REVISED FOUNDATION BLOCK

PATHOLOGY DISCIPLINE

Pathology contents: 15 lectures

Practical sessions: 7 practicals including a supervised tour of the clinical laboratories:

Tutors for male students:

- Introduction to Pathology : Dr. Al-Rikabi (1 lecture)
- Inflammation and Repair : Dr. Al-Rikabi (5 lectures)
- Cell injury : Dr. Al-Rikabi (3 lectures)
- Granulomatous disease : Dr. Al-Humaidi (1 lecture)
- Neoplasia : Dr. Al-Sheikh (5 lectures)

Tutors for female students:

- Drs. Maha Arafah, Hala Kfoury and Shaesta Zaidi

Tutors of practical sessions: Dr. Amer Shafie (male students)
Dr. Shaesta Zaidi (female students)

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INTRODUCTION TO PATHOLOGY (*one lecture and a supervised tour of the laboratories).*

*Objectives:*

The student should:

A] Understands the role of pathology and its various subspecialities in the diagnostic process.

B] Understands the meaning of the terminology used during the study of a disease like aetiology, pathogenesis, prognosis, sequelae, symptoms, signs, etc.

C] Be aware of some of the principle techniques used in pathology like light microscopy, cytology, immunohistochemistry and molecular pathology.

D] Have a basic knowledge of the definition of autopsy and its indications.

Contents:

- **Definition of Pathology.**
- **Subdivisions and subspecialities of diagnostic pathology** with special emphasis on histopathology and cytology.
- **Classification of diseases** based on their pathogenesis and the role of pathology in general and histopathology in particular in reaching a clinical diagnosis. The student should be made able to understand the meaning of essential terminology like disease incidence, aetiology, pathogenesis, symptoms and signs, prognosis and the role of diagnostic pathology in disease management.
- Brief summary and simple introduction to **the techniques** used in histopathology and cytology including light microscopy, immunohistochemistry, immunofluorescence, electron microscopy and molecular pathology.
- Definitions and indications for **hospital autopsy**.

## CELL INJURY (*3 lectures and 2 practicals*).

*Objectives:*

**The students should:**

A] Understands the concept of cells and tissue adaptation to environmental stress including the meaning of hypertrophy, hyperplasia, aplasia, atrophy, hypoplasia and metaplasia with their clinical manifestations.
B] Is aware of the concept of hypoxic cell injury and its major causes.
C] Understands the definitions and mechanisms of free radical injury.
D] Knows the definition of apoptosis, tissue necrosis and its various types with clinical examples.
E] Able to differentiate between necrosis and apoptosis.
F] Understands the causes of and pathologic changes occurring in fatty change (steatosis), accumulations of exogenous and endogenous pigments (carbon, silica, iron, melanin, bilirubin and lipofuscin).
G] Understands the causes of and differences between dystrophic and metastatic calcifications.

*Contents of Lectures 1, 2 and 3:*

Lecture One : **Adaptation to environmental stress**: hypertrophy, hyperplasia, aplasia, hypoplasia, atrophy, squamous metaplasia, osseous metaplasia and myeloid metaplasia.

**Hypoxic cell injury** and its causes (ischaemia, anaemia, carbon monoxide poisoning, decreased perfusion of tissues by oxygen, carrying blood and poor oxygenation of blood).

- **Free radical injury**: definition of free radicals, mechanisms that generate free radicals, mechanisms that degrade free radicals.

Lecture Two : **Types of necrosis** : Coagulative, Liquefactive, Caseous, gangrenous, fibrinoid and fat necrosis.

- **Apoptosis** : definition, morphologic features, regulation of apoptosis and comparison between necrosis and apoptosis.

Lecture Three : **Reversible cellular changes and accumulations:** fatty change, hyaline change, accumulations of exogenous pigments (carbon, silica, iron dust, lead and argyria).

- Accumulations of endogenous pigments: melanin, bilirubin, haemosiderin (haemosiderosis and haemochromatosis), lipofuscin.

- **Pathologic calcifications**: metastatic calcification, dystrophic calcification.

## INFLAMMATION AND REPAIR (*5 lectures and 2 practicals*).

*Objectives:*

**The student should:**

A] Be able to identify the cardinal and systemic signs of inflammation and to understand the underlying mechanisms that produce these signs.
B] Understands the vascular changes occurring as a response to tissue injury.
C] Appreciate the importance of fluid production in inflammation including the differences between exudates and transudates.
D] Have some understanding of the various chemical mediators of inflammation and their link with the complement system and potentially with coagulation factors.
E] Have good knowledge about the types and functions of the various inflammatory cells including their role in both acute and chronic inflammation.
F] Be aware of the various complications of the inflammatory response, formation of pus and the production and manifestations of chronic inflammation.
G] Understands the concept of healing and repair with wounds healing by first and second intention as an example.
H] Knows the factors leading to poor healing and inadequate tissue repair.

*Contents:*

**Lecture 1** : **Definition of inflammation**, processes of inflammation in general, cardinal signs and causes of inflammation.

**Acute inflammation** – role of adhesion molecules, vasoactive changes, increased capillary permeability and types of inflammatory cells in general (neutrophils, lymphocytes, eosinophils, mast cells and basophils).

Lecture 2 & 3 : **Cellular response of leukocytes** – emigration, Margination, pavementing, rolling, adhesion and transmigration, chemotaxis, chemotactic factors, phagocytosis (opsonization) and intracellu-

lar microbial killing. Exogenous and endogenous mediators of acute inflammation including vasoactive mediators, kinin system and complement system.

**Outcomes of acute inflammation** – resolution, abscess, ulcer, fistulas, scar and conversion to chronic inflammation. Hereditary defects that impair the acute inflammatory response (deficiency of complement components and defects in neutrophils).

Lecture 4 : **Chronic inflammation**: general considerations of processes leading to chronicity like persistent or recurrent injury and the de novo chronic processes without previous acute inflammation.

**Patterns of chronic inflammation**: non specific chronic inflammation and chronic granulomatous inflammation.

Lecture 5 : **Tissue repair include**:

A] Restoration of normal structure: labile cells, stable cells and permanent cells.

B] Cellular proliferation and growth factors like PDGF, epidermal growth factor and fibronectin – transforming growth factor, macrophage derived growth factor.

C] The repair process in wound healing by first and second intention: removal of debris, formation of granulation tissue and scarring.

D] Factors that delay or impede repair.

GRANULOMATOUS DISEASES (*One lecture and one practical)*

*Objectives:*

**The student should:**

A] Appreciate the high prevalence of granulomatous diseases in the Kingdom of Saudi Arabia with special emphasis on tuberculosis.

B] Understands the mechanisms and causes of granuloma formation with special emphasis on interaction between T lymphocytes, macrophages and epithelioid histiocytes.

*Contents:*

GRANULOMATOUS DISEASES (One Lecture).

Lecture 1 : - **Definition and mechanisms of granuloma formation** including cellular constituents of granulomas.

- **Causes** of granulomatous diseases.

NEOPLASIA (5 lectures and 2 practicals).

Objectives:

The student should:

A] Be able to define a neoplasm and knows the differences between benign and malignant neoplasms.
B] Understands the concepts governing the classification of tumours and their nomenclature.
C] Have a basic knowledge of the carcinogenic agents in human tumours including chemical, physical, viral, genetic and hormonal.
D] Understands important modes of tumour spread with common examples including spread of carcinomas and sarcomas.
E] Be aware of the major clinical effects and features of tumours including: obstruction, ulceration, infection, anaemia, cachexia and effects of products of tumours including inappropriate hormone production.
F] Understands the basic of grading and staging of malignant neoplasms with special emphasis on the TNM staging system.
G] Know the role of tumour markers in the diagnosis and prediction of malignant tumours prognosis.

*Contents:*

**Lectures 1 & 2 :**

* Introduction.
* Definitions.
* Nomenclature and classification of tumors.
* Characteristics of benign and malignant tumors.
* Epidemiology.

**Lecture 3 & 4 :**

* Carcinogenesis and molecular basis of cancer.
* Factors inducing carcinogenesis.

**Lecture 5 :**

* Major clinical features of neoplastic disorders.
* Grading and staging of malignant neoplasms.
* Laboratory investigations and tumour markers.

