Cell Adaptation and Cell Death

The normal cell is a highly complex unit in which the various organelles and enzyme systems continuously carry out the metabolic activities that maintain cell viability and support its normal functions. Normal function is dependent on (1) the immediate environment of the cell (2) a continuous supply of nutrients such as oxygen, glucose, and amino acids and (3) constant removal of the products of metabolism, including CO2. The plasma membrane establish a structural and functional barrier between its internal milieu and a hostile environment. In several way:

1- It maintains a constant internal ionic composition against very large chemical gradients between the interior and exterior compartments.

2- It selectively admits some molecules while excluding or extruding others.

3-It provides a structural envelope to contain the informational, synthetic and catabolic- constituents of the cell.

4- It provides an environment to house signal transduction molecules that mediate communication between the external and internal milieus.

At the same time, a cell must be able to adapt to adverse environmental conditions, such as changes in temperature, solute concentrations or oxygen supply, cells encounter many stresses because of changes in their internal environments, and this patterns of response to such stresses comprise the cellular basis of disease.

Reactions to Persistent Stress and Cell Injury:

*Reduced Functional Demand

*Inadequate Supply of Oxygen

*Insufficient Nutrients

*Interruption of Trophic Signals

*Persistent Cell Injury

*Increased Pressure

*Aging

*Chronic Disease

Cellular adaptation Definition

- Changes experienced by cells in response to physiological (e.g., increased muscular mass after exercising, increased number of epithelial breast cells during pregnancy) or pathological (e.g., Barett esophagus due to chronic gastric acid exposure) stimuli.

- These changes usually make it easier for cells to tolerate adverse environments.

- Persistent stress can lead to cell injury (e.g., critical Hypertrophy of the left ventricle → Myofibril damage → Heart failure.

Overview of cellular adaptation:

Atrophy:

1- Hypotrophy (simple atrophy): tissue degeneration caused by a decrease in protein synthesis and cell content (e.g., organelles, cytoskeleton)

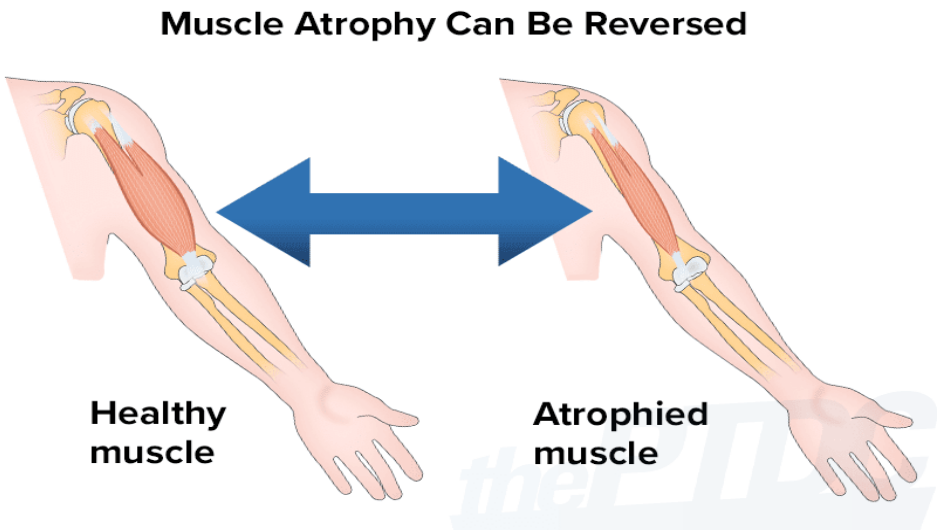
2- Numerical atrophy: reduction in cell number (e.g., due to apoptosis). Forms and examples Involution: Organs are temporarily enlarged and then undergo degradation via atrophic processes (e.g., thymus, breast). Senile atrophy: Physiological aging of cells that affects all organs, Caused by normal wear-and-tear.

Pathological atrophy:

- Generalized atrophy: catabolism, malnutrition, cancer anorexia-cachexia syndrome.

- Localized atrophy inactivity, pressure-induced atrophy, loss of hormonal stimulation (e.g., osteoporosis), ischemia (oxygen/substrate shortage), chronic inflammation.

- Neurogenic atrophy: muscular atrophy via degeneration of neuromuscular transmission.



Dystrophy:

Degeneration of tissue or organ (e.g., due to malnutrition or hereditary disease) Lipodystrophy Leukodystrophy Osteodystrophy

Hypertrophy:

Increased tissue size via enlargement of cells (due to an increase in organelles and structural proteins).

- Physiological hypertrophy: Increased muscle mass through sport. Uterus enlargement due to hormonal changes.
- Pathological hypertrophy: hypertrophic cardiomyopathy due to arterial hypertension.

Hyperplasia:

Controlled proliferation in form of elevated reproduction rate of stem cells and differentiated cells → ↑ cell number → ↑ tissue mass.

-Physiological hyperplasia: Estrogenic stimulation of the endometrium during the menstrual cycle. Reactive bone marrow hyperplasia in hemolytic anemia.

- Pathological hyperplasia: Endometrial hyperplasia due to excess estrogen stimulation BPH caused by androgen and estrogen stimulation.

Hyperplasia without Hypertrophy: Occurs as a response to increase biological demands, for example bone marrow hyperplasia in anemic patients (compensatory hyperplasia); also in a compensatory mechanism for nephrectomy, hyperplasia occurs in the normal kidney after removal of the other one.

Hypertrophy without Hyperplasia: Occurs in Skeletal muscle hypertrophy in athletes, and manual labor, and in Cardiac muscle hypertrophy in heart failure (cardiomegaly) and in hypertrophy of the smooth muscle of the stomach in pyloric stenosis.

Anaplasia:

Loss of mature cellular differentiation (no longer have morphological features of mature cells.

∗ Malignant transformation

Metaplasia is the reversible process in which a well-differentiated cell type is replaced by another well-differentiated cell type of the same germ line. It can be a normal physiological change in the cell type such as ossification of a cartilage into a bone. It can also be a response to an external stimulus such as the change of the respiratory epithelium of chronic smokers into squamous epithelium due to irritation. This means metaplasia involves a change in the cell type depending on the conditions of the body. Some other examples of metaplasia are:

 The change of the cuboidal/columnar/transitional epithelium into stratified epithelium due to vitamin A deficiency;

 The change of transitional cells into stratified squamous epithelium due to warm infestation or kidney stones;

 The change of the squamous epithelium into columnar epithelium (Barrett's esophagus) acid reflux;

 The change of the glandular epithelium into squamous epithelium due to the low pH of the vagina.

Generally, metaplasia can return to the normal conditions when the stimulus is removed. However, some metaplasia conditions such as Barrett's esophagus may be pre-cancerous. In addition, a metaplasia unaddressed for a considerable time period can become dysplasia and turn into cancer.

Dysplasia "bad growth"

Dysplasia is the disordered growth due to the loss of cellular uniformity as well as architectural organization, especially in the epithelium. It can range from low-grade to high-grade.

Dysplasia is also reversible at the initial stage. However, dysplasia shows a delay in tissue maturation, expanding immature cells, which in turn, decreases the number and the location of mature cells within the tissue. Hence, it can be considered the earliest form of pre-cancerous lesions. Therefore, high-grade dysplasia is synonymous with 'carcinoma in situ'. Neoplasia is the condition in which the entire epithelium becomes dysplastic.

Genetic alterations such as inactivation of tumor suppressor genes and activation of oncogenes are often a cause for dysplasia. Therefore, it can be reversible only by shedding off the diseased cells from the epithelium during its low-grade level.

Similarities Between Metaplasia and Dysplasia

 Metaplasia and dysplasia are two types of cellular changes that occur under the influence of various factors.

 Both are abnormal changes in the nature of a tissue.

Difference Between Metaplasia and Dysplasia

- Definition Metaplasia refers to the conversion of a mature, differentiated cell into another form of a mature cell type, often following injury or insult whereas dysplasia refers to the development of abnormal types of cells within a tissue, which may signify a stage preceding the development of cancer.
- Type of change That is, the metaplasia is the conversion in cell type while the dysplasia is the change in the phenotype of cells or a tissue.
- Occurs in Furthermore, Metaplasia occurs in various types of tissues while dysplasia mainly occurs in the epithelium.
- Causes Moreover, metaplasia is an adaptive process that occurs due to an external stimulus while dysplasia occurs due to the alteration of genetic material.
- Reversibility Also, the metaplasia is a reversible process while high-grade dysplasia is an irreversible process.
- Malignancy Importantly, metaplasia does not lead to the formation of cancers while dysplasia may cause cancers.
- Conclusion Metaplasia is the conversion of one form of differentiated cells into another form of differentiated cells in response to an external stimulus. On the other hand, dysplasia is an abnormal growth form of an epithelium, which can be pre-cancerous in its high-grade conditions. The main difference between metaplasia and dysplasia is the type of transformation.

Proliferation: Rapid division and an increase in the number of cells.

∗ Labile tissue: Short-lived, rapidly dividable cells with constant cell division or renewal Primarily established by replication of stem cells (e.g., mucous membranes in the gastrointestinal and respiratory tracts, skin, hematopoietic tissue)

∗ Permanent tissue: cells with little to no replication throughout life (e.g., cardiac muscle, neurons).

∗ Stable tissue: expandable tissue (e.g., exocrine and endocrine glands, connective tissue, liver and renal parenchyma, bones).

