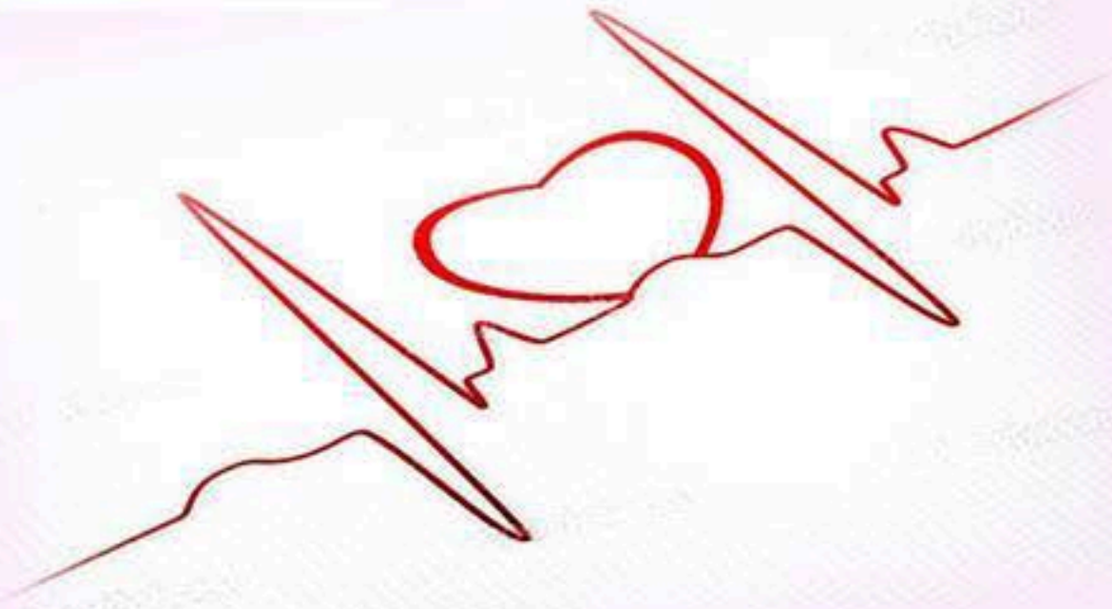
PATHOLOGY

Medical Committee
The University of Jordan

■ SHEET

□ SIIDE



Lecture Number: 1

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بسم الله نبدأ

Introduction to pathology

What is pathology?

*Pathology is **NOT** what a pathologist does!

*Pathology is the core of your medical education, and it's the link between basic scientific researches and clinical practice.

*Pathology provides scientific bases for your medical education and provides a clinical purpose to your scientific research

*So pathology is the study of diseases .

*A pathologist is someone who identifies diseases on tissues, cells and fluids extracting from the body.

>> To understand your clinical practice, you must understand the pathological bases of the disease, otherwise you will be following a flowchart as a monkey!!

Nomenclature

*Etiology: is why a disease is there. (the origin of the disease)

Etiology could be:-

-Genetic

^Hereditary: (born with it).

^Acquired: (genetic change during your life).

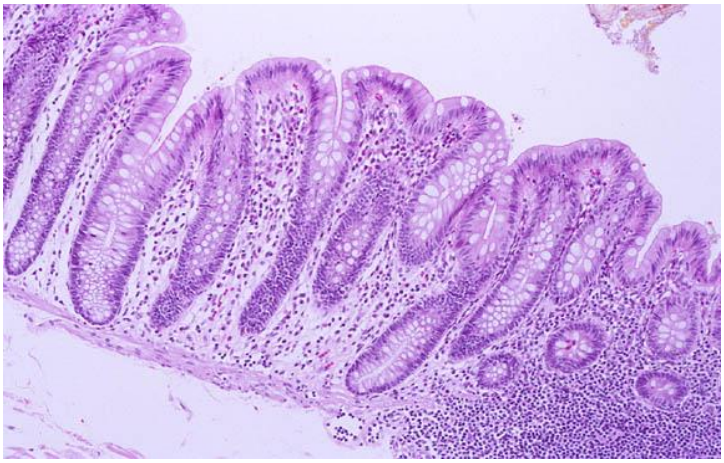
-so genetic doesn't necessarily mean inherited it could be Hereditary of acquired .