## FOUNDATION BLOCK PRACTICAL CLASSES

**Tutors:** **Male students:** **Dr. Amer Shafie.**
**Female students:** **Dr. Shaesta Zaidi.**

**Total number of practical sessions:** **7.**

**Site:** **Students laboratories at KKUH and the Girls College.**

*Format:*

1] Introductive explanatory lecture.
2] Powerpoint projection of gross specimen and microscopic sections.
3] Students will be asked to examine pictures, microscopic slides and pathology museum jars representing organs and tissue sections of the lesions included in the curriculum.
4] The students will also be given a CD including all the gross and microscopic slides studied in order to encourage self directed learning.

*Contents* will consist of gross and microscopic pictures of various lesions and diseases which are related to/or are examples of cell injury lesions, inflammatory disorders, granulomas, circulatory disorders and neoplastic lesions.

FOUNDATION BLOCK

PATHOLOGY DISCIPLINE

PRACTICAL SESSIONS

| | | |
|---|---|---|
| Coordinators | : | Dr. Ammar Al-Rikabi<br>Dr. Maha Arafah |
| Tutors: Male students | : | Dr. Amer Shafie |
| Female students | : | Dr. Shaesta Zaidi |
| Location | : | Students lab at KKUH and Girls Medical College |
| Total number of sessions | : | Seven (7) |

Objectives:

At the end of these practical sessions, every student will be able to:

- Describe the pathological changes (both macro and micro) which can occur and are seen in the diseases and lesions studied in the foundation block.
- Identify the clinical manifestations of each pathological lesion.
- Correlate the morphological features with the clinical manifestations seen in the lesions and diseases studied.
- Differentiate between the normal structure and the pathological changes of the given tissue.

Format:

Each practical session will consist of the following:

- Short powerpoint presentation by the tutor which include explanation of the gross and microscopic preparations studied including correlation with relevant diseases and their clinical manifestations.
- Students will be asked to examine microscopic slides and pathology museum specimens relevant to the topic studied in the foundation block lectures.
- Each student will be given a CD containing pictures and explanations of the microscopic and gross specimens studied for self-directed learning.
- The students will be given the opportunity to visit the laboratories and familiarize themselves with the lab procedures.

Contents:

I. Cell injury

A. Basic introduction to the anatomy and histology of the lung, liver, kidney and heart in order to enable the student to understand the related pathology.
B. Macroscopic and pathology musum specimens:
(1) Fatty liver steatosis.
(2) Coagualative necrosis in a renal infarction.
(3) Liquefactive necrosis of the brain.
(4) Caseous necrosis in tuberculosis of the lung.
(5) Dystrophic calcification of aortic valves.
(6) Atrophy of the brain, kidney and testis.
(7) Left ventricular hypertrophy.
(8) Prostatic hyperplasia.
(9) Endometrial hyperplasia.
C. Microscopic slides and pictures of:
(1) Fattychange of the liver.
(2) Dystrophic calcification in the skin.
(3) Coagulative necrosis in an infracted kidney.
(4) Hyperplasia of the prostate.
(5) Cystic hyperplasia of the endometrium.
(6) Endocervical squamous metaplasia.

II. Inflammation and Repair

A. Macroscopic and pathology museum specimens:
(1) Fibrinous pericarditis.
(2) Chronic cholecystitis with stones.
(3) Acute appendicitis.
(4) Skin pilonidal sinus.
(5) Bronchiectasis and lung abscess.
(6) Brain abscess.
(7) Pyaemic abscesses of the kidney.
B. Histopathology of microscopic slides and pictures:
(1) Acute fibrinous pericarditis.
(2) Acute appendicitis.
(3) Foreign body reaction in pilonidal sinus.
(4) Inflammatory granulation tissue in chronic inflammation.

III. **Granulomas**

A. Gross (macroscopic) and pathology museum specimens:
B. Histopathology of microscopic slides and pictures:
   (1) Tuberculous lymphadenitis.
   (2) Miliary tuberculosis of the lung.
   (3) Tuberculosis of the kidney.
   (4) Bilharziasis of the colon.
   (5) Cutaneous leishmaniasis.

IV. **Circulatory diseases**

A. Gross pathology and museum specimens:
   (1) Chronic venous congestion of the liver.
   (2) Myocardial infarction with mural thrombus.
   (3) Infarction of small intestine.
   (4) Pulmonary embolus withy infarction.
B. Histopathology of microscopic slides and pictures.
   (1) Chronic venous congestion of the liver.
   (2) Chronic venous congestion of the lung.
   (3) Organizing thrombus.
   (4) Myocardial infarction.
   (5) Infarcted kidney.

V. Neoplasia: Benign and malignant tumours:

A. Gross pathology and museum specimens:
   (1) Lipoma of small intestine.
   (2) Adenomatous polyp of rectum/colon.
   (3) Teratoma (Dermoid cyst of the ovary).
   (4) Multiple uterine leiomyomata.
   (5) Carcinoma of the breast.
   (6) Carcinoma of the esophagus.
B. Histopathology of microscopic slides and pictures:
   (1) Intradermal nevus.
   (2) Leiomyoma.
   (3) Chondroma.
   (4) Hemangioma.
   (5) Fibroadenoma of the breast.
   (6) Squamous cell carcinoma of the skin.
   (7) Adenocarcinoma of the large intestine.
   (8) Fibrosarcoma.

# INTRODUCTION TO PATHOLOGY AND THE STUDY OF DISEASES

- Faculty of Medicine -

- Foundation Block -

DR. AMMAR C. ALRIKABI* AND DR. MAHA ARAFAH**

*Associate Professor and ** Assistant Professor

Department of Pathology

King Khalid University Hospital and King Saud University

# INTRODUCTION TO PATHOLOGY AND THE STUDY OF DISEASES (ONE LECTURE)

Dr. Ammar C. Al-Rikabi – Associate Professor in Pathology
Office Phone Number: 01-4671893
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## *OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT:*

Upon completion of this lecture, the student should:

(1) Understands the definition of pathology as an important discipline which provides the link between basic biological sciences and the practice of medicine.
(2) Understands the concept of disease which is defined as a physiological or psychological dysfunction.
(3) Become familiar with the important terminology which is used to study a disease like: epidemiology, aetiology, pathogenesis and prognosis.
(4) Become aware of the general causes of diseases which include: genetic, infective, chemical agents, radiation and traumatic injury.
(5) Understands the meaning of idiopathic or essential disease.
(6) Be familiar with the classification of diseases which is usually based on their pathogenesis.
(7) Have an organized framework for thinking and acquiring informations about diseases which include definition, incidence, age, gender, race and geographical distribution. Clinical signs including symptoms and signs, underlying pathology, differential diagnosis, treatment and management and prognosis.

## *TAKE HOME MESSAGES:*

(1) Pathology is an important discipline which help in the understanding and diagnosis of diseases.
(2) A disease is defined as a physiological or psychological dysfunction.
(3) Study of disease requires an understanding of epidemiology, aetiology and pathogenesis of the illness.
(4) Classification of diseases is usually based on their pathogenesis.

## *FURTHER READING:*

Kumar, Cotran and Robbins: Basic pathology, 8th edition.

**Keywords**: Pathology, disease, incidence, aetiology, epidemiology, pathogenesis, idiopathic, prognosis, symptoms and signs.

## Introduction

**Pathology** is an important discipline which provides **the link** between basic biological sciences and the practice of medicine. In broad terms, the study of pathology encapsulates the way we think about diseases and about their causes, prevention and classification. Using a more limited definition, **pathology is the study of changes which occur in cells and tissues as a result of inborn genetic, extraneous environmental or behavioural damage.**

- Pathology is the study of disease processes.
- Epidemiology provides a broad context for understanding pathology.
- Both (pathology and epidemiology) provide a useful framework for classifying and understanding mechanisms of disease.

## Health, illness and disease

Normal health or well being is a state which most of us experience most of the time. Illness, however, is the subjective state of not feeling well and sickness is a state of social dysfunction, i.e. a role that the individual assumes when ill. There is a wide range of normality and the human body can readily adapt to changes in the environment (e.g. by an increase in hemoglobin at an altitude where oxygen levels are low). Disease or ill health occurs when these limits or normality are overreached.

**Disease is defined as a physiological or psychological dysfunction**. It can be caused by an obvious structural abnormality such as a broken bone or a tumour or may be less well defined, as in the case of anorexia nervosa. All diseases have certain aspects which can form the basis of a classification and these include:

- Epidemiology.
- Aetiology.
- Pathogenesis.

