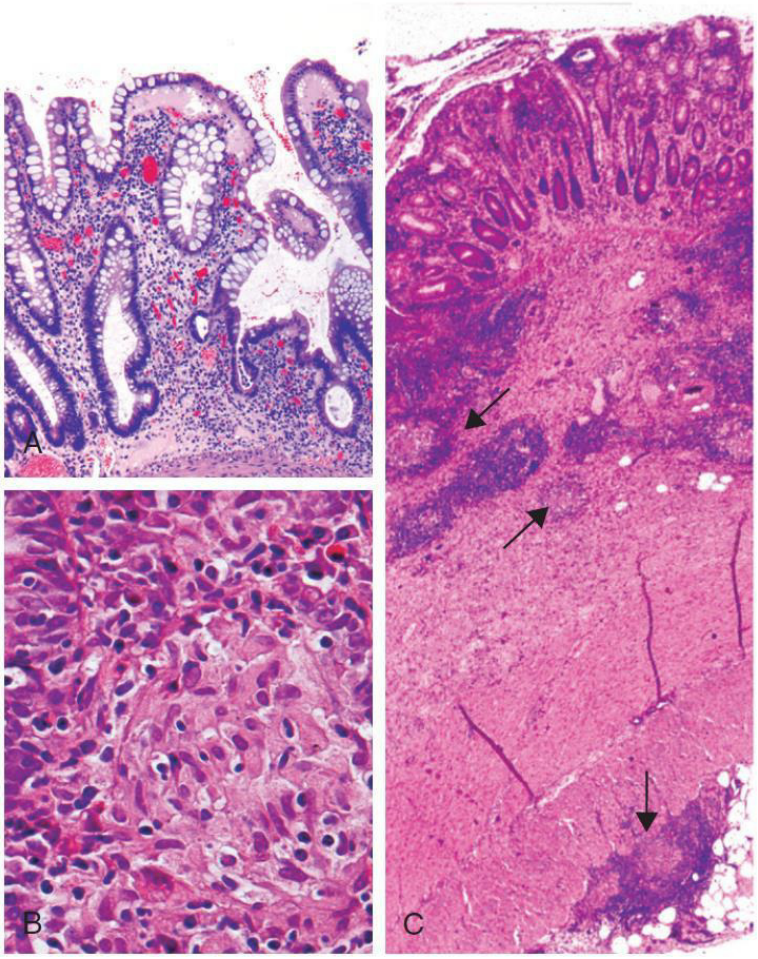
- **If the disease is extensive , that's when you get creeping fat**

In crohn's disease you will find abundant neutrophils and some of these neutrophils can concentrate at the bottom of the crypts and because that area could be easily closed off , that can create a crypt abscess ,destroying the crypt.

Now , your epithelial cells in the intestine are **labile tissues** which means in response to inflammation , they are going to regenerate, so they are trying to recreate that crypt >> this ends up with creating a very haphazard ,i.e. in every which direction architecture of crypts , these are definitely not normal looking crypts and you'll find lots of inflammatory cells infiltrate in the submucosa .

-You can see the abnormal crypt shapes and branching .
**crypt branching is abnormal , it's always one line from the top to the bottom ,when it starts branching , you know that there is an abnormal process .
- you can also find **non-caseating granulomas ,**
**These (noncaseating granulomas)are hallmarks of crohn's disease , if you find noncaseating granuloma , you are more likely dealing with crohn's disease than with ulcerative colitis .However , *the absence of non-caseating granulomas isn't a good negative predictive factor* ,so if they aren't there , it doesn't mean that it is not crohn's disease ,it could still be crohn's disease without non-caseating granulomas.

**just to remember , caseating granulomas occur it TB .



Cycles of destruction & regeneration lead to abnormal crypt shapes/branching (A) - Noncaseating granulomas are a hallmark of CD (B & C)

Clinical features of crohn's disease :

The *major thing* that you really need to worry about after inflammation , stricture formation ,& fistula formation ,is that you have all sorts of obstructions , perforations , peritonitis , and it may also involve extra-intestinal fistulas towards, for e.g, the urinary or genital system ,which means they are going to be bacteria where they shouldn't be , which means you can get also all sorts of infections because of these kinds of bacteria that could involve the bladder , vagina , even in the abdominal or perianal skin . so, the fistula actually opens to the outside .

-Colon if it's involved , you can get iron deficiency anemia and risk of adenocarcinoma .

- If the small intestine is involved , you're talking about malabsorption (protein , B12) .So, the general intestinal manifestations are very similar to malabsorption syndrome , and we've already mentioned perforations and peritoneal abscesses because you got whole wall involvement and frequent perforations .

-If there are *extra-intestinal* manifestations related to the immune component of the disease , for some reason , uveitis , pericholangitis and primary sclerosing cholangitis may occur .

-If the joints are involved : sacroiliitis , migratory polyarthritis , ankylosing spondylitis , erythema nodosum , and clubbing of the fingertips may be present .(look them up ☹)

The differential diagnosis of crohn's disease

AA : acute appendicitis ,and perforation (whenever you have perforations you should have this in the back of your mind , it could be a case of crohn's disease.)

