PATHOLOGY

◉ Sheets ○ Slides

Number: 1

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Subject: Introduction

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In this sheet I will explain every single point discussed in the lecture. Don't memorize the examples, the doctor mentioned them for a better understanding.

The required book is – **"Robbins Basic Pathology"** – 9th Edition

Exam questions will be very precise and they will come from the book.

The doctor's academic website – his slides, office hours, and announcements – will be found here: eacademic.ju.edu.jo/m.alsalihi

 10:00

What is "Pathology"?

The study of medical diseases. Pathology is the trunk of the tree of medicine. It connects the basic science of medicine to the clinical practise. Clinicians and research scientists will use pathology in their study or treatment. So Pathology is not limited to what a pathologist does.

You need to understand the diseases that you are treating and as a research scientist needs to study and understand the diseases that you're trying to find an answer for.

Now there are a couple of things we need to define and understand that will help us in the upcoming lectures.

(1) **Etiology:** Basically it is the cause of the disease. "Why" did this disease arise?

For example: Type 1 diabetes is caused due to beta cells of the pancreas stopping the production of insulin.
What is the etiology of Type 1 diabetes? We ask ourselves "Why do those cells stop producing insulin"? There may be more than one etiology [hereditary or antibodies attacking B-cells. Etc.]
The treatment for any disease is based on the etiology of it.

(2) **Pathogenesis:** Molecular Changes → Cellular Changes → Physiological Changes in the cell.
So it is basically the "how" the disease developed.
We used to detect and study the cellular and physiological changes but now we are in the era of molecular medicine so we look at the

molecular changes too, as example two tissue samples may look alike but molecularly they are different and therefore the treatment will be different.

We will be looking at the morphological (structural) and functional changes that lead to the disease.

Etiology may be genetic or environmental, note that genetic may be acquired or inherited, as example radiation causes genetic mutations which cause diseases.

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- Note that a one disease may develop from different causes, also a disease may develop in different ways.

If you understand the molecular mechanism of a disease you will be able to treat more than one disease separate from the disease symptoms itself, ex a polymorphism in the nicotinic receptors may cause several diseases to the lung, heart, etc.(you don't have to memorise examples right now will talk about them later).

We have a tissue that we want to study and carry experiments on; but first how do we decide that this is a normal tissue?

We sample hundreds of one thousand (majority) then we compare the samples to come out with "how the normal tissue looks".

Morphological Knowledge Database – Multiple samples from regular and diseased patients will be tested for the purpose of understanding the morphological changes that occur due to a certain disease.

Let's take an example regarding the esophagus. A normal person has an esophagus that contains simple stratified squamous epithelium.

On the other hand the majority of patients that have "heart burn" have an esophagus that is made up of simple stratified cuboidal epithelium. This is what we call an adaptive cellular process.

Heart Burn causes the acid to reflux from the stomach into the esophagus, which is a long-going and untreated pathway. There will be a different mechanism that will change the epithelium from one type to another [a

more acid resistive type]. This will cause intestinal metaplasia, a change in phenotype of differentiated cells.

The differentiated cells in our example are the bottom cells ,that are responsible for regenerating the upper layer, have changed the differentiation pathway from cuboidal cells into other cuboidal cells or columnar but not squamous[since they are not acid resistant]

- A history of the clinical examination for the diseased tissue must be given to a pathologist to give a precise diagnosis, otherwise he will give different diagnosis.

So Along with a thorough history and clinical examination a pathological examination will result in:

1- Precise diagnosis.

2- Degree of deviation from the physiological norm (grading).

3-How far along we are in the disease process (staging)

Let's talk about the stages in the esophagus example [Heart Burn].

If we have a sample of esophagus but the epithelium is still squamous, this is called the early stage.

When the esophagus changed into cuboidal shape, this will be called the mid stage.

As the disease moves on we start getting more metaplasia, this will lead to mutations then will lead to esophageal cancer. In here we reached the late [advanced] stage.

