Pathology

● Sheet ○ Slide

number 6

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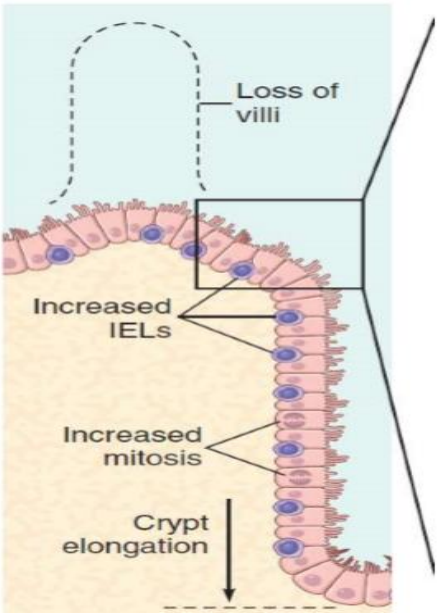
Malabsorption diseases

1- Celiac Disease

Also known as gluten-sensitive enteropathy (affecting 2 age groups), it's an abnormal response to a normal dietary staple.
* Gluten is present in wheat and similar grains, it's essentially our daily bread.

When you are sensitive to gluten you essentially have an inappropriate immune response to a basic dietary staple and this causes all sorts of problems in your intestine.
This immune response causes your villi to atrophy, we lose our surface area; moreover, we end up with signs and symptoms we mentioned in our previous lecture which are:



1- Diarrhea
2-Weight loss
3-Abdominal pain
4-Flatus

Even when we take a biopsy and examine it we will find a lot of **intraepithelial lymphocytes (IELs).** This is abnormal and because of all the inflammatory mediators, epithelial cells will start to proliferate in order to fix the damage.

Epithelial cells normally proliferate in order to replace the dying cells but if the proliferation rate is too high rather than differentiating, this means that the epithelial cells will not be able to normally absorb or digest other materials (causing additional malabsorption).

Our crypts will start to elongate trying to compensate for the lack of villi (the surface area never even gets close to what it used to be) and it's also a by-productive bacterial proliferation.
Because of the reduction in the surface area we will have malabsorption and anemia (Iron, B12, Folate deficiency).

Treatment: Gluten-free diets. (Disadvantages: Not very appetizing, not many people stick to them).

- We can find other consequences such as; cancer and lymphocytosis.

There are two age groups affected by gluten-sensitive enteropathy:

Group 1: Classical infantile age group

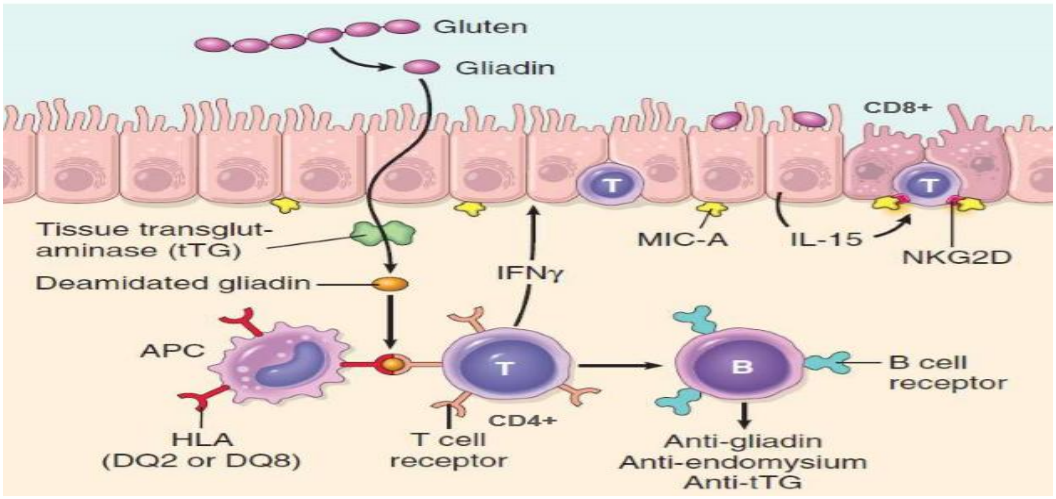
It occurs in infants when they start eating gluten in their diet.
Symptoms: fussy, will not be able to eat, abdominal pain and diarrhea, distended child.
* 10% of infants will have a rash that looks like a herpes infection called **dermatitis herpetiformis** which is a result of celiac disease so if we see this in a patient that is not eating well, feeling fussy, dropping below their percentiles for their age when it comes to their weight and height, then we should start thinking of celiac disease.
- Some patients do not present classically and can show off later on in life.