*Epidemiology*

Epidemiology include sex and age, prevalence of a particular disease in addition to geographics distribution and incidence. **Prevalence** means the number of cases in a population at any one time while **incidence** is the number of new cases in a population over a given time. **Aetiology** is the direct cause of a disease while **pathogenesis** is the mechanism of disease production.

Epidemiology provides a wider context for the study, classification and diagnosis of diseases. Data recorded about incidence, prevalence, morbidity and mortality relate to populations, rather than individuals.

Knowledge of epidemiology is important for:

- Providing causal clues.
- Identifying risk factors and risk markers.
- Planning and executing disease prevention and health promotion.
- Providing adequate health care facilities.
- Setting up population screening programmes. (Screening is defined as identifying a disease in an apparently healthy population).
- Evaluating health care interventions.

Factors which affect the incidence (number of new cases occurring in a defined population over a defined time period) and prevalence (number of cases found in a defined population at a stated time) of disease include:

- Time: how the disease has varied over the course of time.
- Place: how the disease varies geographically.
- Person: what are the personal characteristics of those who suffer from the disease and how they differ from those who do not suffer from the disease, e.g. in age, sex, occupation, race, social class, behavior.

Changes in the incidence of disease with time may result from preventative measures, such as immunization programmes, or may reflect changes in social conditions. For example, increased smoking has led to an increase in heart disease and lung cancer.

Many diseases show significant **geographical** variations: in developed countries, heart disease, cancer and psychiatric illnesses are common whereas in underdeveloped countries, malnutrition and infection are often the commonest health problems. Different infectious agents are common in different geographical areas.

There are many well documented associations between diseases and occupation:

- Ship builders and insulation workers: asbestosis (asbestos-related scarring in the lungs); mesothelioma (malignant tumour of the lung pleura).
- Rubber and dye workers: bladder cancer through the effect of chemicals.
- Hardwood manufacturing: nasal cancer as a result of inhalation of wood dust.

*Aetiology (causes of disease)*

Diseases result from the interaction between individuals and their environment. Some diseases are the inevitable result of environmental factors (e.g. being run over by a bus) whereas others result from an environmental or behavioural factor acting in conjunction with a genetic predisposition, e.g. smokers with a strong family history of heart disease.

Some examples are:

- Genetic: Down's syndrome (extra chromosome 21).
- Infective: bacteria, viruses, fungi.
- Chemical: cirrhosis of the liver caused by alcohol damage; respiratory failure as a result of a paraquat poisoning affecting lungs.

- Radiation: Post-radiation cancer (e.g. skin cancer, squamous cell carcinoma) developing in the skin of a breast irradiated for mammary carcinoma).
- Mechanical: traumatic crush injury.

**Idiopathic disease**. In some instances, the underlying cause of a disease is obscure. Many euphemisms are used for this, including idiopathic, cryptogenic, essential and spontaneous. **Cause unknown** is a simpler and more honest way of saying the same thing.

*Pathogenesis (mechanisms of disease)*

The pathogenesis of a disease is the mechanism by which the cause(s) interact with the target cells or tissue to produce injury. Cells and tissues are relatively limited in the ways in which they can respond to insult or injury. There are a few fundamental processes which underlie most diseases:

- **Inflammation**: response to injury in living vascularized tissue.
- **Degeneration**: deterioration of cell function resulting from metabolic disease or ageing.
- **Carcinogenesis**: process of transformation of cells from the normal, controlled to the neoplastic autonomous state.
- **Immune reactions**: specific responses to foreign organisms or material.

Classification of disease

The most useful disease classification is based on the pathogenesis or underlying mechanism. Broadly speaking, diseases can be classified into two categories: "congenital" or "acquired". **Congenital diseases** are present at birth even though they may not be recognized or recognizable at that time. **Acquired diseases** only occur after birth. Both congenital and acquired diseases can be classified further (see table).

## Classification of diseases based on their pathogenesis

| Type | Basis | Examples |
|---|---|---|
| **Congenital** | Genetic | Reduction or absence of blood clotting factor VIII leads to haemophilia A (X chromosome linked). |
| | Non-genetic | Cleft lip and palate. |
| **Acquired** | Inflammatory | Dermatitis (eczema, inflammation of the skin), rheumatoid disease (inflammation of joints/arthritis). |
| | Vascular | Atherosclerosis (deposition of lipid with thickening of blood vessels) leading to a cerebrovascular accident (stroke), myocardial infarction (heart attack). |
| | Growth disorder | Cancer. |
| | Degenerative | Alzheimer's disease, Parkinson's disease. |
| | Drug induced | Bone marrow suppression, skin rashes, renal failure. |
| | Infective | Viral, bacterial or fungal diseases. |
| | Metabolic | Gout: deposition of uric acid crystals in joints and tissues.<br>Diabetes mellitus: abnormal metabolism of carbohydrates and lack of insulin. |

## Ways of thinking about diseases

It is useful to have a logical framework for thinking about diseases. There are several ways of organizing information about diseases which include:

- **Definition**: clinical or pathological.
- **Epidemiological:** incidence, age/gender, geography, race.
- **Clinical presentation**: symptoms and signs. (The word symptom refers to the patient complaint while signs are clinical features discovered by the examining physician).
- **Underlying pathology**: understanding mechanisms of disease with changes in tissues visible by naked eye (macroscopic), changes seen only down the microscope (microscopic) and tissue function (pathophysiology).
- **Differential diagnosis**: other diseases which may be similar.
- **Treatment and management**: drugs, surgery, counseling.
- **Prognosis:** natural history of disease, disease outcome.

Diseases are often discussed in terms of their morbidity (degree of "illness" involved) and mortality. 5- and 10-year survival rates are often used as an expression of the disease outcomes. For example, in some types of lung cancer, the 5-year survival rate is 0%.

## The diagnostic process

Patients present with symptoms and a clinical examination elicits signs which suggest a diagnosis. Examination of specimens (blood, urine, faeces, tissue samples) in the various pathology laboratories helps confirms this diagnosis and monitor treatment.

- Diagnosis involves clinical skills and laboratory tests.
- Specialist pathological techniques can aid in diagnosis.

## Diagnosis

Diagnosis is the act of identifying a disease in an individual patient and is based on clinical history, physical examination and investigation. An understanding of and ability to integrate a knowledge of the classification, epidemiology and mechanisms of disease processes are essential. Making a diagnosis involves:

- Taking a clinical history of symptoms: what the patient has noticed is wrong (e.g. cough, breathlessness, pain).
- Clinical examination for signs: what the doctor finds wrong on examination (e.g. lumps, rashes, abnormal lung sounds).

The clinician then works through a series of questions:

- Which organ system is most likely to be affected?
- Which category of disease do the signs and symptoms most likely suggest, e.g. inflammation, malignancy or poisoning?
- Do other factors such as race, age, sex, behavioural patterns or occupation of the patient provide clues to the diagnosis?

The diagnostic process involves testing a series of hypotheses based upon the clinician's knowledge of the frequency of occurrence of the symptoms and signs in different disease states and upon the probability of these occurring in the population from which the patient is drawn. A list of possible diagnoses is constructed, known as the **differential diagnosis**, beginning with the most likely disease and progressing to include diagnoses which are less likely but are important to exclude. Reaching a diagnosis enables the clinician to start treatment and to give the patient some idea of the outcome of the disease (prognosis).

## The role of the pathologist

The pathologist can help the clinician to make a diagnosis by looking at samples of tissue (biopsies) and by using a range of specialized laboratory techniques to refine the differential diagnosis. It is important to remember that pathology includes a large number of sub-specialities. Each of these investigates disease processes by examining or studying different body samples. For example, haematologists are concerned with disorders of the blood, whilst immunologists are concerned with disorders of the body's immune system. The clinical diagnosis can often only be made after several samples of blood, urine and tissue have been examined and the results assessed in the light of the parent's history and the clinical findings.