Regeneration: **Complete recovery** (cellular adaptation) or healing:

only possible in labile and minimally damaged stable tissue (e.g., regeneration of skin without scarring, regeneration of liver tissue after resection. **Incomplete regeneration:** Tissue loss is replaced by tissue of an inferior quality: **Partial recovery** (cellular adaptation) or repair: occurs in permanent tissue and stable tissue with pronounced damage (e.g., healing of skin with scar formation).

Injury to a cell may be nonlethal or lethal.

Lethal Injury (Necrosis):

Lethal injuries to the tissues of a living individual cause cell death (necrosis). Necrosis is accompanied by biochemical and structural changes and is irreversible. The necrotic cells cease to function; if necrosis is sufficiently extensive, clinical disease results.

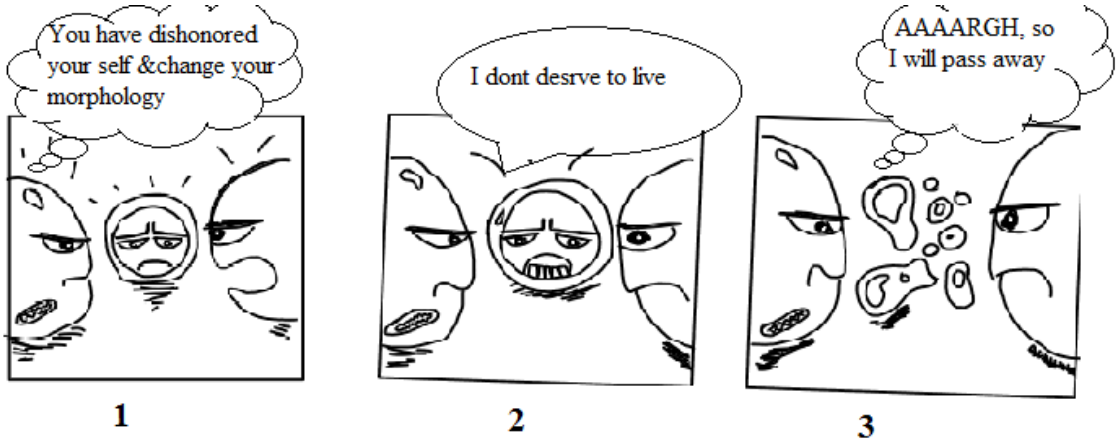
Nonlethal Injury (Degeneration):

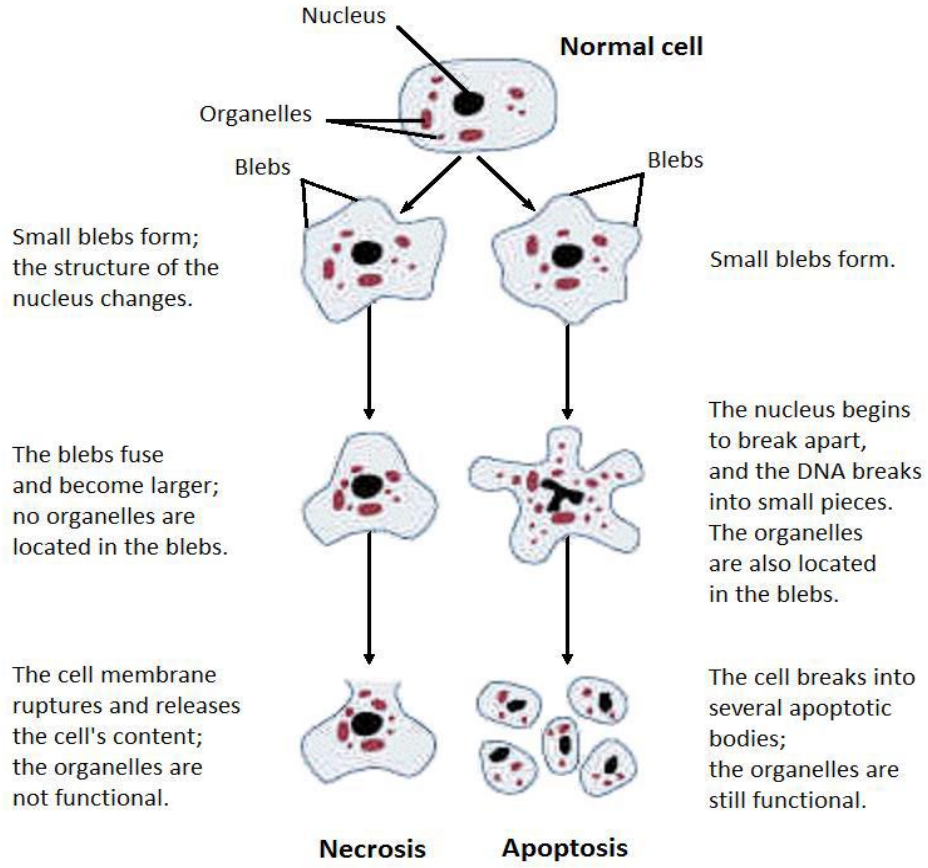
Nonlethal injury to a cell may produce cell degeneration, which is manifested as some abnormality of biochemical function, a recognizable structural change, or a combined biochemical and structural abnormality. Degeneration is reversible but may progress to necrosis if injury persists. When it is associated with abnormal cell function, cell degeneration may also cause clinical disease.

Programmed Cell Death (Apoptosis):

It is worth remembering that cell degeneration and cell death are ongoing phenomena in multicellular organisms and that in the healthy state, they are balanced by cell renewal. This process, through which effete cells are removed from normal tissue, is termed apoptosis. **It differs** from necrosis in that apoptotic cells are rapidly removed by phagocytes and there is no overt inflammation associated with their removal. In addition, apoptosis typically is initiated within the cell by nuclear fragmentation (pyknosis) and cytoplasmic condensation. Cell membranes remain intact in the early stages,

leading to small shrunken cells containing cytoplasmic or nuclear debris (apoptotic bodies).





Certain growth control genes may initiate apoptosis.

*Protein synthesis: Shortly after unloading, protein synthesis decreases.

*Protein degradation: Particular ubiquitin-related specific protein degradation pathways.

*Gene expression: There are selective decreases in transcription of genes.

*Signaling: The checks and balances that control the levels of up regulation and down regulation of intracellular signaling species change.

*Energy utilization: A selective decrease.

*Dysplasia: Is disordered growth and maturation of the cellular components of a tissue, it is a preneoplastic lesion, in that it is a necessary stage in the multistep cellular evolution to cancer.

*Calcification :May occur as part of normal development or as a reflection of an abnormal process, “Metastatic” calcification reflects deranged calcium metabolism, in contrast to dystrophic calcification, which has its origin in cell injury.

*Hyaline: Refers to any material that has a reddish, homogeneous appearance when stained with Hematoxylin and Eosin.

*Hydropic Swelling: Is a reversible increase in cell volume, characterized by a large, pale cytoplasm and a normally located nucleus reflects acute reversible cell injury. Subcellular changes include Endoplasmic reticulum, Mitochondria, Plasma membrane and Nucleus.

*Ischemic Cell Injury: Usually results from obstruction to the flow of blood.

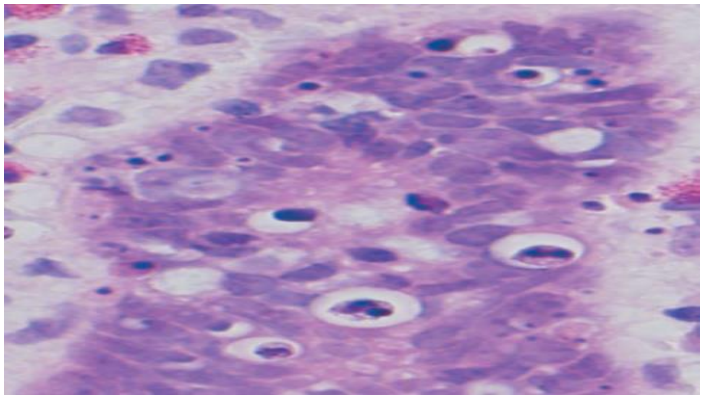
*Oxidative Stress: Is a key trigger for cell injury and adaptive responses. Included reactive oxygen species (OH), hydroxyl radical H2O2 with ferrous iron (Fe2_), Peroxynitrite interaction of two free radicals.

The effectiveness of cellular defenses against oxygen free radicals may determine the outcome of oxidative injury

* Detoxifying Enzymes

* Scavengers of ROS

Mutations: my impair cell function without causing cell death.



Morphologic appearance of apoptotic cells. Apoptotic

cells in a normal crypt in the colonic epithelium

are shown. Note the fragmented nuclei with condensed

chromatin and the shrunken cell bodies

Bone disease

BONES

Bones are composed of a unique type of mineralized connective tissue that undergoes mineralization
with a distinctive admixture of organic matrix (35%) and inorganic elements (65%).
The bone-forming cells include osteoblasts and osteocyte

CONGENITAL DISORDERS OF BONE AND CARTILAGE

The more common lesions include *aplasia* (e.g., congenital absence of a digit or rib), the formation of extra bones (e.g., supernumerary digits or ribs).

abnormal fusion of bones (e.g., premature closure of the cranial sutures or congenital fusion of the ribs). Such malformations may occur as isolated, sporadic lesions or as components of a more complex syndrome.

Osteoporosis

Osteoporosis is an acquired condition characterized by reduced bone mass, leading to bone fragility and susceptibility to fractures.