Group 2: (30-60 yr.) age group

It isn't fully understood how this disease happens to this age group, there are a lot of questions about it.
What we do understand about the molecular biology of celiac disease is that gluten is digested into non-digestible **Gliadin**.
Gliadin is then transported across the epithelium where tissue trans-glutaminase will deaminate it in the beginning process of digestion of Gliadin. However, some people have certain HLA (major histocompatibility proteins) **types: DQ2 or DQ8** present on antigen presenting cells, this deaminated gliadin inappropriately associates with them and those antigen presenting cells that have HLA molecules will stimulate T-cell response (CD4+ cells) which releases cytokines, stimulating B cells. Then these stimulated B cells will start producing anti-bodies against what they think is going wrong based on what's being presented, so we will end up with:

- anti-tissue transglutaminase antibodies (IgA (because we're talking about mucosal inflammation) or IgG)

- anti-deamidated gliadin antibodies
- anti-endomysial antibodies (**Dx**) (cross-reactivity)



***** Endomysium is the muscle sheath.

These 3 antibodies have nothing to do with pathogenesis of the disease. However, they are useful diagnostically.

Note: Sensitivity is "no false negative."

100% sensitive → you can catch all the diseased cases. However, sensitivity does not mean specificity (you may be causing a lot of false positive)

A specific test will only show those who are diseased and exclude those who are not diseased.

-Other definitions in Biostatistics are The Positive Predictive Value and The Negative Predictive Value

**The first 2 are sensitive (used for screening) the last one is highly specific (diagnostic).

(Mins 0:00-11:00)

- Interferons are among the cytokines that CD4 cells produce. Interferon gamma is not particularly friendly to the epithelial tissue. Epithelial cells become stressed, they start loosening their tight junctions which means more gliadin is coming in. Additionally, when they're stressed they start expressing **MIC-A** which is a stress protein and is recognized by a

receptor called **NKG2D** (we talked about it last semester in natural killer cells). Some T-cells also express NKG2D (MIC-A receptor) when the T-cells have been stimulated (under stress conditions) the epithelium will produce not only the MIC-A surface molecules but also **Interleukin 15** which stimulates CD8 T-cells.

So we'll end up with a **specific CD4 response that stimulates B-cells and produces Interferon gamma** and **a non-specific CD8 response (CD8 cells are cytotoxic directly to the epithelium)** more gliadin will come in so damage will occur. (Gliadin→Inflammation→Damage to the epithelium…and the cycle goes on).

-That's what's understood about celiac disease so far, a treatment has not been found yet but for now the only treatment for celiac disease is a Gluten-free diet.

-What does Celiac disease look like under the microscope?
A biopsy is taken from the second half of the duodenum or the proximal jejunum (that's where most of the gliadin is found). When observed under the microscope, **villi are missing** and the **crypts are hyper proliferative**. Also, when we look closely, a lot of **T-cells are interspersed between the epithelial cells.**

-How do we tell them apart? (epithelial cells from T-cells):
1-Shape (epithelial cells are typically elongated).
2-Nuclei; they are larger and less dense when it comes to chromatin in epithelial cells, whereas in T-cells they are more rounded and smaller and more densely stained.

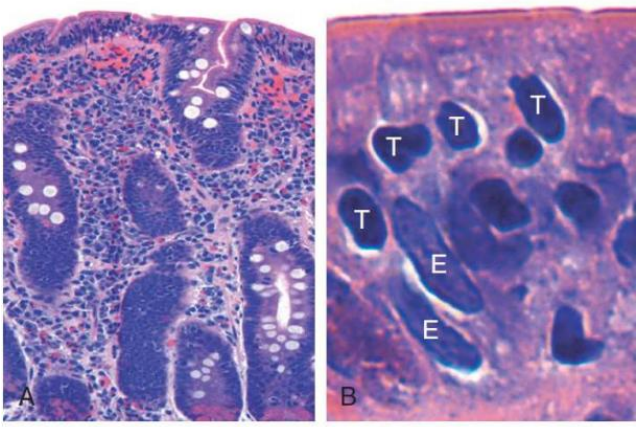
So, if you find increase in epithelial lymphocytes and villus atrophy and crypt hyperplasia along with the signs and symptoms of celiac disease you have a good diagnosis when you add serology to it (cannot be diagnosed without serology).
*Serology: examination of blood serum, especially with regard to the response of the immune system to pathogens or introduced substances

