GENERAL PATHOLOGY / 3rd

INTRODUCTION TO PATHOLOGY Assist Prof. Mustafa Gheni

The ultimate goal of pathology is the identification of the cause of diseases (etiology) and its effects that can eventuate in disease prevention and/or successful therapy.

I. Learning Objectives

1. Define pathology
2. Discuss the core aspects of disease in pathology
3. Know the diagnostic techniques used in pathology
4. Know the various categories of the causes of diseases
5. Know the course, outcome, consequences of diseases

II. The core aspects of diseases in pathology

Pathology is the study of disease by scientific methods. The word pathology came from the Latin words “patho” & “logy”. ‘Patho’ means disease and ‘logy’ means study, therefore pathology is a scientific study of disease. Diseases may, in turn, be defined as an abnormal variation in structure or function of any part of the body. Pathology gives explanations of a disease by studying the following four aspects of the disease.

1. Etiology,
2. Pathogenesis
3. Morphologic changes and
4. Functional derangements and clinical significance.

1. Etiology

Etiology of a disease means the cause of the disease. If the cause of a disease is known, it is called primary etiology. If the cause of the disease is unknown, it is called idiopathic. Knowledge or discovery of the primary cause remains the backbone on which a diagnosis can be made, a disease understood, & a treatment developed. There are two major classes of etiologic factors: genetic and acquired (infectious, nutritional, chemical, physical, etc). Detailed

discussion will be given in subsequent topics. The etiology is followed by pathogenesis.

2. Pathogenesis

Pathogenesis means the mechanism through which the cause operates to produce the pathological and clinical manifestations. The pathogenetic mechanisms could take place in the latent or incubation period. Pathogenesis leads to morphologic changes.

3. Morphologic changes

The morphologic changes refer to the structural alterations in cells or tissues that occur following the pathogenetic mechanisms. The structural changes in the organ can be seen with the naked eye or they may only be seen under the microscope. Those changes that can be seen with the naked eye are called gross morphologic changes & those that are seen under the microscope are called microscopic changes. Both the gross & the microscopic morphologic changes may only be seen in that disease, i.e. they may be specific to that disease. Therefore, such morphologic changes can be used by the pathologist to identify (i.e. to diagnose) the disease. In addition, the morphologic changes will lead to functional alteration & to the clinical signs & symptoms of the disease.

4. Functional derangements and clinical significance

The morphologic changes in the organ influence the normal function of the organ. By doing so, they determine the clinical features (symptoms and signs), course, and prognosis of the disease.

In summary, pathology studies: -

Etiology ➔ Pathogenesis ➔ Morphologic changes ➔ Clinical features & Prognosis of all diseases.

Understanding of the above core aspects of disease (i.e. understanding pathology) will help one to understand how the clinical features of different diseases occur & how their treatments work. This understanding will, in turn, enable health care workers to handle & help their patients in a better & scientific way. It is for these reasons that the health science student should study pathology. In addition, the pathologist can use the morphologic changes seen in diseases to diagnose different diseases. There are different diagnostic modalities used in pathology. Most of these diagnostic techniques are based on morphologic changes.

III. Diagnostic techniques used in pathology

The pathologist uses the following techniques to the diagnose diseases:

1. Histopathology
2. Cytopathology
3. Hematopathology
4. Immunohistochemistry
5. Microbiological examination
6. Biochemical examination
7. Cytogenetics
8. Molecular techniques
9. Autopsy

A. **Histopathological techniques** Histopathological examination studies tissues under the microscope. During this study, the pathologist looks for abnormal structures in the tissue.

Tissues for histopathological examination are obtained by biopsy. Biopsy is a tissue sample from a living person to identify the disease. Biopsy can be either incisional or excisional.

Once the tissue is removed from the patient, it has to be immediately fixed by putting it into adequate amount of 10% Formaldehyde (10% formalin) before sending it to the pathologist. The purpose of fixation is:

1. to prevent autolysis and bacterial decomposition and putrefaction
2. to coagulate the tissue to prevent loss of easily diffusible substances
3. to fortify the tissue against the deleterious effects of the various stages in the preparation of sections and tissue processing.
4. to leave the tissues in a condition which facilitates differential staining with dyes and other reagents.

Once the tissue arrives at the pathology department, the pathologist will exam it macroscopically (i.e. naked-eye examination of tissues).

Then the tissue is processed to make it ready for microscopic examination. The whole purpose of the tissue processing is to prepare a very thin tissue (i.e. five to seven µm or one cell thick tissue) which can be clearly seen under the microscope. The tissue is processed by putting it into different chemicals. It is then impregnated (embedded) in paraffin, sectioned (cut) into thin slices, & is finally stained. The stains can be Hematoxylin/Eosin stain or special stains such as PAS, Immunohistochemistry, etc... The Hematoxylin/Eosin stain is usually abbreviated as H&E stain. The H&E stain is routinely used. It gives the nucleus a blue color & the cytoplasm & the extracellular matrix a pinkish color. Then the pathologist will look for abnormal structures in the tissue. And based on this abnormal morphology he/she will make the diagnosis. Histopathology is usually the gold standard for pathologic diagnosis.