-Environmental

*Pathogenesis: is how a disease progresses from one stage to the next

-Pathogenesis covers molecular to cellular and organ physiology changes that lead to morphological and functional changes that you will know about in pathology insha'ALLA.

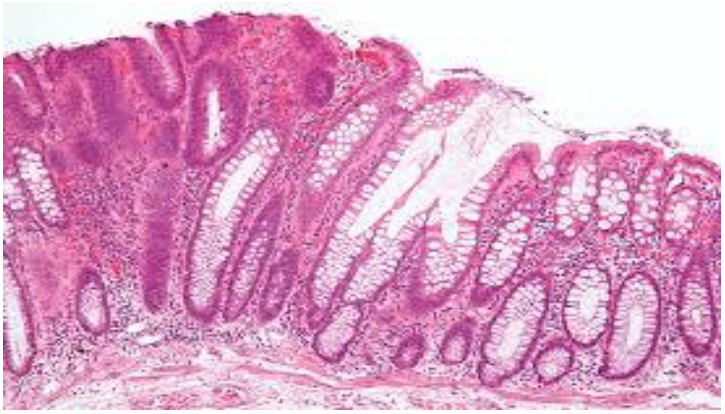
Example: we will talk about Adenoma- carcinoma pathway of cancer



As you can see in the slides this is typically how your colon looks like in histology

*Normal specimen (picture 1) shows nice basement membrane and crypts, within these crypts you have different types of cells,

Crypt (intestinal gland) :- it's a gland that is found in the epithelium lining the intestines and colon it contains a lot of cells including : globule cells , enterocytes ,paneth cells and stem cells



*Abnormal (picture 2) specimen shows basement membrane expand into the lumen, you can still see some crypts, some goblet cells (nice white emptiness)

So the sequence is :

etiology(could be hereditary or acquired)>> a genetic code mutation>> adenomatous polyps(abnormal growth of cells that grow in the lining of colon that has a high risk of becoming cancer)>> leads to lots of polyps and then become cancer .

so that sequence over here is pathogenesis and it's the process of cancer .

*In (picture 3) the morphology is completely destroyed, you rarely see any crypts and rarely see any mucus producing cells, NO goblet cells and crypts even divided into multiple branches which is not normal, and not sure if there is a basement membrane.

The disease progress from polyps to tumors (pathogenesis) and over the expression of some proteins like COX-2 and EGFR which are important in pathogenesis of polyps.

>> This underlying molecular changes cause morphological changes which leads to functional changes. This is the pathway of all diseases > Etiology + pathogenesis.

Morphological database

The grandfather of the modern pathology is Rudlof Virchow who built what is called the morphological pathway.

He try to built a morphological database for what disease and normal tissues look like through microscopes (and this required countless cases).

*So if you take a section from normal esophagus you can see nice smooth muscles in the bottom, basement membrane, some blood vessels, mostly cuboidal cells and cells that proliferate and transition into stratified squamous epithelium .

That is the vast majority of patients that do not have a disease of esophagus, that mean you look to so many patients to establish an abnormal specimen, this is knowledge taken by granted so he take so many cases to establish the database and what a normal esophagus looks like .

*Now if you take section from a patient who had a heartburn (abnormal esophagus) you can see the smooth muscles in the bottom and the basement membrane and you can see that there is more blood supply to get support to cells and the cells become more cuboidal, to get a better resistance to acids.

>> It's all about morphology, but morphology is not the whole story!

For example 2 morphological identical shapes may have very different underlying molecular causes.

>> Another important thing to know that the morphological database is useless without a history and clinical examination .

For example if 2 samples from 2 different parts of the body were gives to the pathologist and he had no knowledge from where they came from they will look very similar to him ..