The bone loss may be confined to
1- localized to certain bones or regions,
2- generalized, involving the entire skeleton.
Generalized osteoporosis
may be
A- primary cause
1-Postmenopausal
2- Senile
B-secondary to a large variety of insults, including metabolic
diseases, vitamin deficiencies,
and drug exposures

B-Secondary

Endocrine Disorders

Hyperparathyroidism

Hypo or hyperthyroidism

Hypogonadism

Pituitary tumors

Diabetes, type 1

Addison disease

Neoplasia

Multiple myeloma

Carcinomatosis

Gastrointestinal Disorders

Malnutrition

Malabsorption

Hepatic insufficiency

Vitamin C, D deficiencies

Idiopathic disease

Drugs

Anticoagulants

Chemotherapy

Corticosteroids

Anticonvulsants

Alcohol

Osteoporosis occurs when the dynamic balance between bone formation by osteoblasts and bone resorption by osteoclasts tilts in favor of resorption.

Meaning of bone resorption involves the removal of hard bone tissue by osteoclast followed by the laying down of new bone cells by osteoblast cells

FRACTURES

Fractures rank among the most common pathologic conditions of bone. They are classified as follows:

A• *Complete* or *incomplete*
B• *Closed,* in which the overlying tissue is intact,
or *compound,* in which the fracture extends into the overlying
skin
C • *Comminuted fracture is abreak or splinter of the bone into more than fragment*
D• *Displaced: bone breaks into two or more pieces and moves out of alignment*

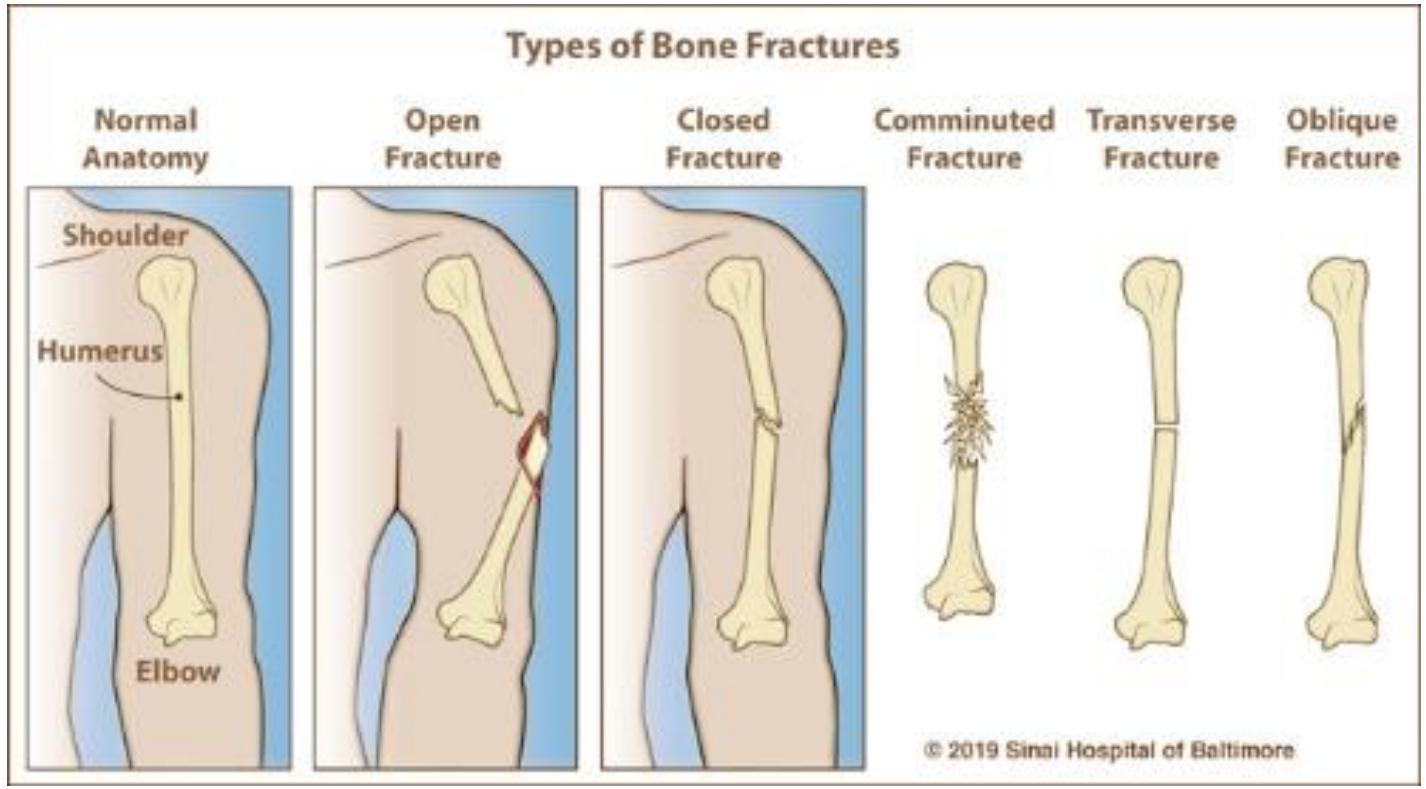
If the break occurs at the site of previous disease (e.g., a bone cyst, a malignant tumor, or a brown tumor associated with elevated PTH), it is termed a *pathologic Fracture(secondary fracture)*

A *stress fracture* develops slowly over time as a collection of microfractures associated with increased physical activity, especially with new repetitive mechanical loads on bone

Types of Fractures

Fractures have a variety of names. Below is a listing of the common types that may occur:

- Greenstick - Incomplete fracture. The broken bone is not completely separated.
- Transverse - The break is in a straight line across the bone.
- Spiral - The break spirals around the bone; common in a twisting injury.
- Oblique - Diagonal break across the bone.
- Compression - The bone is crushed, causing the broken bone to be wider or flatter in appearance.
- Comminuted - The break is in three or more pieces and fragments are present at the fracture site.
- Segmental - The same bone is fractured in two places, so there is a "floating" segment of bone.


Types of Bone Fractures
Normal Anatomy
Open Fracture
Closed Fracture
Comminuted Fracture
Transverse Fracture
Oblique Fracture
Shoulder
Humerus
Elbow
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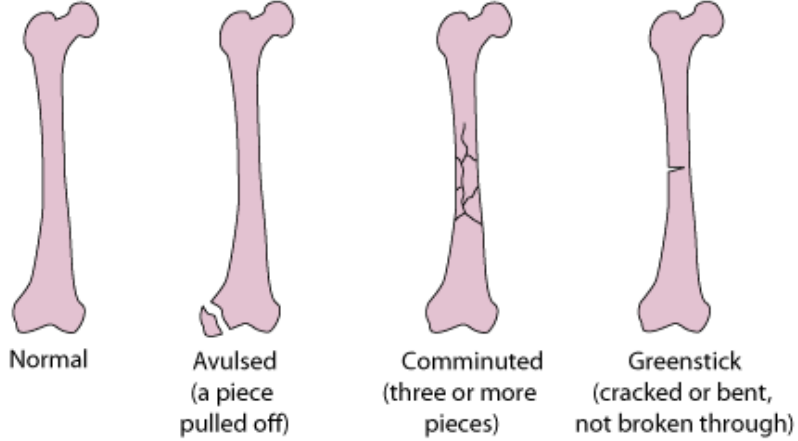
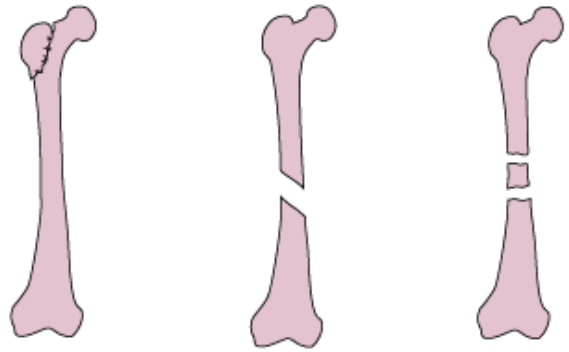


Normal

Avulsed
(a piece
pulled off)

Comminuted
(three or more
pieces)

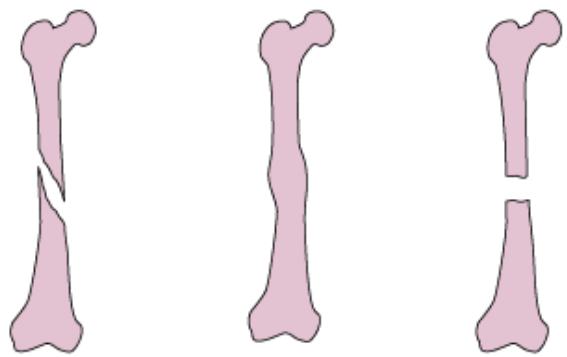
Greenstick
(cracked or bent,
not broken through)



Impacted
(broken ends
jammed into
each other)

Oblique
(broken in
a straight
diagnonal line)

Segmental
(a type of
comminuted
fracture)