B. Cytopathologic techniques

Cytopathology is the study of cells from various body sites to determine the cause or nature of disease.

Applications of cytopathology:

The main applications of cytology include the following:

1. Screening for the early detection of asymptomatic cancer For example, the examination of scrapings from cervix for early detection and prevention of cervical cancer.

2. Diagnosis of symptomatic cancer Cytopathology may be used alone or in conjunction with other modalities to diagnose tumors revealed by physical or radiological examinations.

It can be used in the diagnosis of cysts, inflammatory conditions and infections of various organs.

3. Surveillance of patients treated for cancer For some types of cancers, cytology is the most feasible method of surveillance to detect recurrence. The best example is periodic urine cytology to monitor the recurrence of cancer of the urinary tract.

Advantages of cytologic examination

Compared to histopathologic technique it is cheap, takes less time and needs no anesthesia to take specimens. Therefore, it is appropriate for developing countries with limited resources like Ethiopia. In addition, it is complementary to histopathological examination.

Cytopathologic methods

There are different cytopathologic methods including:

1. Fine-needle aspiration cytology (FNAC)

In FNAC, cells are obtained by aspirating the diseased organ using a very thin needle under negative pressure. Virtually any organ or tissue can be sampled by fine-needle aspiration. The aspirated cells are then stained & are studied under the microscope. Superficial organs (e.g. thyroid, breast, lymph nodes, skin and soft tissues) can be easily aspirated. Deep organs, such as the lung, mediastinum, liver, pancreas, kidney, adrenal gland, and retroperitoneum are aspirated with guidance by fluoroscopy, ultrasound or CT scan. FNAC is cheap, fast, & accurate in diagnosing many diseases.

2. Exfoliative cytology

Refers to the examination of cells that are shed spontaneously into body fluids or secretions. Examples include sputum, cerebrospinal fluid, urine, effusions in body cavities (pleura, pericardium, peritoneum), nipple discharge and vaginal discharge.

3. Abrasive cytology

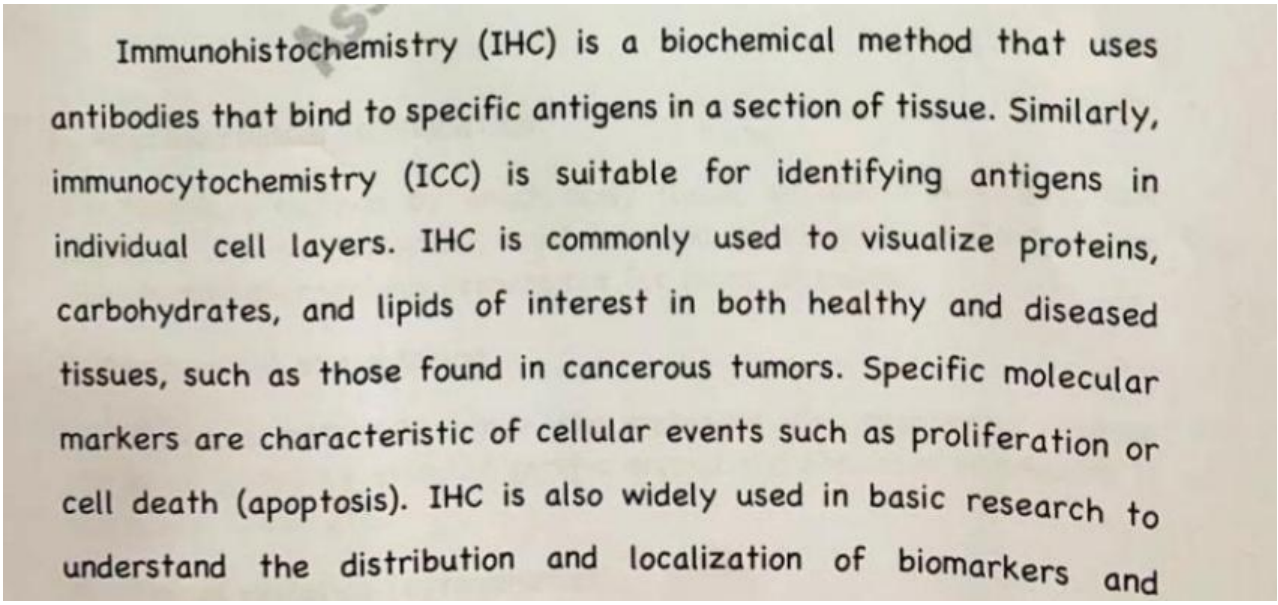
Refers to methods by which cells are dislodged by various tools from body surfaces (skin, mucous membranes, and serous membranes). E.g. preparation of cervical smears with a spatula or a small brush to detect cancer of the uterine cervix at early stages. Such cervical smears, also called Pap smears, can significantly reduce the mortality from cervical cancer. Cervical cancer is the most common cancer in Ethiopian women.