- In here we can deduce the stage of the disease by taking a sample from a diseased patient. We can also get the prognosis [prediction] of the disease.

  The prognosis will depend on both the disease and the treatment available.

 30:00

Molecular Knowledge Database – Depending on the karyotype [number and appearance (structure) of the chromosomes of a cell]. Caused by mutations that we can see on a karyotype.

Example: Translocation Mutation in which genetic material can be exchanged between chromosomes leading to production of new genes, as example a translocation between chromosomes pairs number 9 and 22 result in production of fusion proteins (these proteins weren't there before).

Such translocations can be detected by molecular probe that has fluorescent markers on them (as example the normal case will show a 2 red dots for pair 9 and 2 green dots for pair 22,but as the result of the translocation you will notice more red and green dots).

When we understand the molecular basis of the disease, we will simply know its molecular etiology. Knowing its etiology will help us produce a drug that specifically targets those fusion proteins and therefore treating the patients (karyotype doesn't tell us everything so we have to understand and study the molecular basis) (karyotype still looks at morphology).

Some mutations are small (mutations at the level of one gene) those cannot be detected by fluorescent probe.

As example of such mutations, the one that's affect the APC gene (small region on chromosome #5).

In the normal case you will see a nice and clean colon but if there is a hundreds of polyps you should suspect that there is a mutation in the APC gene especially if there is a family history with colon cancer.

As we mentioned such mutation will not be detected in a karyotype so we will have to sequence that gene, as sequencing is expensive a new technique is being used these days which is called "Micro arrays".

The procedure of "microarray" is simple: on a chip we put hundreds of DNA pieces that have APC (as example) mutations, then we

harvest a DNA from the patient, chop it and add fluorescent markers, if the patient has an APC mutation, his DNA will hybridizes (binds) to the DNA pieces on the chip and as a result the fluorescent markers will produce colours, (if the patient has no APC mutation=no binding=all of his DNA will wash away).

PS: refer to YouTube for further explanation about Microarray.
What if the promotor of a gene got mutated where it is no longer active, the result will be that the protein which correspond to that gene won't be synthesised.

- Promotor is a region of DNA that initiates transcription of a particular gene.

Another way of detecting whether there is more of protein or less of it to look at the amount of mRNA inside the cell which represents the amount of protein that will occur after translation.

Reverse transcription PCR: is reverse transcribe from mRNA back to DNA. (Called complementary DNA "cDNA").

- **PCR**: polymerize chain reaction
- A reverse transcriptase (RT) associated with retroviruses accomplish this process.
- After we get the cDNA we amplify it then apply it to the microarray then harvest mRNA from the patient, add markers.
- This will tell us if there is over expression of the proteins or under expression.
- This procedure is followed to diagnose lots of diseases.

Two samples may look morphologically alike but when we look at and detect certain protein we will find differences, as example we probe both of these sample with an antibody which can detect COX-2 and the results showed that even if they morphologically similar but molecularly they may be very different from each other therefore the treatment will be different.

40:00

Lots of leukaemia tissue samples looks similar under the microscope. But for each different type of leukaemia, a different type of antibody will be produced to inhibit the formation of fusion proteins.

- So understanding the molecular base of a disease gives you diagnosis and prognosis and treatment function.

- Before figuring out these fusion products (in the case of leukaemia), they were considered as poor prognosis patients. But after the treatment has been found (i.e. antibody) they've been considered as good prognosis patients.
- Prognosis: your prediction of "how well" or "how poorly" the patient will do, based on the disease and available treatments.

As example Colon cancer patients are divided into 2 groups Patients who over expressed COX-2 and patients who have low expression of COX-2, at the survival curves patients who have low expression of COX-2 showed a better "disease free" and "overall" survival rate, That means that molecular bases of a disease can also give us A description of how to treat these patients

The molecular pathogenesis will also determine whether the drug we have can treat multiple diseases or not.

50:00

Good Luck☺