What do we gain from looking at the morphology of the tissue?

1) Diagnosis

2) How deviated the tissue is from normal physiological tissue (**Grading**) -important for cancer-

3) How far along we are in the disease process, where we are in pathogenesis (**Staging**)

The difference between the grade and the stage in morphology :-

- the grade is how abnormal cell or tissue looks

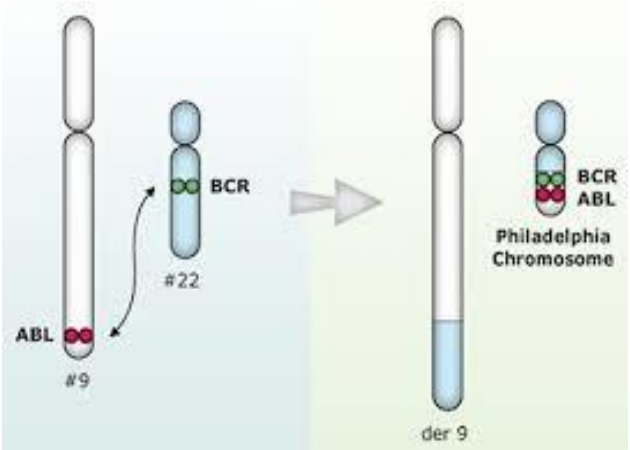
- the stage is how advance the disease is

*So if a cell normally looks cuboidal and nice nucleus and another cell lost its apical shape and you start seeing mitotic figures(cells undergo mitosis), that mean that the grade of these cell has move away, but a cancer with low grade means the cells still resemble their normal looks, but **high grade** means that tissue looks **very different** from the original architecture.

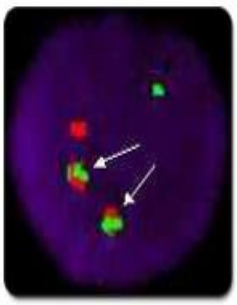
*Now stage of cancer, for example, stage1 is localized disease (there is a tumor, it maybe a lower or a higher grade tumor) but it's still in its original tissue, not invading other tissues. Stage2 means it's invading other tissue. Stage3 means it's go for the lymph nodes Stage4 means it's going to distal tissue away from original one.

Molecular databases

First molecular signs discovered by looking to chromosomes in certain types of Leukemia, it is the **Philadelphia Chromosome Translocation which is a specific chromosomal abnormality associated with leukemia as a result of that there will be a translocation between chromosome 22 and chromosome 9 this leads that 2 genes which are normally not next to each other to be near each other** (this leads to an over expression and molecular abnormality that leads to Leukemia)



This essentially the same thing this is called **fluorescence in situ hybridization**, a cleaner way, showing that you chromosome 9 and chromosome 22 are fused, this is a big mutation that you can see by microscope, **this is molecular diagnose knowledge not morphological**



Philadelphia positive cell showing translocation indicated by the green-orange fusion signals

We were talking about Big mutations BUT what happens if we talking about small mutation! we can't detect this mutation by the fluorescence in situ hybridization .

So for example, **APC** (a small region on chromosome # 5) which is a genetic code for adenomatous polyposis coli any mutation on APC gene leads to colorectal cancer ,

You will not see a morphological changes on colon in normal case you will seea nice and clean colon but if there is a mutation in APC gene it will lead to form hundreds of polyps that can develop into cancer and of this is form a point mutation .

Remember: from gene to protein we have transcription from DNA to mRNA) and translation from mRNA to protein)

So when we have DNA change to a form that can do a mutation of mRNA, from this mRNA we can read the protein.

A mutation can happen in a one nucleotide of DNA so that's mean that mRNA can be different and then the result protein will be different as well ,

Silent mutation is the change in one nucleotide lead to change in the codon but this codon represent the same amino acid that will result in translation so there is no change in the resulted protein .

But in the case of APC the point mutations are plenty, especially in patients that come with a family history of multiple polyps, the first thing that comes to mind is mutations in APC so we sequence the APC gene, meaning the diagnosis is no longer based on the morphology of the tissue it depends on a molecular basis .