## Techniques used in diagnostic histopathology:

Basic histological techniques involve the fixation and processing of biopsied or excised tissues so that they can be finely slided to a thickness of no more than 4-5 microns (μm) and stained on a glass slide to be

looked at under **the light microscope**. Cells can be scraped or aspirated from various parts of the body and placed directly on glass slides and stained; this is called **cytology.** In these preparations, abnormal cell morphology can be identified. Sometimes, clinicians require a very urgent diagnosis during surgery and small amounts of tissue can be quickly frozen, sectioned and looked at within a few minutes (**'frozen section'**).

It is also possible to look at tissues at a much higher magnification using **the electron microscope**. This is an expensive and specialized technique, not used routinely, but it enables us to see cell structures to the level of individual mitochondria, nuclei and smaller. This is known as **ultrastructural examination**. Viral particles in cells can be seen by electron microscopy.

## The autopsy

Pathologists also perform autopsies, i.e. the examination of the body after death. **The main purpose of the autopsy is to determine the cause of death,** but the pathologist can also confirm a clinical diagnosis made in life, as well as identifying diseases or conditions which were not apparent in life. Discussions between clinicians and pathologists about autopsy findings often lead to new insights into the causes and outcomes of disease. Autopsies provide useful material for teaching, and the "post-modrtem demonstration" is a popular format in which students can see and discuss at first hand the pathological process in disease.

KING SAUD UNIVERSITY

FACULTY OF MEDICINE

FOUNDATION BLOCK

# INFLAMMATION AND REPAIR

DR. AMMAR AL-RIKABI
Associate Professor and Consultant
Department of Pathology
King Khalid University Hospital

**Objectives** that should be achieved through teaching the concepts and principles of inflammation.

**Inflammation** is a central area in general pathology. The medical student should be able to:

A] Identify the cardinal signs of inflammation.

B] Understand the underlying mechanisms that produce these signs.

C] Appreciate the vascular and microvascular response of the tissue to any injury.

D] Understand the importance of fluid accumulation during inflammation and the differentiation between exudates and transudate fluids.

E] Acquire a basic knowledge of the chemical mediators of inflammation and their link with complement and coagulation factors.

F] Know the types and functions of the various inflammatory cells.

G] Become aware of the complications resulting from the inflammatory response.

H] Understand the mechanisms of resolution of the inflammatory response and the process of healing and repair.

I] Appreciate the relationship between acute inflammation, healing and repair and chronic inflammation.

## Chapters and paragraphs that should be read from Robbins Basic Pathology – International 8th Edition:

1) Figure 2-1 in page 32 and the general features of inflammation.
2) Figure 2-2 in page 33 – major local manifestations of acute inflammation.
3) Figures 2-3 and 2-4 in pages 34 and 36.
4) Figures 2-5 and 2-7, pages 38 and 40.
5) Table on sequence of events in acute inflammation page 42.
6) Figures 2-8 and 2-9 in page 43.
7) Morphologic patterns of acute inflammation, pages 43-44 and figures 2-12 and 2-13 in page 45.
8) Table 2-4 page 46 (the actions of principal mediators of inflammation).
9) Page 50 – Summary of major cell derived mediators of inflammation.
10) Page 54 – chronic inflammatory cells and mediators.
11) Summary of features of chronic inflammation, page 57.
12) Systemic effects of inflammation, pages 57-58.
13) Figure 3-1, page 60.
14) Figure 3-11, page 71.
15) Figure 3-15, 16 and 17, pages 75, 76 and 77.

# INFLAMMATION AND REPAIR

## Inflammation

Inflammation, the local response of tissue to injury, is fundamentally a vascular phenomenon. The suffix "itis" is added to the base word to state the condition as in appendix/appendicitis and spleen/splenitis. The 5 ancient cardinal signs of inflammation are:

Tumor-swelling
Rubor – redness
Calor – warmth
Dolor – pain
Functio Laesa – loss of function
Systemic manifestations of inflammation include: fever, chills, increased sedimentation rate and increased levels of C reactive protein.

Causes of tissue injury leading to inflammation are those physical and chemical agents; they range from simple mechanical tissue disruption to the effects of irradiation. The inflammation can be caused by bacteria, viruses, parasites, fungi, thermal injuries, immunological injuries, foreign bodies and toxic substances. The inflammatory process consists of: cellular events, vascular changes and effects of chemical mediators.

**Cells of the inflammatory process. Neutrophils** phagocytize a foreign material (e.g. bacteria) and then attempt to oxidize and digest it through oxidase and proteases. These are the first inflammatory cells on the scene after tissue injury. **Eosinophils** are also phagocytic and possess many of the enzymes of the neutrophil. In addition, they can dispense antihistamine in an area of histamine release. The **eosinophil** is also associated with allergic responses. It is seen in both acute and chronic inflammation and become increased in parasitic infestations.

**Lymphocytes** are simple-appearing cells with varied and complex functions. Briefly, some lymphocytes are in the T-cell system and produce various type of lymphokines, which have local effects. Immunoglobulins or antibodies can also be produced by this cell as a B cell. The lymphocyte characterizes chronic inflammation. Antibody production is the function of **the plasma cell**, a specialized B cell, which is also found in chronic inflammation. It is especially prominent in chronic inflammation involving mucosal surfaces.

Cells of Inflammation

| Cell | Activity | Phagocytosis | Inflammation |
|---|---|---|---|
| Neutrophil | Proteases, oxidases | + | Acute |
| Eosinophil | Antihistamine | + | Acute, chronic |
| Macrophage (modified monocytes) | Antigen processing and digestion | + | Late acute, chronic |
| Lymphocyte | Lymphokines | - | Chronic |
| Plasma cell | Antibody production | - | Chronic |

## Vascular changes occurring during inflammation and types of inflammation

Classically, inflammation has been divided into acute (immediate, short duration) and chronic (protracted) varieties. Granulomatous inflammation is also regarded as a type of chronic inflammation.

*Acute inflammation*. Systemically, acute inflammation may be accompanied by fever. There may be a peripheral blood leukocytosis, especially of neutrophils, along with increased number of immature (band neutrophils) forms of neutrophils ("left shift").

Locally, it is **the vascular response** to tissue injury that is fundamental. The initial response to tissue injury is an episode lasting from seconds to 5 minutes of arteriolar **vasoconstriction**, probably occuring as a direct effect on the vessels. In several minutes, the precapillary arterioles dilate, resulting in greater blood flow to the area. This lasts as long as the acute inflammation persists. The injured area reddens from **increased blood flow**; this is accompanied by **increased vascular permeability**. As a consequence, **interstitial edema** (swelling) occurs owing to the escape of intravascular fluid, called an exudate. Then, the lymphatic vessels admit the escaped fluid into the lymphatic system and after several days the swelling subsides.

A. **Transudate, exudate and pus**. A **transudate** results when increased intravascular fluid escapes into the interstitial tissues related **to increased hydrostatic pressure** in the vessels. A good example is the pedal (ankle) edema seen in congestive heart failure. This fluid has low protein content and specific gravity (< 1.020). In acute inflammation, the edema is caused by the escape of fluid into the interstitial tissues related to increased vascular permeability. This fluid is called an **exudate**. Because more protein escapes with the fluid compared with that which occurs with a transudate, an exudate has a higher protein content and specific gravity (> 1.020). **Pus** consists mostly of neutrophils and necrotic derbis, being high in protein content with a specific gravity greater than 1.020.

B. **Cellular events in acute inflammation**. Cellular events begin soon after vasodilatation. Leukocytes (especially polymorphouclear leukocytes) move from the center of the blood column in a vessel to the periphery (margination) and begin to adhere to the endothelium (pavementing). At the same time, the leukocytes move from the vessels into the interstitial tisues (emigration). Initially, it is the neutrophils that emigrate in the greatest number, whereas lymphocytes, macrophages and eosinophils also take part in this process, initially in fewer numbers. As the inflammation regresses, decreasing numbers of neutrophils emigrate, whereas more lymphocytes and macrophages make the trip and finally predominate when the process becomes chronic with the disappearance of the neutrophils.

C. **Chemical mediators of the acute inflammatory response.** Attraction of the interstitial leukocytes to the area of tissue injury occurs through **chemotaxis** or attraction by chemical agents. Numerous chemical mediators are responsible for the vascular events surrounding the acute inflammatory process.