-We do mention The extraintestinal manifestations because they sometimes can develop before the intestinal manifestations become apparent .So, if you have a patient with these extraintestinal manefistations ,you should always remember that there may be an intestinal component .

So if you have a patient with uveitis! التهاب القزحية , ask him about his bowel , it may be due to crohn's disease.

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❖ Ulcerative Colitis :

- Typically limited to the colon and rectum.

-If there is involvement of the whole colon, which is called pancolitis; in *severe cases of pancolitis the ileum might be involved in what is called* ***Backwash ileitis.***

-Unlike Crohn's disease, there are no skip lesions and there is a *very sharp demarcation between abnormal granular –appearing tissue to the normal mucosa.*

-So, there is *no cobblestone appearance*. It's very fine line you can see between normal and abnormal tissue. In Crohn's, it's not quite so clear cut line.

-The *ulcers rather than being deep* that can cause *fissures and perforations*, they are broad- based ulcers typically affecting the superficial layers, i.e mucosa and submucosa.

-You could have some *pseudopolyps*, i.e. they look like polyps but aren't really polyps, because like Crohn's disease,in ulcerative colitis you are destroying epithelial cells,your enterocytes, which are (the enterocytes) labile tissue which are going to regenerate. So, these enterocytes are actually islands of regeneration, they don't really have the cobblestone appearance, they look more like polyps, i.e these cells are trying to recreate the normal structure of the colon.

-If the disease has been going for a long time and you have exhausted your labile cells, you could end up with mucosal atrophy in a very flat-looking intestine and even the folds are gone.

**** Unlike Crohn's disease :**

1-There is no thickening

2-Serosal structure is normal.

3-Strictures don't occur.

4-There is almost NO fistula and there is no obstruction.

- However, if the *inflammation damages the muscularis propria* and disturbs the neuromuscular function and you lose peristalsis, what's going to happen?

There is going to be a dilatation in the colon and you could end up with toxic megacolon, which is different than the congenital Hirschsprung's disease although the presentation is very similar, but the *age group is very different*.

In this case (toxic megacolon) ,there is a significant risk and perforation.

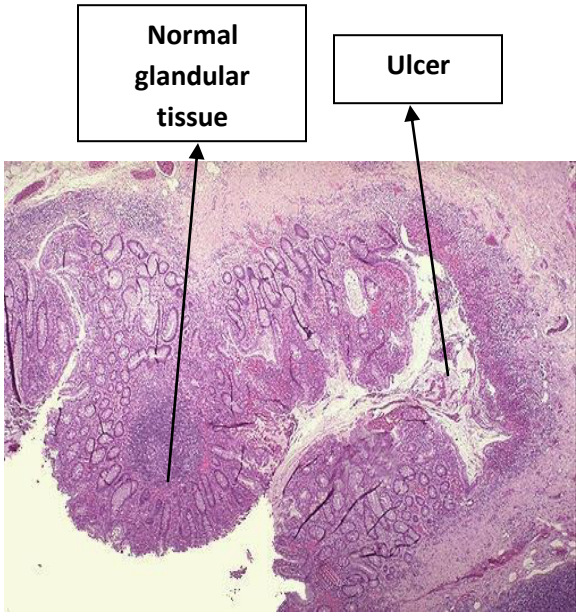
Now, perforation compared to Crohn's diease ,isn't because the ulcers are deep, but because *the peristalsis has stopped because you've damaged your muscles and the neuromuscular junctions.*

Histopathology of the ulcers :

-At the place of ulcer ,The glandular structure is gone; still you can see significant tissue underneath, so it is a **very shallow ulcer.**

-histology similar to CD,under the microscope.

Yes, the different is that granulomas aren't present. But as you know if granulomas aren't present, it doesn't mean that it's not crohn's disease .



The extra-intestinal manifestations of ulcerative colitis are very similar to CD.

-Actually, *pericholangitis and primary sclerosing cholangitis* are more common in UC than in CD.

Pericholangitis: inflammation in the wall of the gall bladder.

-Again, we are talking about immune complexes affecting the joints: sacroiliitis , spondylitis , peripheral arthritis and erythema nodosum.

Clinical features:

- Relapsing attacks of bloody diarrhea with stringy expulsion, i.e. typical diarrhea from inflammatory condition.

-The triggers for UC and CD aren't very well defined; however, there is one significant difference between them.

-For some reason, in **CD smoking is a trigger**, *but* **in UC cessation of smoking is a trigger**. So because of that, there were several trails thinking that may be nicotine has something to do with IBD, unfortunately they weren't successful.

-It seems ,and this is one of the very rare instances, that smoking protects you from UC.

Now, colectomy; this is an area where you can resect the colon.

-In CD, because its patching all over the place, you can actually take out the whole intestine, but if there is a severe disease that prompts a colostomy or if there is a risk of adenocarcinoma because you have found dysplasia in a certain part of the colon, especially if its multi-focal

dysplasia, that means the WHOLE COLON is at a higher risk for adenocarcinoma and that typically prompts a colostomy.
-the Colectomy will solve the intestinal manifestations, but it doesn't solve the extra-intestinal manifestations.