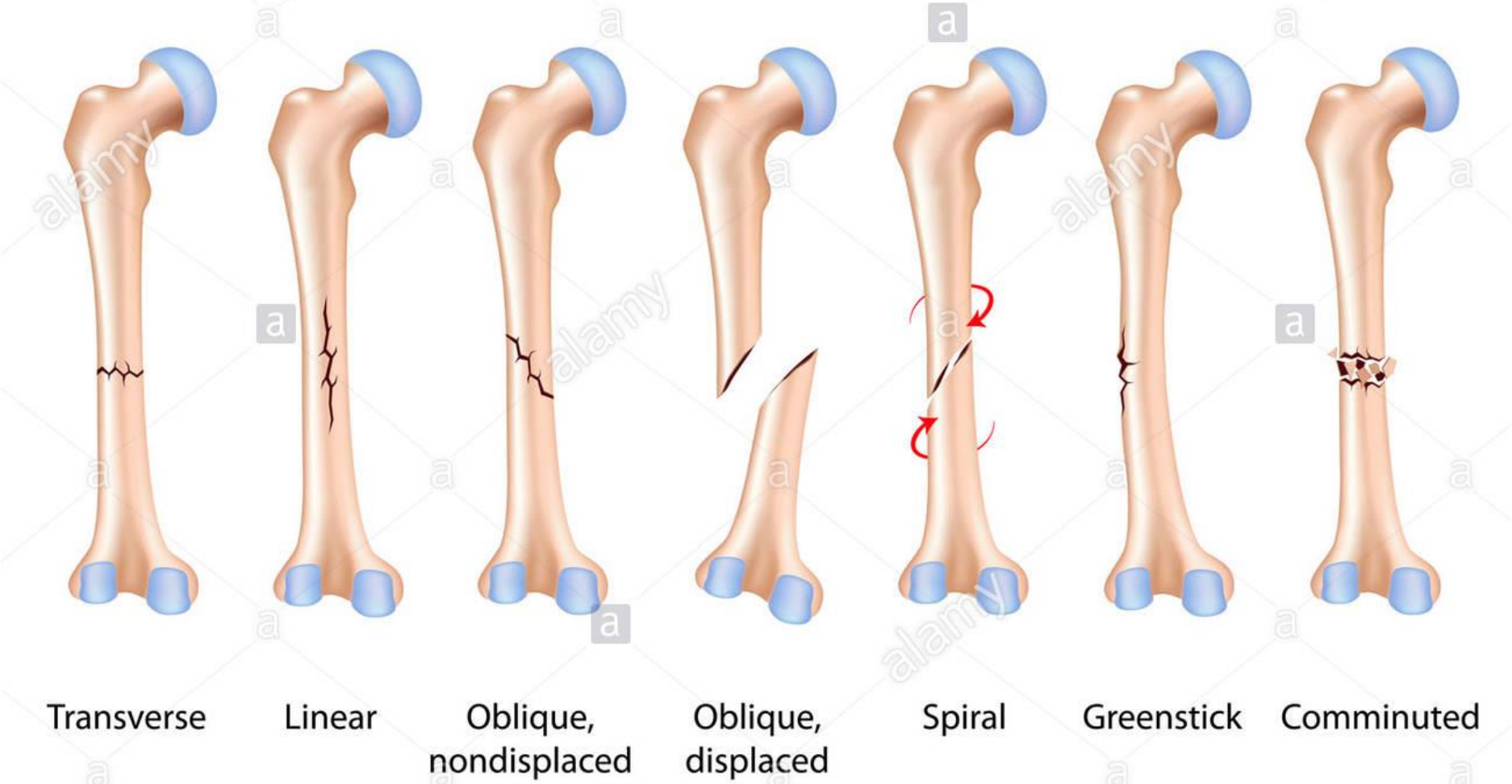


Spiral
(pieces
twisted apart)

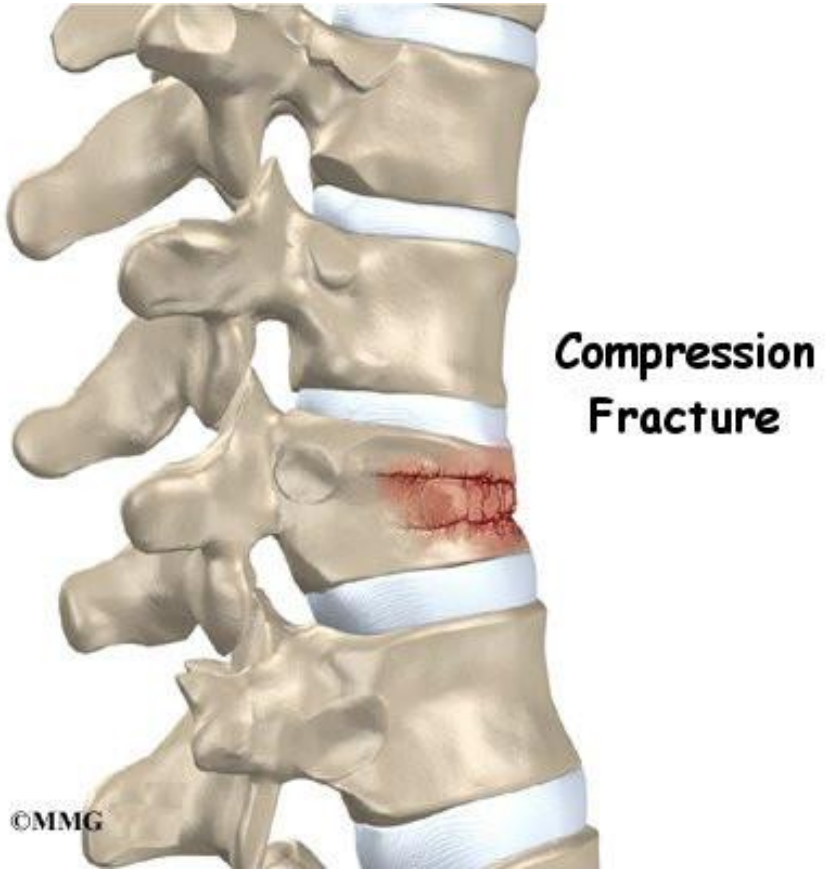
Torus
(buckled, not
broken)

Transverse
(broken straight
across)

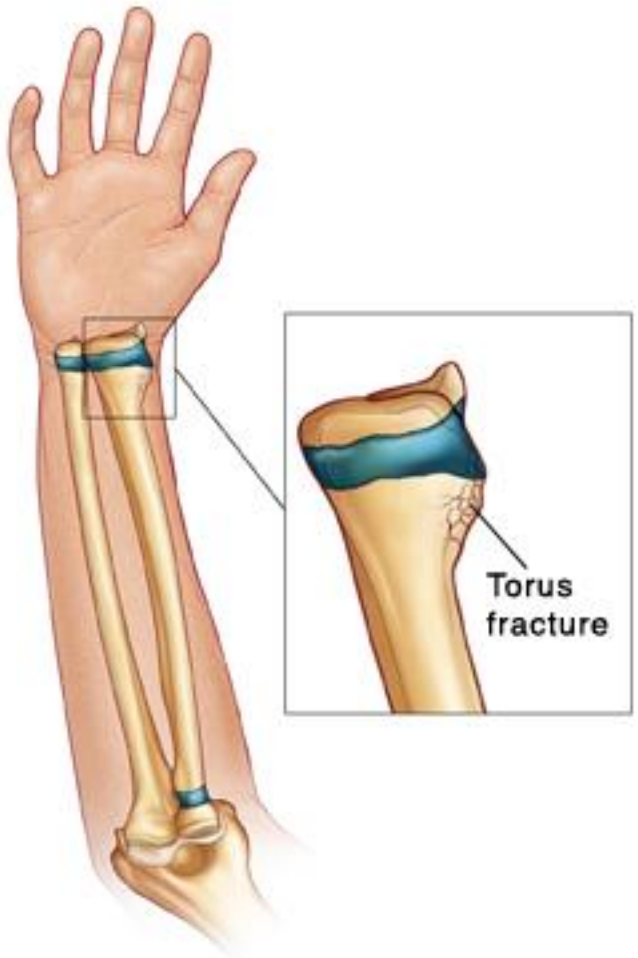
Types of Bone Fractures



A **compression fracture** is a collapse of a vertebra. It may be due to trauma or due to a weakening of the vertebra (compare with burst fracture). This weakening is seen in patients with osteoporosis or osteogenesis imperfecta, lytic lesions from metastatic or primary tumors,[1] or infection.[2] In healthy patients, it is most often seen in individuals suffering extreme vertical shocks, such as ejecting from an ejection seat. Seen in lateral views in plain x-ray films, compression fractures of the spine characteristically appear as *wedge deformities*, with greater loss of height anteriorly than posteriorly and intact pedicles in the anteroposterior



Torus fracture, also known as a **buckle fracture** is the most common **fracture** in children. It is a common occurrence following a fall, as the wrist absorbs most of the impact and compresses the bony cortex on one side and remains intact on the other, creating a bulging effect



3ed sage **General Pathology** **Dr. Tariq Al- kattab**

Human Genetic

Johann Gregor Mendel was born in Austria on 1822. He faces poverty and ill health in his childhood and youth. It took him almost eight years to complete his initial experiments on pea plants.Mendel's work did not get recognition during his lifetime. He passed away in 1884, but his work immortalized him as the 'father of modern genetics'.

Inheritance or heredity: The process of transmission of characters from one generation to the next (parents to children).

Deoxyribonuclic acid (DNA): it is macromolecules that encoded the genetic material needed for reproduction and protein synthesis. It is a double stranded helical that composed of nucleotides which consist of four nitrogenous bases that carry the genetic information and divided into 2 groups:

- The purine bases, adenine and guanine which have two nitrogen ring structure.
- The pyrimidine bases, thymine and cytosine which have one ring.