## Characteristics of transudate, exudate and pus

| Fluid type | Condition | Content | Specific gravity |
|---|---|---|---|
| Transudate | Increased hydrostatic pressure | Low protein | < 1.020 |
| Exudate | Acute inflammation | High protein | > 1.020 |
| Pus | Acute inflammation | High protein plus neutrophils | > 1.020 |

## The Actions of the Principal Mediators of Inflammation

| Mediators | Source | Principal Actions |
|---|---|---|
| Cell-Derived | | |
| Histamine | Mast cells, basophils, platelets | Vasodilation, increased vascular permeability, endothelial activation. |
| Serotonin | Platelets | Vasodilatation, increased vascular permeability. |
| Prostaglandins | Mast cells, leukocytes | Vasodilatation, pain, fever. |
| Leukotrienes | Mast cells, leukocytes | Increased vascular permeability, chemotaxis, leukocyte adhesion and activation. |
| Platelet-activating factor | Leukocytes, endothelial cells | Vasodilatation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst. |
| Reactive oxygen species | Leukocytes | Killing of microbes, tissue damage. |
| Nitric oxide | Endothelium, macrophages | Vascular smooth muscle relaxation; killing of microbes. |
| Cytokines (e.g. TNF, IL-) | Macrophages, lymphocytes Endothelial cells, mast cells | Local endothelial activation (expression of adhesion molecules), systemic acute-phase response in severe infections, septic shock. |

❖ Bradykinin is a metabolite of the Kinin system which is activated by the action of Hageman's factor (factor 12 of coagulation).

| Mediators | Source | Principal Actions |
|---|---|---|
| Plasma Protein-Derived | | |
| Complement | Plasma (produced in liver) | Leukocyte chemotaxis and activation, opsonization, vasolidalation (mast cell stimulation). |
| Kinins | Plasma (produced in liver) | Increased vascular permeability, smooth muscle contraction, vasodilatation, pain. |
| Proteases activated during coagulation | Plasma (produced in liver) | Endothelial activation, leukocyte recruitment. |

- IL-1, interleukin-1, TNF- tumor necrosis factor.

## Role of Mediators in Different Reactions of Inflammation

| | |
|---|---|
| Vasodilatation | Prostaglandinds<br>Nitric oxide<br>Histamine |
| Increased vascular permeability | Histamine and serotonin<br>C3a and C5a (by liberating vasoactive amines from mast cells, other cells)<br>Bradykinin<br>Leukotrines C4, D4, E4<br>Platelets activating factor<br>Substance P |
| Leukocyte recruitment and activation | TNF, IL-1<br>Chemokines<br>C3a, C5a<br>Leukotrienes B4 (Bacterial products, eg., *N*-formyl methyl peptides) |
| Fever | IL-1, TNF<br>Prostaglandins |
| Pain | Prostaglandins<br>Bradykinin<br>Neuropeptides |
| Tissue damage | Lysomal enzymes of leukocytes<br>Reactive oxygen species<br>Nitric oxide |

- IL-1, Interleukin-1, PAF, Platelet activating factor, TNF, tumor necrosis factor.
- Prostaglandins and Leukotrienes are arachidonic acid metabolites.

**Chronic inflammation**. The preponderance of lymphocytes, plasma cells and macrophages in acute inflammation indicates the transition from acute to chronic inflammation. **Chronic inflammation may also arise de novo**. Whereas acute inflammation lasts days to weeks, chronic inflammation lasts months to years. Chronic inflammation is seen following acute inflammation when tissue injury persists. De novo chronic inflammation may be due to low-pathogenicity bacteria or chemical and physical agents that produce lower levels of tissue damage. Macrophages, lymphocytes, plasma cells, occasionally eosinophils, and even a few neutrophils are seen in chronic inflammation.

A. **Granulation tissue and chronic inflammation**. **Granulation tissue** is often associated with chronic inflammation. It represents a healing phase following acute inflammation. **Endothelial proliferation** is prominent. At first, the interstitial tissue is edematous with an admixture of acute and chronic inflammatory cells; later, it is dominated by chronic inflammatory cells. Eventually, fibroblasts dominate in the interstitial tissues. Externally, granulation tissue has a red granular appearance due to endothelial proliferation.

B. **Granulomatous inflammation**: a type of chronic inflammation: Substances present in the inflammatory response that are not digestible by neutrophils may evoke granlomatous inflammation. Characteristic of this type of chronic inflammation are granulomas, which form 0.5 to 2.0 mm aggregations of epithelioid macrophages surrounded by a rim of lymphocytes. Epithelioid macrophages have an appearance suggestive of squamous epithelial cells due to their abundant pink cytoplasm. Granulomatous inflammation may be caused by foreign bodies, mycobacterial infection (e.g. tuberculosis, leprosy, Schistosomiasis, the gumma of tertiary syphilis, cat-scratch disease, lymphogranuloma venereum, tularemia and others). **At times, the granuloma contains caseous (cheese-like) necrosis as in tuberculosis.** Multinucleated giant cells form from the cytoplasmic fusion of macrophages. A variation of the multinucleated or foreign body giant cell is the Langhan's giant cell which has nuclei arranged peripherally.

**Gross configurations of acute and chronic inflammation**. Acute and chronic inflammation conform themselves into several appearances. **Fibrinous inflammation** consists of neutrophils admixed with fibrin (e.g., fibrinous pericarditis). An effusion of fluid under acute inflammatory conditions from a surface (often mesothelial) is called **serous inflammation**. **Suppurative inflammation** exudes pus, a mixture of neutrophils and necrotic debris. An enclosed collection of pus is called an **abscess.** Mucosa-lined surfaces may exhibit **catarrhal inflammation** with the outpouring of **watery mucus**. Any **ulcer** is a focal defect usually on an epithelial surface where the epithelium is entirely lacking; the exposed tissue is covered by a fibrinopurulent exudate

(mixture of fibrin and neutrophils). Finally, the term **cellulitis** denotes a spreading acute inflammation through interstitial tissues.

## Regeneration and repair

Regeneration and repair of a damage tissue occur through the reproduction of the normal, parent tissue or fibrosis (scar). Whether regeneration or repair or both occurs depends on the regenerative capacity of the original damaged cells. **Labile cells** are rapidly regenerating cells (short life span), which can be readily regenerated. Epidermis is an example. **Stable cells** are longer-lived cells with a slower mitotic rate, but given proper conditions, these cells can regenerate to some extent. Liver and renal tubular cells are an example. Lastly, **permanent cells** have a long life span with no mitotic activity in post natal life. The neurons of the central nervous system are an example.

**Supporting tissues**. **The collagens**, a series of complex polypeptides, bind epithelial and the various connective tissues to themselves and each other where appropriate, thus providing tensile strength. **Fibroblasts** secrete collagen.

Basement membranes lie at the interface of cells and stroma. They support the overlying cells. Materials found in basement membranes include entactin, heparin sulfate, laminin, proteoglycan and type IV collagen.

**Healing by first intention (primary union).** Healing by first intention occurs when wound edges are approximated and the wound is quickly covered with epithelium and bound together by collagen. At first, the surface epithelial gap and apposed edges of the connective tissue contain blood clot and debris. Epithelium is regenerated from the edges of the wound. Capillaries, neutrophils, macrophages and fibrocytes migrate into the clot. Within a few days, the scab (patch of dried, clotted blood) at the surface falls revealing re-epithelialization and the blood clot in the apposed tissues is removed by macrophages. Endothelial cells proliferate with the laying down of collagen by fibroblasts, **producing granulation tissue**. The phagocytic neutrophils progressively decrease in number as macrophages increase. As collagen in the gap increases, the blood vessels in the area decrease in number, and the scar begins to contract. Healing by first intention is best exemplified by the healing of an apposed surgical incision.

**Healing by second intention (secondary union).** Edges of the wound cannot be apposed in healing by second intention, leaving a defect containing blood clot and debris.

The process of wound healing is similar to that of first intention, but it takes much longer. The same cells take part in this process. Granulation tissue is much more pronounced.

In both types of healing, the wound contracts in the later stages due to the presence of the **myofibroblast,** a contractile cell that has properties of both fibroblasts and smooth

muscle cells. Tensile strength of the wound in both kinds of healing gradually increases with more fibroblast activity and the laying down of collagen.