Non-specific Change + Serology → Specific diagnosis

-Some Patients have a biopsy taken for some other reason, they are non-symptomatic (same observations and some serological changes)→ these are called **Silent Celiac Disease Patients** (they have the same consequences as those with active symptomatic disease).

Latent→ those people don't have villus atrophy but they have the serology (positive serology).

It's not quite understood how the latent patients fare when it comes to long term, because it's hard to get them to go on a gluten free diet because no symptoms are showing and there are no immediate consequences.

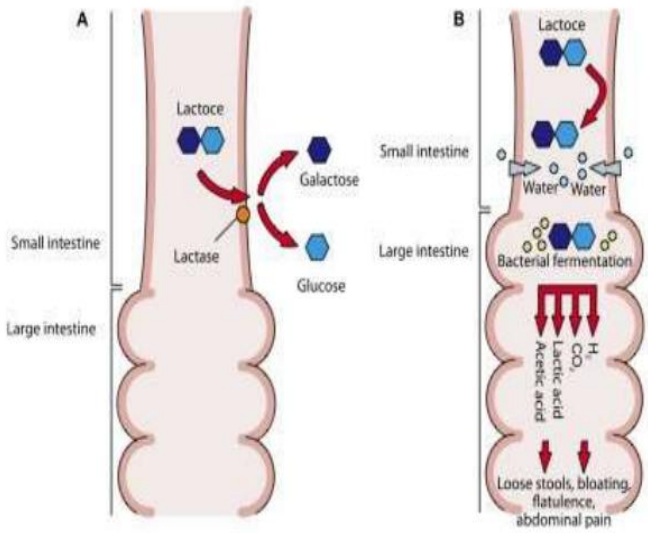


2- <u>Environmental Enteropathy:</u>

-It was previously known as "Tropical Sprue".
-Occurs in a lot of tropical and subtropical countries (mostly developing countries).
- The molecular mechanism is not fully understood, it is only known that children at 2-3 years of age have recurrent diarrhea and do not grow properly (stunted growth). We don't know if it's a bacterial pathogen or if it's an autoimmune response but we do know that by supplementing them with other food or vitamins and minerals does not fix it.
-Histology is very similar to celiac disease but it has nothing to do with gluten.
-So, this disease is identified by exclusion (all the other diseases that can be dealt with or treated are excluded, ending up with environmental enteropathy).
-Is mostly detected in: Gambia, South America, some parts of Mexico, Australia (aboriginals).

3- Lactase Deficiency

-There are two types of lactase deficiency:



1- **Congenital**:
It is autosomal recessive and presents at birth (first time breastfeeding), signs (such as diarrhea) are seen. In addition to all the problems that occur when milk is fermented rather than broken down by lactase.

2- **Acquired**:
This type is subdivided into two:

a- When there is a bacterial or viral infection causing Gastroenteritis and milk is consumed right after gastroenteritis has subsided, symptoms are back, not because of the bacteria or the virus but because lactase (which is on the apical brush border) is the first thing to go when the brush border has been destroyed by the bacterial or viral infection, therefore, the patient becomes temporarily lactose intolerant.

b- Natural Selection: Normal people are autosomal recessive to a specific locus (not the lactase locus but the one responsible for continuing to express lactase on the brush border). We, as a region in the Middle East, Europe and North America consume a lot of dairy products therefore natural selection over generations has given an advantage to people who consume lactose (it has pushed us all to be autosomal recessive). If you don't have both copies of the gene that allows you to continue producing lactose, then after 6 months of age you down-regulate lactase in your intestine therefore you become lactose intolerant (e.g. Africans, Chinese and Native Americans) . And that's the second type (being autosomal dominant instead of autosomal recessive).

Note: As you grow older, the ability to digest lactose decreases because the amount of lactase produced is decreased.