C. Hematological examination

This is a method by which abnormalities of the cells of the blood and their precursors in the bone marrow are investigated to diagnose the different kinds of anemia & leukemia.

D. Immunohistochemistry

This is a method is used to detect a specific antigen in the tissue in order to identify the type of disease.



Immunohistochemistry (IHC) is a biochemical method that uses antibodies that bind to specific antigens in a section of tissue. Similarly, immunocytochemistry (ICC) is suitable for identifying antigens in individual cell layers. IHC is commonly used to visualize proteins, carbohydrates, and lipids of interest in both healthy and diseased tissues, such as those found in cancerous tumors. Specific molecular markers are characteristic of cellular events such as proliferation or cell death (apoptosis). IHC is also widely used in basic research to understand the distribution and localization of biomarkers and

differentially expressed proteins in different parts of biological tissue.

IHC STAINING AND DETECTION

Following tissue preparation and antigen retrieval pretreatment, visualizing the antibody-antigen interaction can be accomplished in a number of ways. One common method uses a primary antibody that is conjugated to an enzyme, such as horseradish peroxidase or alkaline phosphatase, that catalyzes a color-producing reaction. Alternatively, the immunofluorescence (IF) method uses an antibody that is tagged to a fluorophore, such as fluorescein, rhodamine, or Alexa Fluor. Another option is to use an unlabeled primary antibody, with indirect antigen detection by a labeled secondary antibody or more complex detection systems. In this case, the optimal titer of both the primary and secondary antibody should be determined for each assay

E. Microbiological examination

This is a method by which body fluids, excised tissue, etc. are examined by microscopical, cultural and serological techniques to identify micro-organisms responsible for many diseases.

F. Biochemical examination

This is a method by which the metabolic disturbances of disease are investigated by assay of various normal and abnormal compounds in the blood, urine, etc.

G. Clinical genetics (cytogenetics),

This is a method in which inherited chromosomal abnormalities in

the germ cells or acquired chromosomal abnormalities in somatic cells are investigated using the techniques of molecular biology.

H. Molecular techniques

Different molecular techniques such as fluorescent in situ hybridization, Southern blot, etc... can be used to detect genetic diseases.

I. Autopsy

Autopsy is examination of the dead body to identify the cause of death. This can be for forensic or clinical purposes.

the relative importance of each of the above disciplines to our understanding of disease varies for different types of diseases. For example, in diabetes mellitus, biochemical investigation provides the best means of diagnosis and is of greatest value in the control of the disease. Whereas in the diagnosis of tumors, FNAC & histopathology contribute much. However, for most diseases, diagnosis is based on a combination of pathological investigations.

IV. The causes of disease

Diseases can be caused by either environmental factors, genetic factors or a combination of the two.

A. Environmental factors

Environmental causes of disease are many and are classified into:

1. Physical agents 2. Chemicals 3. Nutritional deficiencies & excesses 4. Infections & infestations 5. Immunological factors 6. Psychogenic factors

1. Physical agents These include trauma, radiation, extremes of temperature, and electric power. These agents apply excess physical energy, in any form, to the body.

2. Chemicals With the use of an ever-increasing number of chemical agents such as drugs, in industrial processes, and at home, chemically induced injury has become very common. Their effects vary:

- Some act in a general manner, for example cyanide is toxic to all cells.
- Others act locally at the site of application, for example strong acids and caustics.

- Another group exhibit a predilection for certain organs, for example – the effect of paracetamol and alcohol on liver. Many toxic chemicals are metabolized in liver and excreted in kidney, as a result, these organs are susceptible to chemical injury.

3. Nutritional deficiencies and excesses Nutritional deficiencies may arise as a result of poor supply, interference with absorption, inefficient transport within the body, or defective utilization. It may take the form of deficiency either of major classes of food, usually protein and energy, or vitamins or elements essential for specific metabolic processes, e.g. iron for haemoglobin production. Often, the deficiencies are multiple and complex.

On the other hand, dietary excess plays an important role in diseases in Western countries. Obesity has become increasingly common, with its attendant dangers of type 2 diabetes, high blood pressure and heart disease.