**Abnormal repair**. Wound repair does not always go well. The laying down of excessive collagen results in **keloid and fibrous adhesions formation**. **Bacterial infection of the wound,** the presence of **foreign bodies**, **poor blood supply**, and **lack of mobility** may retard healing. Deficient scar formation may result from **deficiencies of vitamin C or severe protein deficiencies.** Retarded wound healing and deficient scar formation may cause wound separation at wound margin: a **wound dehiscence**. If a large wound cannot be totally covered by epithelium, the resulting ulcer may require a skin graft. **Wound contractures** is related to the action of myofibroblasts. **This is seen especially following burns.**

# CELL INJURY, CELLULAR ACCUMULATIONS, CALCIFICATION AND CELLULAR ADAPTATIONS TO INJURY

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# CELL INJURY AND CELLULAR ADAPTATIONS TO INJURY. CELLULAR ACCUMULATIONS AND PATHOLOGIC CALCIFICATIONS (THREE LECTURES AND TWO PRACTICALS)

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## *OBJECTIVES AND KEY PRINCIPLES TO BE TAUGHT:*

Upon completion of this lecture, the student should:

(1) Understand the concepts of reversible and irreversible (lethal) cell injury.
(2) Know the causes of cell injury.
(3) Be aware of the mechanisms of cell injury which include the actions of bacterial toxins, free radicals, hypoxia, alcohol intake and effects of viruses and radiation on cellular nuclei.
(4) Know the pathological changes leading to cell death and apoptosis including the major causes of and differences between apoptosis and necrosis.
(5) Be able to list the various types of necrosis with clinical examples.
(6) Understand the pathological changes leading to abnormal accumulations of pigments and other substances in cells. These include fatty change, haemosiderin, melanin and lipofuscin accumulations in cells.
(7) Know the main types and causes of calcifications (dystrophic and metastatic).
(8) Be aware of the various aspects of cellular adaptation to injury such as atrophy, hypertrophy, hyperplasia and metaplasia with clinical examples on each type.

## *TAKE HOME MESSAGES:*

(1) Cellular injury is caused by various elements and could be reversible (sublethal) or irreversible (lethal).
(2) Apoptosis is a form of programmed cell death which could be physiological or pathological.
(3) Necrosis (unlike apoptosis) is associated with inflammatory reaction.
(4) Necrosis has many types which include Coagulative, liquefaction, gangrenous, Caseous and fat necrosis.
(5) Metastatic calcifications is usually associated with hypercalcaemia (unlike the dystrophic calcification).
(6) Metaplasia is a type of reversible cellular adaptation which can be seen in the bronchial tree as a result to smoking.

## *FURTHER READING:*

Kumar, Cotran and Robbins: Basic pathology, 8th edition.

**Keywords:** cell injury, apoptosis, necrosis, free radicals, calcification, atrophy, hypertrophy, hyperplasia, metaplasia.

## Introduction

Cell injury may be reversible (sublethal) or irreversible (lethal). Many causes may result in reversible injury initially, but if severely injured, the cell may be unable to recover and cell death (necrosis or apoptosis) follows.

## Processes involved in cell injury

### ❖ *Causes of cell injury*

The causes of both reversible and irreversible cell injury are similar. Many of those listed below may result initially in reversible injury. If the injury is of sufficient severity, e.g. length of exposure to radiation or reduced oxygen supply, the cell reaches a "point of no return" and irreversible injury culminating in cell death will occur.

Possible causes include:

- Hypoxia, e.g. myocardial ischaemia (reduced blood flow to, and therefore oxygenation of the heart) as a result of coronary artery atherosclerosis.
- Immunological, e.g. thyroid damage caused by autoantibodies (antibodies produced by the body against its own tissues).
- Infection, e.g. bacterial, viral, fungal infections, etc. (e.g. tuberculosis infection of the lung).
- Genetic, e.g. Duchenne muscular dystrophy.
- Chemical, e.g. acid damage to oesophageal mucosa (accidental or deliberate).

### ❖ *Mechanisms of cell injury*

The structure and metabolic function of the cell are interdependent. Therefore, although an injurious agent may target a particular aspect of cell structure or function, this will rapidly lead to wide-ranging secondary effects. Recognized mechanisms of cell injury include:

- Cell membrane damage
  - Complement-mediated cell membrane lysis via the membrane attack complex (MAC)
  - Bacterial toxins
  - Free radicals

- Mitochondrial damage leading to inadequate aerobic respiration
  - Hypoxia (lack of oxygen)
  - Cyanide poisoning

- Ribosomal damage leading to altered protein synthesis
  - Alcohol in liver cells
  - Antibiotics in bacteria

- Nuclear change
  - Viruses
  - Radiation
  - Free radicals

**Free radicals and cell membrane damage**

Free radicals are highly reactive atoms which have an unpaired electron in an outer orbital. They can be produced in cells in response to a variety of processes, including radiation, normal metabolic oxidation reactions and drug metabolism processes. The most important free radicals are derived from oxygen, e.g. superoxide and hydroxyl ions. Free radicals can injure cells by generating chain reactions, producing further free radicals, which cause cell membrane damage by cross-linking of proteins and by critical alterations of lipids.

❖ ***Consequences of cell injury***

The consequences of cell injury depend on both the cell and the injurious agent. Certain features of cells make them more vulnerable to serious sequelae of cell injury.

## Cell features

**Specialization**. Cells that are enzyme rich, nucleated or have specialized organelles within the cytoplasm may be more vulnerable. The presence of specialized proteins within the cell may make it prone to certain types of injurious agent.

**Cell state**. Cells that have an inadequate supply of oxygen, hormones or growth factors or lack essential nutrients may be more prone to injury.

**Regenerative ability**. The potential of a cell population to enter the cell cycle and divide is important in the response of tissues to injury. Damaged areas in tissues made up of cells which can divided will quickly be restored to normal, while populations of permanent cells will be incapable of regeneration.

## Injury features

In addition, the character of the injury will also affect the severity of the damage.

**Type of injury**. The injury may be ischaemic, toxic, chemical, etc. Different cells will be more susceptible to some injurious agents than others (e.g. heart muscle cells are more susceptible to oxygen depletion than connective tissue cells).

**Exposure time**. The length of time of exposure to a toxin or reduced oxygen concentration will affect the change of a cell surviving the insult, even for those cells relatively resistant to the damaging agent.

**Severity**. The ability to survive an injury will also depend upon its severity, e.g. is the lack of oxygen partial (hypoxia) or complete (anoxia).

❖ *Irreversible cell injury*

When does reversible injury become irreversible? The exact "point of no return" from reversible to irreversible cell injury (leading to cell death) has not yet been defined, although severe mitochondrial damage and cell membrane destruction via free radical generation have been proposed. The light microscopical changes seen in injured cells are well described.

**Early changes**. These are reversible and include:

- Cytoplasmic swelling and vacuolation.
- Mitochondrial and endoplasmic reticulum swelling.
- Clumping of nuclear chromatin.

**Late changes**. These are irreversible and include:

- Densities in mitochondrial matrix.
- Cell membrane disruption.
- Nuclear shrinkage (pyknosis).
- Nuclear dissolution (karyolysis).
- Nuclear break up (karyorrhexis).
- Lysosome rupture.

## Cell death

### *Autolysis*

Autolysis is the death of individual cells and tissues after the death of the whole organism. The cells are degraded by the post-mortem release of digestive enzymes from the cytoplasmic lysosomes.

### *Apoptosis*

It is now known that cell death encompasses a spectrum of cellular processes. At one end of the spectrum, there is **necrosis** where the accidental death of a large number of cell causes an inflammatory

response. At the opposite end of the spectrum is **apoptosis.** This form of cell death occurs in physiological and embryological processes and appears to be a phenomenon whereby tissues control cell population numbers (sometimes called programmed cell death) or pathological processes (inflammation, cancers) in an attempt by the body to arrest cell proliferation and tissue damage.

During apoptosis, the cell activates genes which code for new proteins, many of which contribute to the cell's own death. The enzyme **endonuclease** is produced or activated, causing DNA fragmentation. In contrast to necrosis, apoptotic cells remain viable and their membrane pumps continue to function until the terminal stage of the process. During apoptosis, the cell shrinks, the nuclear chromatin condenses and the cell breaks into a large number of "apoptotic bodies". These can be disposed of by phagocytosis, either by macrophages or uniquely by neighboring normal cells. Phagocytes recognize apoptotic cells by the new membrane signals which they express. It is important to note that apoptosis does not provoke an inflammatory response.