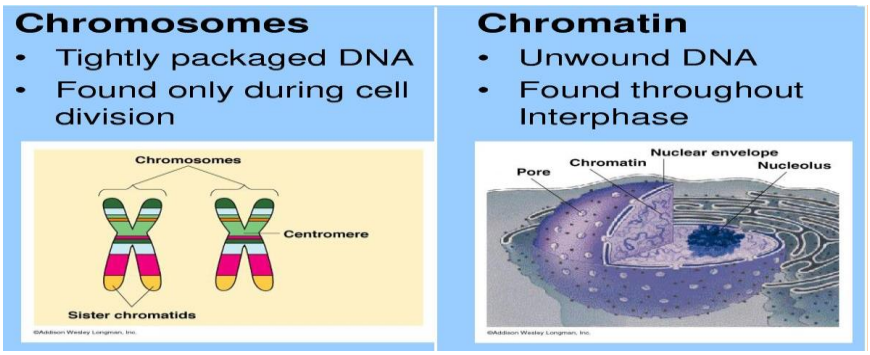
The backbone of DNA consists of alternating groups of sugar and phosphoric acid. DNA is extremely stable macromolecule to maintain the genetic information throughout the meiosis processes to form sperm and ovum and many mitotic cell divisions to form new individual from zygote (fertilized ovum).

Chromatin: is the complex structure of the DNA and DNA-associated proteins present in the nuclear matrix.

Chromosome: a single piece of coiled DNA that is packaged and condensed in chromatin in the nucleus. It forms four arm structure that attached in centromere that divides the chromosome into short arms (called p from petit) and long arms q. Chromosomes are visible only in dividing cells, they arranged in pairs (46

chromosomes in human 2n), one pair from mother (23 n) and the other from father (23 n), 22 is somatic and one pair is sex chromosome (X or Y).

Diploid= 2n, haploid=n, polyploidy= multiple copies of n.

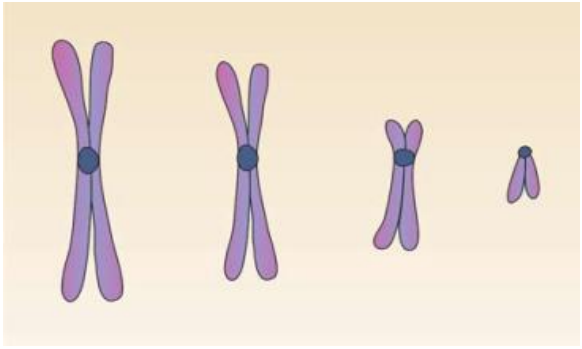


Metacentric: the karyotype of chromosome by which the centromere is in the center and the arms are about the same length.

Submetacentric: the karyotype of chromosome by which the centromere is not in the center and the arms are of different lengths.

Acrocentric: the karyotype of chromosome by which the centromere is near one end.

Telocentric: Centromere located at one end of the chromosome; effectively having only a single arm



Mitochondrial DNA: it is part of the DNA resides in the mitochondria inherited from mother (matrilineal inheritance), several human diseases attributed to mutation in this DNA. Affected males cannot transmit the disease to their offsprings. Common tissues affected are muscles and the nervous tissue that result in a wide range of clinical features including hypotonia of skeletal muscles, cardiomyopathy, encephalopathy, neuropathy, seizures, dementia and stroke.

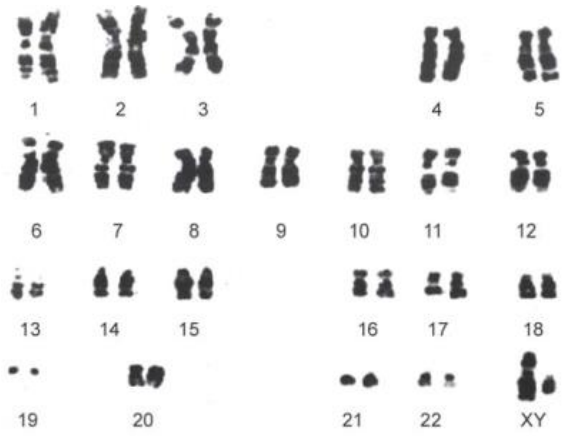
Gene: it is a basic unit of DNA molecule that passed from generation to the next generation (inherited) and contains the information code needed for protein and enzyme synthesis day to day function.

Genetics: it is the science of study genes and the principles that govern the passage of genes from one generation to the next. It has many divisions:

1. Molecular genetics: the study of gene function and regulation of its activity at molecular level.
2. Cytogenetics: the study of chromosomes by cytological appearance.
3. Biochemical genetics: the study of genes products (the enzymes) that control various metabolic processes. This branch deals with the inborn errors of metabolism.
4. Cancer genetics: studies the abnormalities related to these checkpoints of cell cycle to find the reasons that cause cancer.
5. Immunogenetics: deals with the genetics of production of different types of antibodies.
6. Developmental genetics: Deals with the genetic control of development of an embryo.
7. Population genetics: This branch deals with frequencies, distributions and the mutation of genes in human population.

Chromosome staining: by Giemsa stain (G banding technique) that shows alternative pattern of light and dark bands of variable widths.

Karyotype: is a photographic representation of chromosomes that stained in metaphase under the light microscope, the attention is given to their length, the position of centromeres, banding pattern and other physical characteristics.



Mechanism for genetic control of DNA function:

DNA► m RNA► t RNA► r RNA► protein synthesis► control of cell activity

Mitosis: it is the duplication of chromosomes in somatic cell by which each cell receives a full diploid number of chromosomes.

Meiosis: it is reduction of chromosomes in germ cell by which normal diploid number are reduced to single sets (haploid number) in each gamete.

Ribonucleic acid (RNA): it is essential in protein and enzymes synthesis; there are several types of RNA in the cell:

Messenger RNA (m RNA): it contains the transcribed instructions for protein synthesis from nuclear DNA to cytoplasm.

Transfer RNA (t RNA): it reads the instructions and delivers the appropriate amino acid to the ribosome to synthesize a specific protein.

Ribosomal RNA (r RNA): it provides the machinery needed for protein synthesis.

TABLE 3.1: Differences between DNA and RNA molecules

DNA	*RNA*
DNA is present in chromosomes.	RNA is present in nucleolus and cytoplasm.
The sugar molecule in DNA is deoxyribose.	The sugar molecule in RNA is ribose.
DNA is a double-stranded, helical structure formed by nucleotides arranged in a linear sequence.	RNA is single stranded which is formed by nucleotides arranged in a linear sequence.
Four nitrogenous bases are found in DNA (A, T, C and G).	It also contains 4 bases but thymine is replaced by uracil (A, U, C and G).
DNA is the hereditary material and information for life process are encoded in DNA molecules	It is nonhereditary in nature and helps in protein synthesis.

Genotype: it is heritable genetic identity or personal genome sequences.

Phenotype: is a description of actual visible physical characteristics of the individual.

Expressivity: the degree to which a particular gene produces its effect in an individual.

Penetrance: is the proportion of individuals carrying a particular variant (or allele) of a gene (the genotype) that also express an associated trait (the phenotype).

Locus: the position of gene on a chromosome.

Alleles: is a variant form of a given gene resulting in different phenotypic traits. There are two types either homozygous or heterozygous.

Genetic mutation

Mutations are changes that occur in the genetic material of an individual and may be heritable. The 'changes' may range from the smallest unit of a gene (nucleotide) to change in the gross morphology or number of the chromosomes.

Mutation is seen across all living organisms. It is the source of all genetic variations and species evolution by provide new trait to adapt the environment. However, most mutations are damaging to the organism.

Somatic mutations	Germinal mutations
Mutations occur in somatic cells that arises at any stage in the life of an individual.	Mutations occur in germ cells (egg or sperm)
Cannot be transmitted to the next generation	Transmitted to the next generation
It produce phenotype changes in the affected individual	It show-up in the subsequent generations.
Give rise to genetically two different types of cell lines in the individual.	don't produce mosaic offspring as all the cells would contain the anomaly received through a defective gamete

Molecular Basis of Gene Mutation

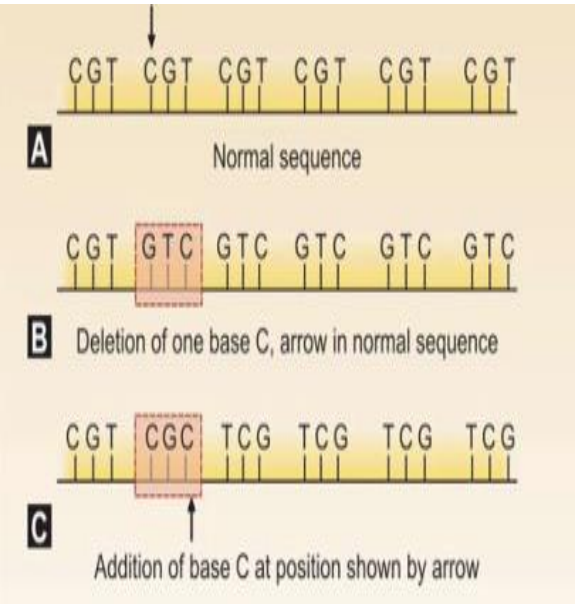
"Loss of Function Mutation": A mutation leads to reduced activity or complete inactivation of gene.

"Gain of Function Mutation": A mutation leads to over expression of a gene (increase in gene product) or activation of a gene in a tissue where it is normally inactive. A majority of such mutations lead to over expression of genes sometimes resulting in cancer.