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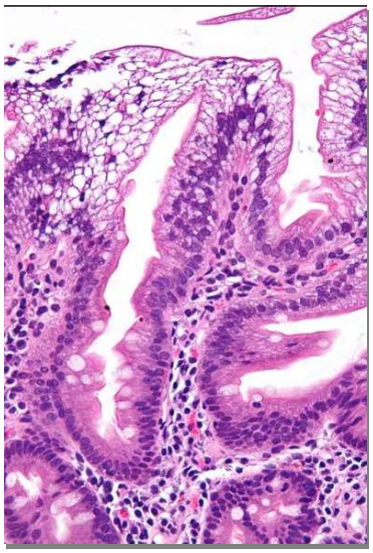
4- Abetalipoproteinemia



Which is autosomal recessive and rare. This is a trans-epithelial transport malabsorption disease. Your epithelial cells are able to take up the fats, the TAGs, the fatty acids and they are not able to re-export them down the lines so they end up accumulating in epithelial cells (fat vacuoles).

These patients don't have the ability to secrete triglyceride-rich lipoproteins into the lymphatics and they fail to thrive because they need fatty acids for the absorption of vitamins (K, A, D, E) (bleeding problems, vision problems, height problems, antioxidant problems respectively), they also have diarrhea and steatorrhea (fat in stools).

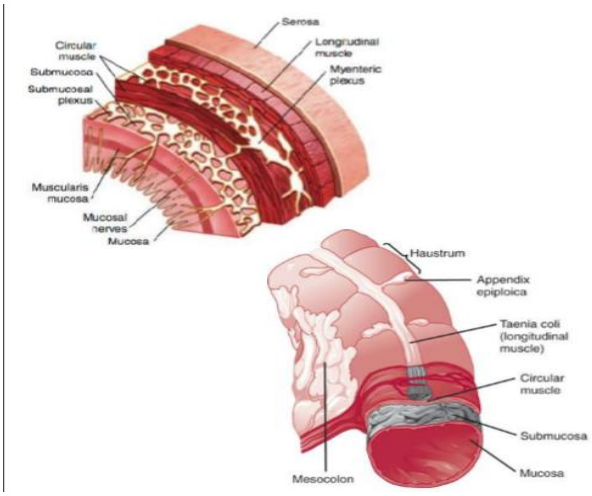
These were in the small intestines. Moving on to the large intestines:

1- Sigmoid Diverticulitis

- Results from elevated intraluminal pressure in the sigmoid colon.

- The **anatomy** of the small intestine and the large intestine:
Our small intestine has a circular muscle layer and a longitudinal muscle layer. Between these two layers we have nerve plexuses and we have blood vessels that will penetrate the circular muscle layer to the mucosa and come back out, so that means your circular muscle area frequently has areas of defects/weakness because you have to allow nerves and blood vessels to come in and out.

What reinforces the circular muscle layer is a longitudinal muscle layer that does not have any of these defects, so increasing pressure in the small intestine is not going to cause diverticula outpouchings in the small intestine. However, in the large intestine rather than having the longitudinal layer covering the whole the intestine it's gathered into three longitudinal fibers called the **Taenia Coli ,** which means any of these defects in the circular muscle layer could potentially allow outpouchings of mucosa and sub mucosa and -very rarely- also some muscularis which means this outpouching is weak and it has a narrow opening so this can cause a lot of problems such as; perforation which means peritonitis and inflammation and even if it hasn't ruptured, because of its small opening it can get infected and become diverticular outpouchings diverticulitis and inflammations ending up with fibrosis, strictures or obstructions.



- Signs and symptoms are rare.

We can give the patients antibiotics but that is rare also.