**Physiological apoptosis.** This can occur in a number of situations:

- Embryogenesis: formation of digits.
- Menstrual cycle: endometrial cell loss.
- Breast feeding: reversal of changes in the lactating breast once breast feeding is finished.
- Immune cell development: deletion of immune cells (T cells) that may react with the body's own tissues.

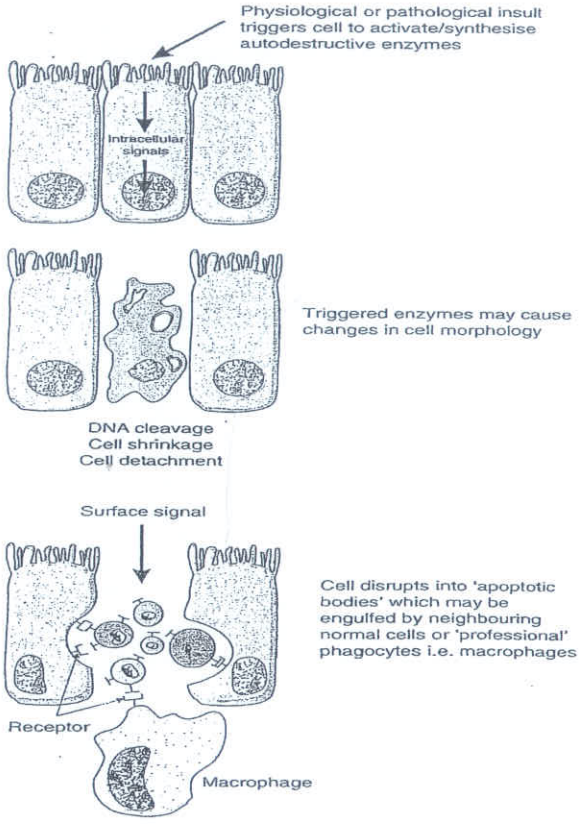
**Pathological apoptosis.** Individual cell death occurs in a number of pathological conditions:

- Tumours (often accompanied by necrosis).
- Atrophy (virtually never accompanied by necrosis).

- Viral illness (e.g. hepatitis – individual hepatocytes can be seen in apoptotic forms).

The control of apoptosis is crucial in the process of neoplasia. Some genes involved in cancer formation (e.g. the bcl-2 oncogene) seem to be able to switch off apoptosis, allowing cells to live forever.

**Apoptosis**

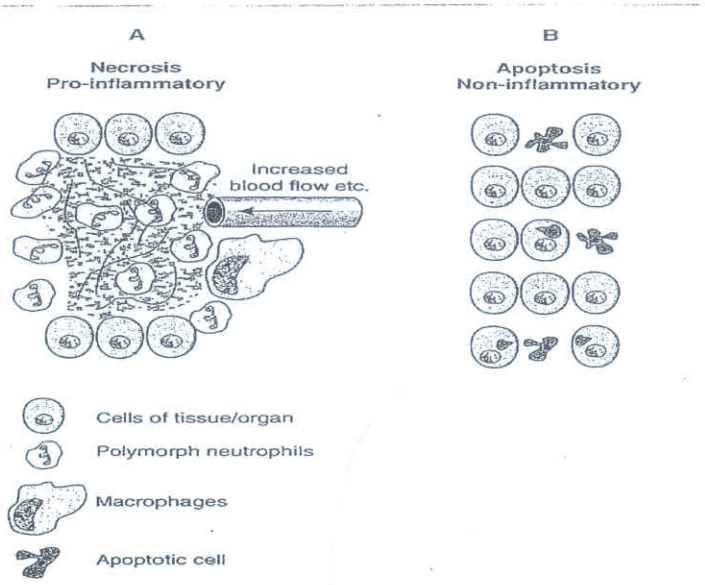



*Necrosis*

Necrosis is defined as the morphological changes that result from cell death within living tissues. In necrosis, death of a large number of cells in one area occurs, as opposed to the selective cell death of apoptosis. These changes occur because of digestion and denaturation of cellular proteins. In fact, the final appearance of the necrotic area will depend on

the balance between these two processes. There are several forms of necrosis.

## Diagrammatic comparison of necrosis and apoptosis

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The results of cell death can include:

- Cessation of function of a tissue or organ.
- Release of cellular enzymes, these can sometimes be detected in the blood and used as markers of the extent or timing of damage to a particular organ, e.g. cardiac enzyme after myocardial infarction.
- Initiation of the inflammatory response (vital reaction).

Types of necrosis

There are five main types of necrosis:

- Coagulative
- Caseous
- Liquefaction
- Fat
- Gangrenous

**Coagulative necrosis**. Denaturation of intracellular protein (analogous to boiling the white of an egg) leads to the pale firm nature of the tissues affected. The cells show the microscopic features of cell death but the general architecture of the tissue and cell ghosts remain discernible for a short time. Coagulative necrosis is typically seen in the kidney and heart and is usually caused by ischaemia.

**Caseous necrosis**. This type of cell death is only seen in tuberculosis (TB). The creamy white appearance of the dead tissue is probably a result of the accumulation of partly digested waxy lipid cell wall components of the TB organisms. The tissue architecture is completely destroyed.

**Liquefaction necrosis**. This results from release of hydrolytic lysosomal enzymes and leads to an accumulation of semi-fluid tissue. It is usually seen in the brain.

**Fat necrosis**. This can result from direct trauma (common in the fatty tissues of the female breast) or enzyme released from the diseased pancreas. Adipocytes rupture and the released fat undergoes lipolysis catalyzed by lipases. Macrophages ingest the oily material and a giant cell inflammatory reaction may follow. Another consequence is the combination of calcium with the released fatty acids.

**Gangrenous necrosis (gangrene)**. This life-threatening condition occurs when Coagulative necrosis of tissue is associated with superadded infection by putrefactive bacteria. These are usually anaerobic gram-positive Clostridia spp. Derived from the gut or

soil which thrive in conditions of low oxygen tension. Gangrenous tissue is foul smelling and black. The bacteria produce toxins which destroy collagen and enable the infection to spread rapidly. If fermentation occurs, gas gangrene ensues and infection can become systemic (i.e. reach the bloodstream, septicaemia). The commonest clinical situation is gangrene of the lower limb caused by poor blood supply and superimposed bacterial infection. This is a life-threatening emergency and the limb should be amputated.

## Degeneration

Nowadays, degeneration is used to describe pathological processes which result in deterioration (often with destruction) of tissues and organs. Therefore, osteoarthritis is an example of degenerative joint disease in which gradual destruction and deterioration of the bones and joint occurs. Alzheimer's disease is an example of a degenerative neurological disease where there is a progressive deterioration in brain function. Other pathological terms in skin and renal pathology imply degeneration of tissues. An example would be the UV-induced degeneration of the connective tissue in skin solar elastosis.

## Accumulation

Cells may accumulate pigments or other substances as a result of a variety of different pathological or physiological processes. The accumulations can be classified as endogenous or exogenous.

### *Fatty change*

Fatty change represents accumulation of triglyceride in cells and is usually an early indicator of cell stress and reversible injury. The most common cells in which fatty change is seen are in the liver, which has a central role in fat metabolism. Excessive alcohol consumption is a common cause of this, but there are other causes. In the liver, fatty accumulation occurs when cell damage compromises the ability of the hepatocyte to bind fat to protein and transport it through the cell. Fatty change is also seen in cardiac muscle cells as a result of severe anaemia or starvation (anorexia nervosa).

### *Haemosiderin*

Haemosiderin is a golden yellow to brown pigment found in lysosomes within the cell cytoplasm. It is composed of aggregates of partially degraded ferritin, which is protein-covered ferric oxide and phosphate. When there is an excess of iron, e.g. when there is a breakdown of red blood cells or haemorrhage, haemosiderin accumulates in cells. It can be visualized using the Prussian blue reaction, when haemosiderin appears dark blue.

Primary haemochromatosis is an inherited disease in which there is excessive accumulation of iron and widespread deposition of haemosiderin in the tissues, especially the liver, pancreas and skin. The iron is toxic to the tissues and leads to fibrosis of the liver (cirrhosis) and pancreas (leading to diabetes mellitus).