Point mutation: smallest changes may involve an addition, deletion or substitution of a single nucleotide pair in the DNA molecule. These changes are invisible through the microscope yet may have profound phenotypic effects in an individual. It is divided into the following types:

1. **Substitution mutations:** the nitrogenous base of a triplet code of DNA is replaced by another nitrogenous base. The alteration of the codon now codes for a different amino acid. Substitution of the GAG triplet code (coding glutamic acid) by U alters it to a GUG codon (coding Valine) in the mRNA during transcription of Beta-globin chains of Hemoglobin leads to sickle cell anemia. A substitution mutation may not always be lethal as seen in the sickle cell disease. Nondeleterious mutations are known as silent mutations. However a gene mutation may be beneficial at times as seen in sickle cell mutation that imparts resistance to malaria.

2. **Frame Shift Mutation:** An insertion or deletion of a nitrogenous base in between the sequences in DNA or mRNA that reads the sequences of the codons. Such mutations may occur during transcription or during translation. It is often a lethal mutation because all the triplet codes beyond the point of mutation are misread.



Mutagens

Majority of mutations usually are spontaneous mutations (unprompted). Other mutations developed due to exposure to certain environmental agents. These agents are known as mutagens. Mutagens can be classified into two groups:

1. Physical and Chemical mutagens: Physical agents (high temperature), chemical agents (mustard gas, formaldehyde, benzene and thalidomide).

2. Radiations: natural (sun ray radioactive elements of thorium, radium and uranium present in the earth) and artificial ionizing radiations (X-rays, gamma rays, alpha, beta and neutrons rays (particles). Radiations may cause breaks in DNA involving the sugar phosphate backbone of the polynucleotide strands resulting in severe anomalies.

Mechanism of DNA repair

The DNA damage by chemicals and radiations are automatically repaired by specific and precise molecular mechanisms:

Damage	Repaired enzyme
Small slits in the DNA strand	DNA ligase
Damaged or mismatched nucleotides in DNA	AP endonuclease
Large damage in the DNA strand	The damaged area is cleaved by the enzyme endonuclease, the damaged portion is removed by the enzyme exonuclease, newly synthesized DNA strand is inserted with the help of the enzyme DNA polymerase and sealed by DNA ligase enzyme.

Classification of genetic diseases

1. Disorders due to mutation in single gene
2. Disorders due to chromosomal abnormality
3. Multifactorial disorders

Disorders due to mutation in single gene: Single gene mutations are responsible for these disorders and they follow laws of Mendelian inheritance. These disorders may be autosomal dominant, autosomal recessive or X-linked. Thousands of disorders can be categorized in this group. Some examples related to dentistry are:

Autosomal Dominant	Autosomal Recessive	X-Linked Dominant	X-Linked Recessive
Achondroplasia Dentinogenesis imperfecta Amelogenesis imperfecta Osteogenesis imperfecta	Cystic fibrosis	Vit. D resistant rickets.	Hemophilia Ectodermal dysplasia

Achondroplasia: is sporadic or an autosomal dominant trait of defect in Fibroblast Growth Factor Receptor (FGFR) or Cartilage Oligomeric Matrix Protein (COMP) that lead to defect skeletal growth characterized by short stature, bossing and exaggerated cranial growth, depression at the bridge of the nose.

Thus, in sporadic case most affected children are born to parents of ordinary stature, one of whom has a germline mutation. In the children of two parents with achondroplasia (Dd × Dd), most affected offspring are heterozygous (Dd), which suggests that the homozygous dominant genotype (DD) is lethal.

Amelogenesis imperfecta (AI): abnormal formation of the enamel affects both the deciduous and permanent teeth. It results mutation in genes which encode for enamel matrix proteins (ameloblastin, enamelin, tuftelins and amelogenin), it has several phenotypes: Hypomaturation Type of AI, Hypocalcified Type of AI, and Hypoplastic Type of AI.

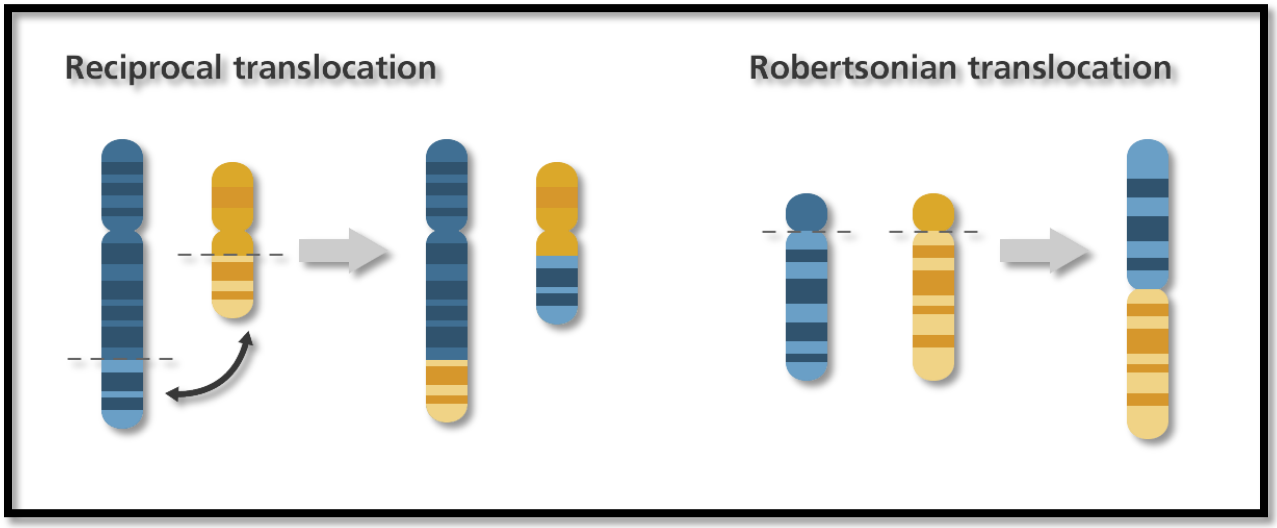
Dentinogenesis imperfecta (DGI): is a genetic defect in dentine formation affects both the primary and permanent teeth results in poorly formed dentine with an abnormal low mineral content, the enamel is normal but the pulp chamber and pulp canal are obliterated. The associated teeth are discolored (dusky blue to brownish) and rapidly wear down.

Disorders due to chromosomal abnormality: This group includes gross structural anomalies that give rise to alterations in the number of chromosomes (absence of a chromosome or presence of an extra chromosome), i.e. Trisomy 21 (Down's syndrome) or Turner's syndrome (XO). This class also includes disorders, which result due to abnormality in the structure of chromosomes such as deletions and translocations. The invention of banding and FISH (fluorescent in situ hybridization) techniques has helped to detect even minor abnormalities in chromosomes. The most important syndromes caused by this type of abnormality are:

1) **Down's syndrome**: it is the most common chromosomal disorder and is the commonest cause of mental retardation, it occurs due to nondisjunction during meiosis in one of the parents resulting in trisomy 21 in about 95% cases. The incidence of syndrome increase in mothers over 35 years of age.
2) **Klinefelter syndrome**: it is the most important example of sex chromosome trisomy. About80% cases have 47, XXY karyotype while others are mosaics. Typically, these patients have testicular dysgenesis. In general, sex chromosome trisomies are more common than trisomies of autosomes.
3) **Turner's syndrome**: it is an example of monosomy (45, X0) most often due to loss of X chromosome in paternal meiosis. Look normal female with ovarian failure, Normal intelligence and Short stature.
4) **Edward's Syndrome (Trisomy 18):** is a genetic disorder caused by the presence of all or part of an extra 18th chromosome. The patient die during the fetal stage; infants who survive experience serious defects and commonly live for short periods of time. Defects involving the brain, heart, craniofacial structures, kidneys and stomach.

Structural chromosomal abnormalities: it results from chromosomal breakage followed by rearrangement or loss of broken part, we can diagnose this changes by cytogenetic, it is many types:

1) **Translocation**: exchange of fragment of chromosomes, it is in 2 types:
    a. **Reciprocal** in about two-third (is the exchange of genetic material between two chromosomes without involving centromere (acentric).
    b. **Robertsonian** in one-third cases (is less common than reciprocal translocation. In this, there is fusion of two acrocentric chromosomes (having very short arms) at the centromere (centric fusion) with loss of short arms. The result of this fusion is one very large chromosome and the other very small one).



2) **Deletion** Loss of genetic material from the chromosome may be from the terminal or middle portion of the chromosome. The examples of deletion are: **cri du chat** (named after cry of infant like that of a cat) syndrome (deletion of short arm of chromosome 5).
3) **Inversion** is a form of rearrangement involving breaks of a single chromosome at two points. Inversion may be **pericentric or paracentric**, depending upon whether the rotation occurs at the centromere or at the acentric portion of the arm of chromosome. **Inversions are not associated with any abnormality.**
4) **Ring chromosome:** is formed by a break at both the **telomeric (terminal)** ends of a chromosome followed by deletion of the broken fragment and then end-to

end fusion. The consequences of ring chromosome depend upon the amount of genetic material lost due to break. Chromosome **22 Ring** is a rare disorder characterized by abnormalities of the 22nd chromosome. Associated symptoms and findings may be extremely variable from case to case. However, the disorder is typically associated with moderate to severe mental retardation.

5) **Isochromosome:** When centromere divides horizontally rather than dividing parallel to the long axis of chromosome, it results in either two short arms only or two long arms only called isochromosomes. Ex; 15% of Turner Syndrome and neoplasia.

Marfan syndrome is caused by a mutation in a gene called *FBN1*. The mutation limits the body's ability to make proteins needed to build connective tissue, Marfan syndrome can damage the blood vessels, heart, eyes, skin, lungs, and the bones of the hips, spine, feet, and rib cage. Some complications of Marfan syndrome can be treated or prevented, including heart disease, bone deformities such as a curved spine, eye conditions, crooked teeth, and collapsed lungs. Some complications of Marfan syndrome can be very serious, like an aneurysm (bulge) of the aorta, the main artery that takes blood away from the heart.