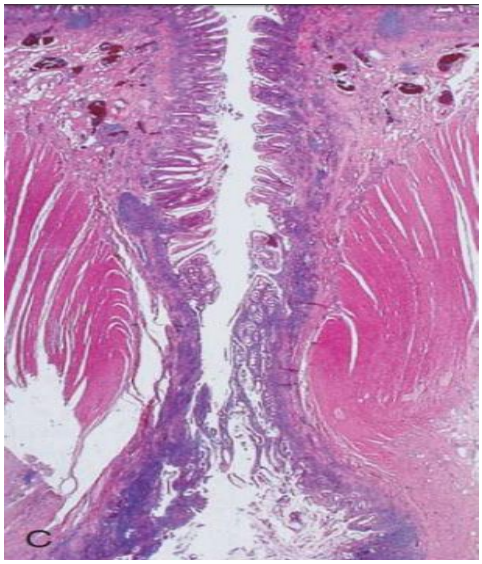
Increase in intraluminal pressure can be found in a patient who is on a low fiber diet; the peristalsis has to move fairly solid stools which means the pressure is going to increase. Western populations are mostly on a low fiber diet. Our populations is on a mixed diet (fiber and non-fiber diet). People who are on a non-fiber diet as they get older (elderly patients) they will then get these outpouchings.

Now to differentiate between **acquired diverticula** and **congenital diverticula:**

-Acquired diverticula for the most part involve generally two layers; mucosa and sub mucosa. It's very rare to reach the muscularis.

-Congenital diverticula involve all layers and they are much less likely to proliferate.

If we look at the diverticula under the microscope we can see the epithelium, the mucosa, the sub mucosa and the muscularis and then this outpouching down here to the muscularis stops there and only the mucosa and sub mucosa are remained (flask-shaped).



Mucosa and submucosa outpouchings (because of increased pressure):
- Flattened or atrophic mucosa
- Compressed submucosa
- Attenuated muscularis propria (often absent)

The diverticula have a regular distribution, and are most common in the sigmoid colon because of the high pressure as it makes the S shape, which means when you go through bends the pressure is increased and also because it's terminal.

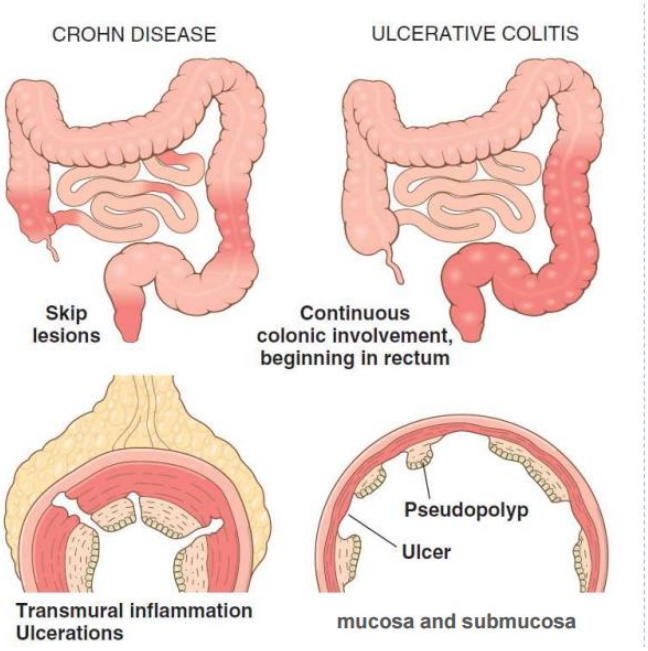
(Mins 23:00-32:00)

2- <u>Inflammatory Bowel Disease (IBD):</u>

-This disease is exactly as it sounds: it's an inflammation in the bowel. An inflammation in the bowel leads to so many different things depending on the region of inflammation.

-IBD is generally divided into two main types:

1) <u>Crohn Disease:</u> skip lesions (patching). It can involve both large intestine and small intestine. It's non-continuous. The inflammation causes fissures all the way through the three layers. It is a **transmural inflammation**.



2) <u>Ulcerative Colitis:</u>

-From its name, affects the colon. In severe cases, it can affect the entire colon and some of the ileum in what is called **"Backwash Ileitis".** For the most part, it does not affect the small intestine and rather than the transmural (in Crohn's disease), it is mostly mucosal and submucosal.

** Transmural inflammation ulcerations: fairly deep fissure, broad based ulcer, with hyper-proliferative regions between ulcers trying to compensate for the damage because of inflammation.
** Mucosa and submucosa: Pseudopolyps, because all around them are large ulcers.

-Generally, females are more affected than males, especially younger females.