### *Melanin*

Melanin is the brown/black pigment which is normally present in the cytoplasm of cells in the basal cell layer of the epidermis, called melanocytes. Melanin is derived from tyrosine, stored in melanosomes and distributed to the other epidermal cells. The function of melanin is to block harmful UV rays from the epidermal nuclei. Melanin may accumulate in excessive quantities in benign or malignant melanocytic neoplasms and its presence is a useful diagnostic feature melanocytic lesions. In inflammatory skin lesions, where the epidermis is damaged, melanin may be released from injured basal cells and taken up by dermal macrophages. This gives rise to post-inflammatory pigmentation of the skin. Melanin can be identified in tissue sections by the use of the Masson-Fontana stain.

### *Lipofuscin*

This is the yellow/brown "wear-and-tear" pigment seen in atrophic tissues, particularly in heart muscle.

### *Other pigments and dyes*

Pigments and insoluble substances may enter the body from a variety of sources. They may be toxic and produce inflammatory tissue reactions or they may be relatively inert. Indian ink pigments produce effective tattoos because they are engulfed by dermal macrophages which

become immobilized and permanently deposited. Inhaled substances such as coal dust and silica are engulfed by pulmonary macrophages. Although pure carbon is inert, silica and coal dust are toxic and ultimately cause serious lung fibrosis (pneumoconiosis).

*Calcification*

There are two main types of calcification:

- Dystrophic.
- Metastatic.

**Dystrophic calcification**

This type of calcification occurs within diseased tissues. The plasma calcium and phosphate levels are normal. The exact mechanism by which dystrophic calcification occurs is not known. The best examples include calcification within foci of old tuberculosis and in atheromatous plaques. In both these cases, the calcification can often be seen, incidentally, on radiographs.

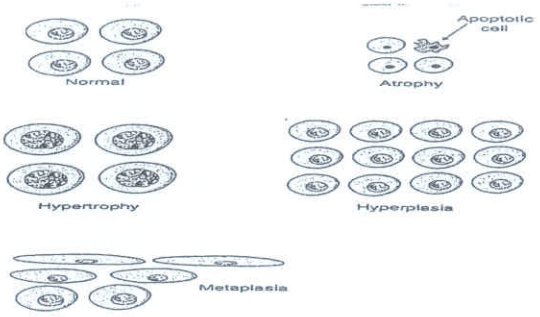
**Metastatic calcification**

Metastatic calcification often occurs in normal tissues as a consequence of raised plasma calcium concentrations (hypercalcaemia). Common causes of hypercalcaemia include widespread metastatic cancer in the bones , hyperparathyroidism and multiple myeloma. Hypervitaminosis D (excess intake of vitamin D) may also cause hypercalcaemia.

## Cellular adaptation

The normal growth and development of cells is under complex genetic and environmental control. Cellular adaptations, such as atrophy, hypertrophy and some types of hyperplasia remain controlled by normal mechanisms and are reversible.

## The Four Main Types of Cell Adaptations




There are four main adaptive cellular states are:

- **Atrophy**: shrinkage of an organ as a result of decreased cell size (and cell number).
- **Hypertrophy**: enlargement of an organ as a result of increased cell size.
- **Hyperplasia**: enlargement of an organ through an increase in cell number.
- **Metaplasia**: the replacement of one differentiated cell type by another in a tissue or organ.

### *Atrophy*

Atrophy is defined as the shrinkage of a cell by loss of the cell substance, which leads to a reduction in size of the whole organ. The cell retreats to a smaller size at which survival is still possible and sequesters its internal structures. In many cases of atrophy, individual cells may undergo apoptosis.

**Physiological situations leading to atrophy**:

- Reduction/loss of endocrine stimulation, e.g. shrinkage of testes and ovaries with age.

**Pathological causes of atrophy:**

- Denervation, e.g. wasting of muscle caused by a lack of nerve stimulation, for example in poliomyelitis.
- Reduced blood supply, e.g. shrinkage of brain caused by atherosclerosis of carotid arteries.
- Inadequate nutrition, e.g. wasting of muscles and major organs in starvation.
- Decreased workload (disuse) e.g. wasting of muscles and bone (osteoporosis) after immobilization of a bone fracture in a plaster cast.

**Cell structural components are reduced in atrophy:**

- Less mitochondria.
- Less endoplasmic reticulum.
- Fewer myofilaments.

**The metabolic rate is reduced:**

- Less amino acid uptake.
- Less oxygen consumption.
- Less protein synthesis.

In atrophy, there is an increase in the number of autophagic vacuoles (intracellular dustbins) which contain fragments of intracellular debris awaiting destruction. Lipofuscin granules are yellow/brown in color and represent non-digestible fragments of lipids and phospholipids combined with protein within autophagic vacuoles. They are commonly seen in ageing liver and myocardial cells.

*Hypertrophy*

Bodybuilders and athletes provide the best example of hypertrophy: muscle hypertrophy in response to increased workload. Individual cells increase in size as a result of an increase in their structural components leading to an overall increase in the size of the organ. Protein synthesis increases and its effect is enhanced by a decrease in protein degradation. Hypertrophy is mainly seen in cells which have no capacity for mitotic division, e.g. cardiac and skeletal muscle cells (permanent cells). The limiting factor for the eventual muscle size is the nutrient and blood supply available for oxidative phosphorylation.

**Physiological causes of hypertrophy:**

- Increased workload, e.g. the bodybuilder's skeletal muscle.
- Hormone stimulation, e.g. the pregnant uterus (smooth muscle hypertrophy).

**Pathological causes of hypertrophy:**

- Increased resistance e.g. cardiac muscle hypertrophy as a result of working agains an increased peripheral resistance in hypertension (high blood pressure).
- Physical obstruction, e.g. bladder smooth muscle hypertrophy in outflow obstruction caused by an enlarged prostate gland.

**Muscle cells**

**Hypertrophic muscle cells show:**

- Increased membrane synthesis.
- Increased amounts of ATP.
- Increased enzyme activity.
- Increased myofilaments.

**Endoplasmic reticulum**

Hypertrophy of smooth endoplasmic reticulum, i.e. hypertrophy at the subcellular level, can also occur. **Drugs** such as phenobarbatone cause an increase in the activity of the mixed function oxidase system of liver cells, which results in increased metabolism of other agents. In some

instances, this is therapeutically beneficial, in others, it can lead to poisoning of the liver cells by toxic metabolites.

*Hyperplasia*

Enlarged, hyperplastic tissues or organs show an increase in the number of their constituent cells. Tissues such as skin, gut epithelium and bone marrow normally have a high rate of cell turnover and are, therefore, the common sites for hyperplastic growth. Cardiac and skeletal muscle and neurons cannot undergo hyperplasia because they are permanent cells and cannot enter the cell cycle. Endocrine organs often undergo hyperplasia in response to excessive hormonal stimulation.

**Physiological causes of hyperplasia:**

- Hormonal, e.g. the female breast at puberty, the pregnant uterus and the proliferative endometrium in the first half of the menstrual cycle.
- Cell loss, e.g. regeneration of the liver after partial hepatectomy and regeneration of squamous epithelium in superficial skin wound healing.

**Pathological causes of hyperplasia:**

- Hormonal e.g. the endometrium in post-menopausal women taking estrogen-only hormone replacement therapy.
- Cell destruction e.g. ulcerative colitis the colonic mucosa undergoes repeated ulceration (destruction), regeneration and hyperplasia.

Pathological hyperplasia usually occurs in tissues which are exposed to inappropriate hormonal stimulation or to repeated episodes of inflammation, destruction and regeneration. It may progress to uncontrolled cell growth (Neoplasia), or it may remain a reversible phenomenon. Since most tissues contain labile and stable and permanent cells, hyperplasia without hypertrophy is uncommon.

*Metaplasia*

This is usually seen in epithelial tissues and is **a reversible change** in which one differentiated, adult cell type is replaced by another. The most common type of metaplasia is the replacement of glandular or

transitional epithelium by simpler and more robust squamous epithelium. Examples of this are:

- Bronchial (pseudo-stratified, ciliated columnar) epithelium changes to squamous epithelium in smokers.
- Transitional bladder epithelium changes to squamous epithelium in people with bladder stones and infection.

**Metaplasia** probably occurs at the level of the stem cell, which differentiates into the new type of epithelium. Metaplasia is often seen next to neoplastic epithelium, indicating that although this adaptive response is potentially reversible, continued insult to the cells may cause uncontrolled growth and the development of cancer.