Albinism: genetic disorders of melanin synthesis. It is caused by mutations of the TYR gene on chromosome 11, which codes for tyrosinase. It affect melanocytes in the skin, the hair follicles, and the eye.

Ehlers-Danlos Syndrome: A genetic defects in collagen V caused by mutations in the COL5A1 and COL5A2 genes, characteristic feature of classic Ehlers-Danlos

syndrome (EDS) are skin hyperextensibility and hypermobility of joints with frequent dislocations/subluxations.

Multifactorial disorders: disorders determined by the interaction of many genes and environmental factors, dental caries, periodontitis, common congenital malformations like cleft lip and palate, hypertension and diabetes mellitus.

Tooth Agenesis: it is deficiency in tooth number and it is one of the most common developmental anomalies in humans. It may occur as sporadic or transmitted as an autosomal dominant, recessive or an X-linked condition. The development of tooth is strictly under the control of many genes (such as Pax-9 and Msx-1). Several mutations in the developmental genes could result into failure of tooth development.
Hypodontia: developmental lack of a few teeth.
Oligodontia: developmental lack of more than six teeth.
Anodontia: very rare complete lack of teeth.

Dental Caries and periodontitis: although certain microorganisms have been the causal factors for dental caries and periodontal diseases but recent researches have pointed that these conditions have a strong genetic predisposition, people have different susceptibility risk for developing dental caries and periodontitis.

Craniofacial Syndromes: defect in the development of craniofacial region during embryogenesis due to genetic and/or environmental factors.

- Cleft Lip, Cleft Palate
- Ectodermal dysplasias
- Cleidocranial dysplasia
- Treacher Collins syndrome
- Apert syndrome:
- Crouzon syndrome:
- Pfeiffer syndrome:

Hemodynamics

Hemodynamics or haemodynamics are the dynamics of blood flow. The circulatory system is controlled by homeostatic mechanisms of autoregulation, just as hydraulic circuits are controlled by control systems. The haemodynamic response continuously monitors and adjusts to conditions in the body and its environment. Thus, haemodynamics explains the physical laws that govern the flow of blood in the blood vessels.

Changes in intravascular volume, pressure, or protein content, or alterations in endothelial function will affect the movement of blood across the vascular wall.

Blood flow ensures the transportation of nutrients, hormones, metabolic waste products, O2 and CO2 throughout the body to maintain cell-level metabolism, the regulation of the pH, osmotic pressure and temperature of the whole body, and the protection from microbial and mechanical harm.

Haemodynamics Disorder:

1- Edema: Increased fluid in the interstitial tissue spaces.

Patho-physiologic Causes of Edema

- Increased Hydrostatic Pressure: Impaired venous return.

- Reduced plasma osmotic pressure (Hypo-proteinemia): Liver cirrhosis, nephrotic syndrome.

- Lymphatic Obstruction: Neoplastic, or postsurgical.

- Sodium Retention: Excessive salt intake with renal insufficiency

- Inflammation: Acute inflammation, Chronic inflammation

Types of edema:

• Anasarca: Generalized edema

• Dependent edema: Prominent feature of congestive heart failure, particularly of the right ventricle.

• Renal edema: Edema as a result of renal dysfunction or nephrotic syndrome is generally more severe than cardiac edema and affects all parts of the body equally.

• Peri-orbital edema: is a characteristic finding in severe renal disease.

• Pitting edema: finger pressure over substantially edematous subcutaneous tissue displaces the interstitial fluid and leaves a finger-shaped depression.

• Pulmonary edema: most typically seen in the setting of left ventricular failure.

2- Hyperemia and Congestion: Both indicate a local increased volume of blood in a particular tissue.

Hyperemia versus congestion. In both cases there is an increased volume and pressure of blood in a given tissue with associated capillary dilatation and a potential for fluid extravasation.

In hyperemia, increased inflow leads to engorgement with oxygenated blood, resulting in erythema.

In congestion, diminished outflow leads to a capillary bed swollen with deoxygenated venous blood and resulting in cyanosis.

3.Hemorrhage: Extravasation of blood due to vessel rupture.

Types:

• Hematoma: accumulation of blood within tissue.

• Petechiae: minute 1 to 2mm hemorrhages into skin, mucous membranes, or serosal surfaces.

• Purpura: slightly larger (≥3 mm) hemorrhages.

• Ecchymoses: larger (>1 to 2 cm) subcutaneous hematomas (i.e., bruises)

• Hemothorax, hemopericardium, hemoperitoneum, or hemarthrosis (in joints): Large accumulations of blood in one of the body cavities.

4-Thrombosis:

Hemostasis and Thrombosis

Normal hemostasis result of a set of well-regulated processes that accomplish two important functions:

1-They maintain blood in a fluid, clot-free state in normal vessels.

2-They are aimed to induce a rapid and localized hemostatic plug at a site of vascular injury

Thrombosis: an inappropriate activation of normal hemostatic processes, such as the formation of a blood clot (thrombus) in uninjured vasculature or thrombotic occlusion of a vessel after relatively minor injury.

Both hemostasis and thrombosis are regulated by three general components:-

– The vascular wall

– Platelets

– The coagulation factors

27. Both hemostasis and thrombosis are regulated by three general components:- – the vascular wall – platelets – the coagulation factors

• Three primary causes for thrombus formation, the so-called Virchow triad:

(1) Endothelial injury

(2) Stasis or slowing of blood flow

(3) Blood hyper-coagulability

Virchow triad in thrombosis. Endothelial integrity is the single most important factor. Note that injury to endothelial cells can affect local blood flow and/or coagulability; abnormal blood flow (stasis or turbulence) can, in turn, cause endothelial injury. The elements of the triad may act independently or may combine to cause thrombus formation.

Thrombi may develop anywhere in the cardiovascular system, but stasis is a major factor in the development of venous thrombi• An area of attachment to the underlying vessel or heart wall, frequently firmest at the point of origin, is characteristic of all thrombosis

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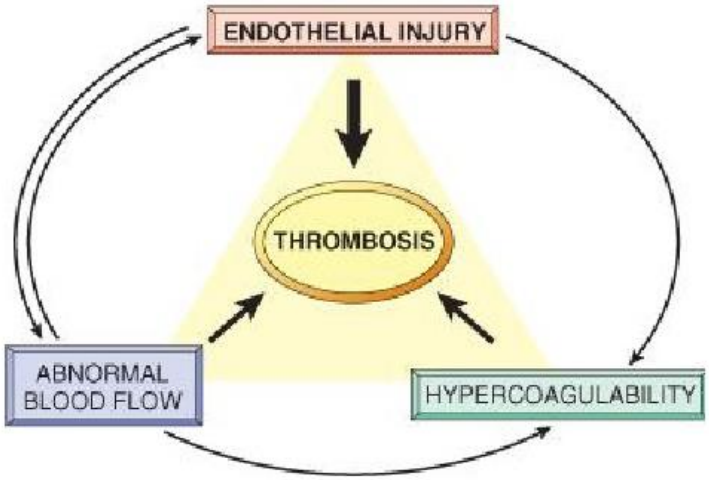
Fate of the Thrombus:

1. Propagation. **2**. Embolization.

3. Dissolution. **4**. Organization and recanalization



5- Embolism: An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.

Emboli lodge in vessels too small to permit further passage, resulting in partial or complete vascular occlusion. Pulmonary Thrombo-embolism. 95% of venous emboli originate from deep leg vein thrombi.

Large embolus derived from a lower extremity deep venous thrombosis and now impacted in a pulmonary artery branch.

6-Infarction: An infarct is an area of ischemic necrosis caused by occlusion of either the arterial supply or the venous drainage in a particular tissue. Nearly 99% of all infarcts result from thrombotic or embolic events, and almost all result from arterial occlusion.

Infarcts are classified on the basis of their color (reflecting the amount of hemorrhage) and the presence or absence of microbial infection.

• Red (hemorrhagic) infarcts occur:

(1) with venous occlusions (such as in ovarian torsion).

(2) in loose tissues (such as lung).

(3) in tissues with dual circulations (e.g., lung and small intestine).

• White (anemic) infarcts occur:

(1) with arterial occlusions in solid organs with end- arterial circulation (such as heart, spleen, and kidney).

(2) Solid tissues

Examples of infarcts: (A) Hemorrhagic, roughly wedge-shaped pulmonary infarct. (B) Sharply demarcated white infarct in the spleen.

Septic infarctions may develop when embolization occurs by fragmentation of a bacterial vegetation from a heart valve or when microbes seed an area of necrotic tissue.

7- Shock: Or cardiovascular collapse, is the final common pathway for a number of potentially lethal clinical events, including severe hemorrhage, extensive trauma or burns, large myocardial infarction, massive pulmonary embolism, and microbial sepsis.

gives rise to systemic hypo-perfusion caused by reduction in: 1. cardiac output 2. the effective circulating blood volume.

The end results are hypotension, followed by impaired tissue perfusion and cellular hypoxia.

Less commonly:1. Neurogenic shock -in the setting of anesthetic accident or spinal cord injury, owing to loss of vascular tone and peripheral pooling of blood.

2. Anaphylactic shock, initiated by a generalized IgE-mediated hypersensitivity response, is associated with systemic vasodilatation and increased vascular permeability.