-In the Western society and in our society, there is a noticeable increase in the incidence of IBD because of what is called '**<u>The Hygiene Hypothesis'</u>**. As you are growing up, you are not getting as much gastroenteritis as your parents and grandparents were when they were growing up. It turns out that allowing the kid to roam, putting all sorts of things in their mouth, is beneficial. It teaches your immune system what is pathogenic and what is not. If the immune system doesn't tell pathogens from non-pathogens, it could end up inappropriately reacting to a normal commensal bacterial component. This is just a hypothesis but it seems to be fairly valid as our food chain has gone more and more

sterile. Consequently, there is an increase in the incidence of IBD. A direct link has not yet been found that's why it is still called a hypothesis.

-Malabsorption is a problem that affects the small intestine more, so malabsorption will be seen more in Crohn's disease.

-There is an increase in malignant potential, i.e. more adenocarcinoma especially when the colon is involved. So, malignancy is more likely to occur in ulcerative colitis. There is also an increase in the possibility of malignancy in Crohn's disease when it affects the colon.

-The **pathogenesis** is not as simple as Celiac disease. It is not fully understood, but a few things can be done regarding the pathogenesis of IBD.
1-It is expected that there is an aberrant host interaction with normal intestinal microbiota.
2- There is an intestinal epithelial dysfunction allowing bits and pieces of the intestinal bacterial components to seep into the submucosa.
3- There is an aberrant mucosal immune response in reaction to the normal bits of bacteria that seep into the submucosa.

Immune response → Damage to the epithelium → more seeping of bacterial components

-**Treatment**: Immunosuppression Modulation (doesn't seem to work in Celiac disease but it does seem to work here).

Let's take a general look at what's happening:

- First, bacterial components that were not supposed to react will somehow activate dendritic cells (which are one of the antigen presenting cells). That activates T-cells; these CD4 T-cells will start releasing cytokines. These cytokines will then produce a variety of T-helper cells (T_h1, T_h2, and T_h17).

-T_h1 and T_h17 are associated with Crohn's disease, whereas T_h2 is associated with Ulcerative Colitis.

Some of these dendritic cells also produce **Interleukin 8**, which will stimulate neutrophils. Neutrophils produce free radicals causing all sorts

of damage (they have Myeloperoxidase which will produce bleach causing all sorts of indiscriminate damage).

Actually, neutrophils are the first cells to be seen in Inflammatory Bowel Disease.

A Fecal Calprotectin test is done to detect calprotectin in feces which is an indication of severe bowel disease. Moreover, it is a measure of how much myeloperoxidase is present. The higher the Fecal Calprotectin, the more likely it is for the patient to have cancer. So, there seems to be a big link between myeloperoxidase, neutrophil activity and cancer.

Then T-helper cells also stimulate macrophages and produce, among other things, Tumor Necrosis Factors (TNF). TNF will affect epithelial cells and tell them to loosen their connections therefore affecting the epithelial barrier, more bacterial components will come in, and therefore a vicious cycle will begin.

This is what generally happens. In more details:

Genetics:

-There is an increased risk with having an affected family member.

How can we differentiate between an environmental disease and a genetic disease?

-Identical twins: studies are done on identical twins.

→ If one gets the disease and the other doesn't, it's more likely that the disease is not genetic. And then we compare to non-identical twins. Let's say both identical twins got the disease, and then non-identical twins also got the disease. This tells us that the disease is environmental. Using that we can tell both types of diseases apart.

-So, using these concordance rates, Crohn's disease was found to be a much more genetically associated disease than ulcerative colitis (so ulcerative colitis may be more environmental, although there are some genetic components of ulcerative colitis, they're just not as consistent with the disease as they are with Crohn's Disease).

-For example, NOD2 binds to intracellular bacterial cell wall products (bits of the bacterial cell wall that have been engulfed in immune cells). And when there is a less effective polymorphism of NOD2, it doesn't bind as frequently. So, these bacterial cell wall products will then activate phagocytic cells, thereby starting the immune response. We have another couple of genes which are related to autophagy. When these genes are not effective, again, we are stimulating an immune response affecting the microbiota, and ending up with Crohn's disease. None of these genes have anything to do with ulcerative colitis.