Major characteristics between ...

Crohn's disease	Ulcerative Colitis
• Skip lesions and cobblestone appearance	• Limited to the colon /rectum and it's all one continuous part of inflammation , i.e. there is no skipping
• The first ulcer : *aphthous ulcer then comes serpentine ulcers .* - very deep and they don't involve wide areas , that's why you get *cobblestone appearance* .	• They are more superficial and broad based ulcers .
• Its complications : Fissures , fistulas and perforation and this is because how deep these ulcers go .	• Its complications : Toxic megacolon and perforations from very different mechanisms because you've destroyed your ability to peristalsis .

• Strictures frequently occur.	• No thickening , no fibrosis , no hypertrophy of the muscles , and no Strictures .
• Can induce creeping fat .	
• Neutrophilic infiltrate/crypt abscesses are present in both , however, in ulcerative colitis they are considerably more superficial .	
• You can get metaplasia of the paneth cell type .	• Rarely get metaplasia , there you actually end with mucosal atrophy after chronic disease .
• The hallmark is non-caseating granuloma .	• The hallmark is regenerative mucosa that looks like pseudopolyps .
• Both are characterized by intermittent attacks of diarrhea , abdominal pain , cramping ,and sometimes bloody diarrhea .	
• Triggers are : stress , smoking And diet .	• Triggers are : Less defined but for some reason cessation of smoking is a frequent trigger .
• If there is a colon involvement , there is iron deficiency anemia .	• Potential blood loss anemia more likely to be from the colon .

• Malabsorption (Protein , B12, Bile salt) occurs more in crohn's disease than in ulcerative colitis . whatever malabsorption syndromes are, they can occur depending on where in the intestine the crohn's disease happens .	• Malabsorption is less of a problem .
• Extra GI fistulas .	• No fistulas .
• The extraintestinal manifestations are similar between both of them as you can resect of large area of the bowel in ulcerative colitis because it's not skipping .	
• Colectomy doesn't change these manifestations .	• We don't do colectomy .

Colitis associated neoplasia :

Inflammation >> free radicals >> which ends up with DNA damage and protein modification which ends up with >> oncogene activation or Tumor suppressor inactivation.

-These are not something magical, not something that one gets activated and the other inactivated; it's survival of the fittest.

-If you activate an oncogene, you give these cells a survival advantage over their neighbors. If you inactivate an oncogene, that's it! The cell goes away, i.e it will eventually die. The same argument for TS inactivation.

- Again, the time and severity of inflammation increase the risk, typically 8-10 years after IBD starts, if there is colon involvement, there is a marked increased risk of adenocarcinoma. So most patients who are diagnosed with IBD, are put on surveillance, they get frequent endoscopies and colonoscopies after 8-10 years of diagnosis (to catch cancer early on so there is a better treatment) with *one exception, Those with primary sclerosing cholangitis* on at a higher risk of getting colorectal-adenocarcinoma from DAY ONE, so they aren't given that 10 years period, they are generally put on surveillance at the time of diagnosis!!

-When do we worry about adenocarcinoma arising ?

When we have dysplasia.

The unique thing about dysplasia ,whether we are talking about CD or UC, is that if you find dysplasia *anywhere* in the colon, that means the whole colon is considerably at higher risk of adenocarcinoma which is why dysplasia, especially multi- focal dysplasia pompts colectomy, especially in UC.

Why I am giving you all this ? because when you become a physician , you may be involved in trails that are beyond the blanket of immune-suppressive therapy or immune-modulating therapy ,As the immune – suppressive therapy is pretty severe for this condition.

- Remember we mentioned that *excessive neutrophils increase the severity of the disease*. What makes them more damaging is that they have an enzyme that produces bleach which is **Myeloperoxidase**.

This is the Dr's research and YES it's not included in the exam.

Because Myloperoxidase and neutrophils are present more in severe diseases, an excess myeloperoxidase is also associated with a higher risk of adenocarcinoma , you can stratify patients on how many neutrophils and how much myeloperoxidase they have in their colon and the more sever patients who get on to have AC are these who have more myoperoxidase.

So, the hypothesis was :

-If you inhibit myoperoxidase, you can potentially treat the disease and prevent AC and this is the trial that is going to start at the cell therapy center, where we are going to inject stem cells that reduce myeloperoxidase activity and try to heal the intestine in IBD patients. Based on these pre-clinical data, these are mice which a model for IBD.*If you stimulate them to become inflamed by giving them a certain chemical, they develop tumors. If you inhibit myeloperoxidase for only one week, there is 50% drop in tumor just by one week .*

Now, when you become clinicians you may find that instead of just immune-suppression and immune modulation, you may find that myeloperoxidase inhibition is part of the therapy for IBD.

*please take in consideration that we inject these cells/drugs locally.

THE END !

Let your dreams be bigger than your fears and your actions louder than your words !

Best of luck ☺

-Special thanks to Reem Al-shiyab and Batool Awaysheh .

Dedication to : Yara Anasweh ;)