Originally the how we do sequencing, we get primer(a strand of nucleic acids that serve as a starting point for DNA synthesis) and start sequencing and look for any changing in the normal sequence.

Micro Arrays is a faster way of detecting mutations and it could be DNA or RNA microarray .

Basically what you do is chip up a lot of pieces of DNA and put it on another chip that is either from a normal or abnormal sample and see if it can stick to the chip for sure if you have specific mutation on the chip then we will get complementing .

DNA complementing if you have a mutation or several mutations and you drain your mutation sample, cut up DNA and then add little florasic markers, if it hybridizes or if it binds to the piece of the DNA on the chip, that will tells us that the patient has a mutation, it's a much faster way to scan a lot of mutations or proteins.

*you better check Wikipedia on this point because we tried to explain what the doctor said and we couldn't understand anything *

So lets move into clinic, a lot of clinics are using micro arrays and sequencing to identify unique mutations in a long disease process.

What about m-RNA?

The amount of mRNA represent the amount of protein that will occur after translation the same way that we use DNA in microarray we can use RNA to look for protein over expressed by looking how much mRNA are produced, it takes time but it's faster than immune-chemistry or looking out sequence.

PCR is polymerize chain reaction (copying DNA)

reverse transcription PCR (copying mRNA) (reverse transcription from mRNA back to DNA)

*Same viruses do this, we also utilize this to see how much mRNA of particular gene is present in the cell as reverse transcription amplifies the production of mRNA in the cell .

We talked about pathogenesis of Adenoma-carcinoma pathway and how COX-2 is a part of the pathogenesis of colon cancer.

*Patients who have over expression of COX-2 move through Adenoma-carcinoma sequence faster. so when we look at PCR Or m-RNA microarray that has been hybridized among other m-RNA , the more hybridized COX-2 mRNA molecule has the worse prognosis.

Why do we need this?

Colon cancer patients are divided into 2 groups:-

Patients that over expresse COX-2 and patients that have low expression of COX-2 . So not only need to understand the molecular bases for diagnosis but it also needed for prognosis (how well this patients will do), so weather its disease free patient survival or overall survival patients who over express COX-2 are of a disadvantage to Cancer patients who do not. That also means that molecular bases of a disease can also give us a description of how to treat these patients .

There are clinical trials in colon cancer patients where they are inhibiting COX-2 to see if that helps improve their prognosis..

This was one example of how molecular bases of disease influence how you view and how you treat patients.

another example:

Alzheimer disease :degenerative neurological disease that has a symptoms that start from forgetting simple things to loss of self awareness , we know a lot of stuff about Alzheimer's because of the morphology on the nervous tissue specimen will Alzheimer (In this morphology you will notice black dots on the neuron caused from the deposition of protein aggregations) so you will have a lot of informations about diseases by knowing the morphology and molecular basis of the disease.

* I don't aspect you memorize every single pathway of molecular piece of machinery, but you should be aware of it specially when your patient does not response to a particular treatment.

A student asked the doctor about the microarrays again and he answered :
This is the surface of your ship, and you attached to it a piece of DNA and you bring a sample with multiple pieces of DNA Some complementary some no , one of them is going to hybridized, before we do this we will add a thoracic marker to each piece of DNA and RNA , then we wash it, the we put it under.....A machine which read the results .

If there is hybridization(molecular mutation) We have 2 chips, we add a normal sample to one and a disease sample to another. For example we are talking about mRNA and there will a certain amount of hybridization in a normal sample, on the disease chip there maybe increase hybridization or no hybridization, If we use a green dye to one sample and red to another so when we put the two chips , if green appear that means the is no hybridization, no expression but if it's appear red so it's a disease sample, lots of hybridization , has high expression,, yellow or thing in between that.....

قال عليه الصلاة والسلام:

(من سلك طريقا يلتمس به علما سهل الله له به طريقا الى الجنة) :)

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