Mucosal Immune Response:

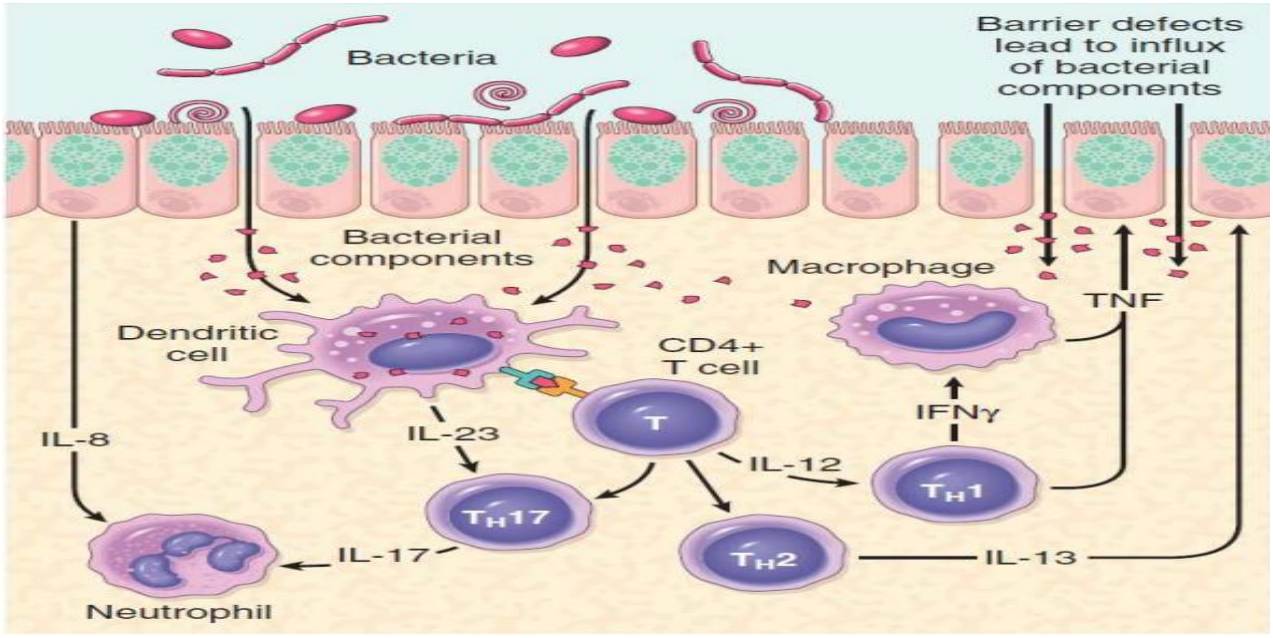
-Like we mentioned, T_h1 and T_h17 are associated with Crohn's disease. If there is a polymorphism in IL-23 receptor (does not respond to IL-23 as it should), this is protective for both: CD (Crohn's disease) and UC (Ulcerative Colitis), which means T_h17 and neutrophils.

* T_h17 → Crohn Disease

*Neutrophils → Both CD and UC

-T_h2 develops in an increase in IL-13 production, which is associated with UC.

-Polymorphisms of IL-10 (the major anti-inflammatory IL) and its receptor (IL-10R) are associated with UC. So, it's both stimulating and regulating the immune response that is affected in UC and CD.



Epithelial Defects

-You have a defect in intestinal epithelial tight junctions which is associated with Crohn's disease.

-If there were abnormal Paneth cell granules (these granules, when they are released, they affect your content of intestinal microbiota). So, if they are abnormal, this is associated with CD more than UC. These Paneth granules are antimicrobial.

Microbiota:

-If we take the **number** of cells in the entire body, our body is only 10% human. 90% of the cells in our body are bacteria. But, given that the bacteria are much smaller than eukaryotic cells, on a **mass** basis we are more human than bacteria.

-Given that you have 10^{12} bacteria/ml of feces (on average), that is a lot of bacteria to make sure that you don't react to. Intestinal bacterial flora (microbiota) are very different from one person to the next depending on environment and diet.
What you eat really affects your intestinal bacterial flora, which has a major effect on UC and CD.
*Metronidazole generally is not absorbed very well, mostly it affects intraluminal bacteria. It can be used to maintain remission of CD, but is not very effective for UC.

-CD patients get worse when they smoke. However, UC patients get better when they smoke. So even though the mechanism seems to be similar, they are 2 different diseases.

**Please refer to the figures in the slides for better understanding.

(Mins 32:00-47:39)

The End

Best of luck