4. Infections and infestations Viruses, bacteria, fungi, protozoa, and metazoa all cause diseases. They may do so by causing cell destruction directly as in virus infections (for example poliomyelitis) or protozoal infections (for example malaria). However, in others the damage is done by toxins elaborated by the infecting agent as in diphtheria and tetanus. Like chemicals, they may have a general effect or they may show a predilection for certain tissues.

5. Immunological factors The immune process is essential for protection against micro-organisms and parasites. However, the immune system can be abnormal which can lead to diseases. The abnormalities of the immune system include:

- Hypersensitivity reaction This is exaggerated immune response to an antigen. For example, bronchial asthma can occur due to exaggerated immune response to the harmless pollen.

- Immunodeficiency This is due to deficiency of a component of the immune system which leads to increased susceptibility to different diseases. An example is AIDS.
- Autoimmunity This is an abnormal (exaggerated) immune reaction against the self antigens of the host. Therefore, autoimmunity is a hypersensitivity reaction against the self antigens. For example, type 1 diabetes mellitus is caused by autoimmune destruction of the beta cells of the islets of Langerhans of the pancreas

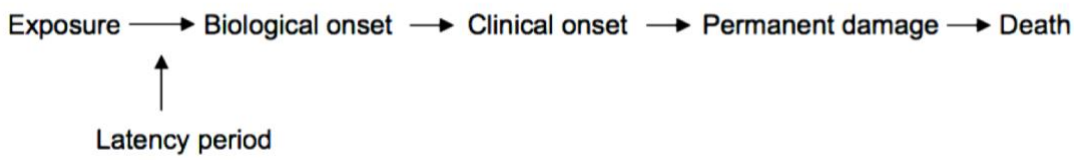
6. Psychogenic factors The mental stresses imposed by conditions of life, particularly in technologically advanced communities, are probably contributory factors in some groups of diseases.

B. Genetic Factors

These are hereditary factors that are inherited genetically from parents. Detailed discussion will be done on this topic in a subsequent chapter.

V. Course of disease

The course of disease is shown with a simplified diagram as follows.



The course of a disease in the absence of any intervention is called the natural history of the disease. The different stages in the natural history of disease include:

a) Exposure to various risk factors (causative agents)

b) Latency, period between exposure and biological onset of disease

c) Biological onset of disease; this marks the initiation of the disease process, however, without any sign or symptom. Following biological onset of disease, it may remain asymptomatic or subclinical (i.e. without any clinical manifestations), or may lead to overt clinical disease.

d) Incubation (induction) period refers to variable period of time without any obvious signs or symptoms from the time of exposure.

e) The clinical onset of the disease, when the signs and symptoms of the disease become apparent. The expression of the disease may be variable in severity or in terms of range of manifestations. f) The onset of permanent damage, and

g) Death

Natural recovery, i.e. recovery without any intervention, can occur at any stage in the progression of the disease.

VI. Outcome and consequences of disease

Following clinical onset, disease may follow any of the following trends: a) Resolution can occur leaving no sequelae,

b) The disease can settle down, but sequelae are left, or

c) It may result in death.

Manifestations of Diseases

1. **Signs** – are objective findings as perceived by an examiner, physician or dentist
2. **Symptoms** – are functional manifestations or evidences of a disease process
3. **Lesions** – are visible changes produced by a disease in the tissues or organs. They are usually local abnormalities which could be benign, cancerous, gross, occult, or primary.
4. **Exacerbations** – a sudden increase in the severity or seriousness of the signs and symptoms during the course of a disease.
5. **Remissions** – become less intense at a time.
6. **Complications** – unfavorable conditions that arise during the course of a disease
7. **Sequelae** – are remote aftereffects produced by a disease.

VII. Clinical & biologic death Clinical death

Clinical death is the reversible transmission between life and biologic death. Clinical death is defined as the period of respiratory, circulatory and brain arrest during which initiation of resuscitation can lead to recovery.

Clinical death begins with either the last agonal inhalation or the last cardiac contraction. Signs indicating clinical death are

- The patient is without pulse or blood pressure and is completely unresponsive to the most painful stimulus.
- The pupils are widely dilated
- Some reflex reactions to external stimulation are preserved. For example, during intubations, respiration may be restored in response to stimulation of the receptors of the superior laryngeal nerve, the nucleus of which is located in the medulla oblongata near the respiratory center.
- Recovery can occur with resuscitation.

Biological Death

Biological death (sure sign of death), which sets in after clinical death, is an irreversible state of cellular destruction. It manifests with irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including brain stem. However, one should notice that there are internationally accepted criteria to diagnose biological death.

Learning pathology

Pathology is best learnt in two stages:

1. **General pathology,** which is concerned with the causations, mechanisms and characteristics of the major categories of disease.
2. **Systemic pathology** is the study of various systems that comprise the body such as cardiovascular pathology, gastrointestinal pathology and so on.