Type of Shock	Clinical Examples	Principal Mechanism
Cardiogenic	- Ventricular rupture - Arrhythmia - Cardiac tamponade - Pulmonary embolism - Myocardial infarction	Failure of myocardial pump owing to intrinsic myocardial damage, extrinsic pressure, or obstruction to outflow
Hypo-volemic	- Hemorrhage - Fluid loss, e.g., vomiting, diarrhea, burns, or trauma	Inadequate blood or plasma volume
Septic	- Overwhelming microbial infections - Endotoxic shock - Gram-positive septicemia - Fungal sepsis	Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage; disseminated intravascular coagulation; activation of cytokine cascades

IMMUNOPATHOLOGY OF DISEASES

Immune System: Defined as a defense mechanism against microorganisms, malfunctioning cells, and foreign particles that enter the body

Steps of Defense Mechanisms: The first defense mechanism against foreign bodies and microorganism is called non-specific external barriers, i.e. skin, mucous membranes, saliva, and HCl in the gastric juice. If these barriers are penetrated, the body responds with innate immune response, i.e., phagocytes and natural killer cells, inflammation, and fever. If the innate immune response is insufficient, the body responds with adaptive immune response cell-mediated immunity, and humoral immunity.

Non-specific Defense Mechanisms

These are designed to prevent infections by organism like viruses and bacteria non-specifically, and they include intact skin, mucus and cilia, phagocytes… etc.

Role of the Skin: Skin is a strong barrier from microorganisms. Moreover, kin cells are constantly sloughed off, making it hard for invading bacteria to colonize, sweat and oils contain anti-microbial chemicals, including some antibiotics.

Role of Mucus, and Cilia: Mucus contains lysozymes, enzymes that destroy bacterial cell walls. The normal flow of mucus washes bacteria and viruses off, and away from mucous membranes. Cilia in the respiratory tract move mucus out of the lungs to keep bacteria and viruses away.

Role of Phagocytes: Phagocytes are several types of white blood cells (including macrophages and neutrophils... etc.) that engulfs and destroys invaders. Some also engulf damaged body cells. Phagocytes are attracted by an inflammatory response of damaged cells. Role of Inflammation: Purpose of inflammation is to get rid of the microorganism, and to wash out toxin and bacteria in the exudates fluid

Role of Fever: The temperature of the tissues may rise, which can kill temperature-sensitive microbes, fever is a defense mechanism that can destroy many types of microbes, fever also helps in fight of viral infections by increasing interferon production.

Role of Innate Immune System: A general response to anything other than a previously recognized antigen. Therefore, it is non-specific response only to the first exposure. The most important cells working in innate immunity include neutrophils, eosinophils, mast cells, basophiles, natural killer (NK) cells, and dendritic cells. All these cells have receptors for pathogens there for not in need of previous recognition of the Ags, NK cell has the natural ability to lyses tumour cells, virally infected cells & IgG-coated target cells .

Specific Defense Mechanisms

Specific defenses are those that give us immunity against certain diseases. The immune system forms memory data for the invading microbe. If the microbe is encountered again, the body reacts so quickly and specifically, that few or no symptoms are felt. Major players in specific immunity are macrophages, T cells (helper, cytotoxic, memory), B cells (plasma, memory) and antibodies.

Adaptive Immune System: A specific immune response formed against a "known foreign" antigen that is previously recognized. Using stored data (memory cells); more cellular or humeral immune response is induced.

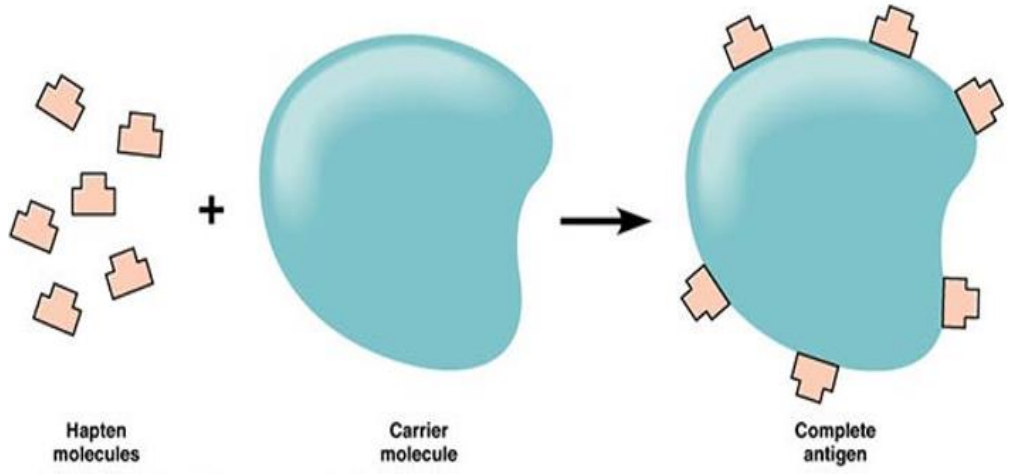
Antibody: A protein produced by the human immune system to tag specific invasive microbes for destruction.

Antigen: any substance that our immune system can recognize. It may be self or non-self-antigen. Specific antibodies are formed to block specific antigens.

Hapten

Hapten is a molecule that reacts with specific antibody but is not immunogenic by itself, it can be made immunogenic by conjugation to a suitable carrier. Many drugs like penicillins are haptens. A hapten is

essentially an incomplete antigen. These small molecules can elicit an immune response only when attached to a large carrier such as a protein; the carrier typically does not elicit an immune response by itself.



Lymphocytes in the Immune Response

Lymphocytes are two types T&B lymphocytes, B-cells mature in bone marrow, then concentrate in lymph nodes and the spleen and produce antibodies. T-cells mature in thymus. B and T cells then circulate in the blood and lymph. Circulation ensures they come into contact with pathogens.

1- B-Lymphocytes:

There are more than 10 million different B-lymphocytes; each of which makes a different antibody that is specific to one Ag. The huge variety is caused by genes coding for ABS changing sites. There are a small group of B-lymphocytes from which antibodies do not leave and are embedded in the plasma membrane of the cell, called antibody receptors. When the receptors in the membrane recognise and antigen on the surface of the pathogen the B-cell divides rapidly.

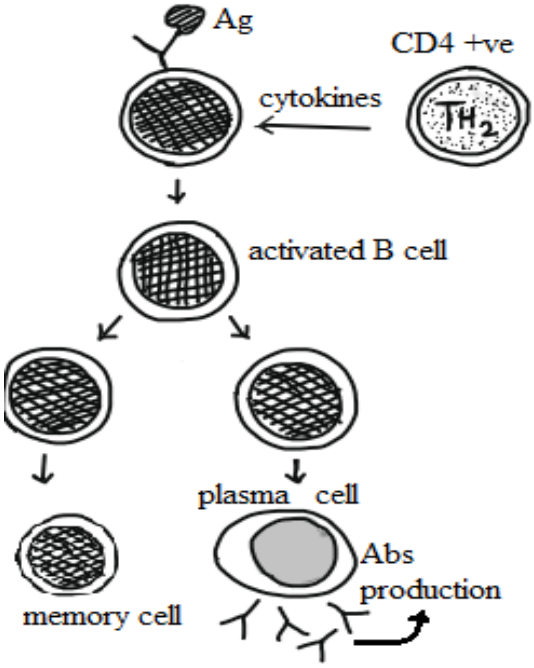


Figure 1: Stimulation of B lymphocyte to produce immunoglobulin

Some activated B cells give rise to plasma cells. These produce lots of antibodies which travel to the blood, lymph, lining of the gut and lungs. Then after a few weeks, numbers of plasma cells number go down while antibodies stay in the blood longer, but eventually their numbers go down too. Some activated B cells become memory cells; memory cells are able to divide rapidly as soon as the antigen is reintroduced once more. When the pathogen infects again it is destroyed before any symptoms appear.

Antibodies: Antibodies are also known as immunoglobulins.

How Abs Work? Some acts as labels to identify antigens and tell the phagocytes. Others work as antitoxins i.e., they block toxins, e.g., diphtheria and tetanus toxins, while others attach to bacterial flagella making them less active and easier for phagocytes to engulf, and some cause agglutination (clumping together) of bacteria, making them less likely to spread.

Immunglobulins Functions

- IgM: The first antibody to be produced; very effective against microorganisms and agglutinating antigens. It is a pentamer and cannot pass through the placenta.

- IgG: Enhances phagocytosis, neutralizes viruses & toxins, passes through placenta and protects fetus & newborn, it is monomer.

- IgA: Provides localized protection on mucosal surfaces. It is dimmers, and cannot pass through the placenta.

- IgE: Monomer and fixed to basophiles and eosinophils, responsible for allergy and the killing of parasites.

Type of Abs	Structure	Pass through the placenta	Functions
IgG	Monomer	Yes	2ndry immune response
IgM	Pentamer	No	1ry immune response
IgA	Diamer	No	Mucosal immunity
IgE	Monomer	No	Allergy

Table: Comparison of immunoglobulins

2- T-Lymphocyte:

T-cells lymphocyte has T cell receptors (TCR) which have a very similar structure of antibodies variable region (FAB) and are specific to one antigen. They become activated when the receptor comes into contact with the Ag on antigen presenting cells (e.g. on a macrophage membrane or an invaded body cell).

After activation, the cell divides to form the following subtypes:

♦ **T-helper Cells:** Which secrete cytokines to help B cell proliferation, and stimulate macrophages to secret more cytokines?

♦ **Cytotoxic T Cells:** Cytotoxic T cells, which Kill cells bound to the specific Abs e.g., virally infected cells.

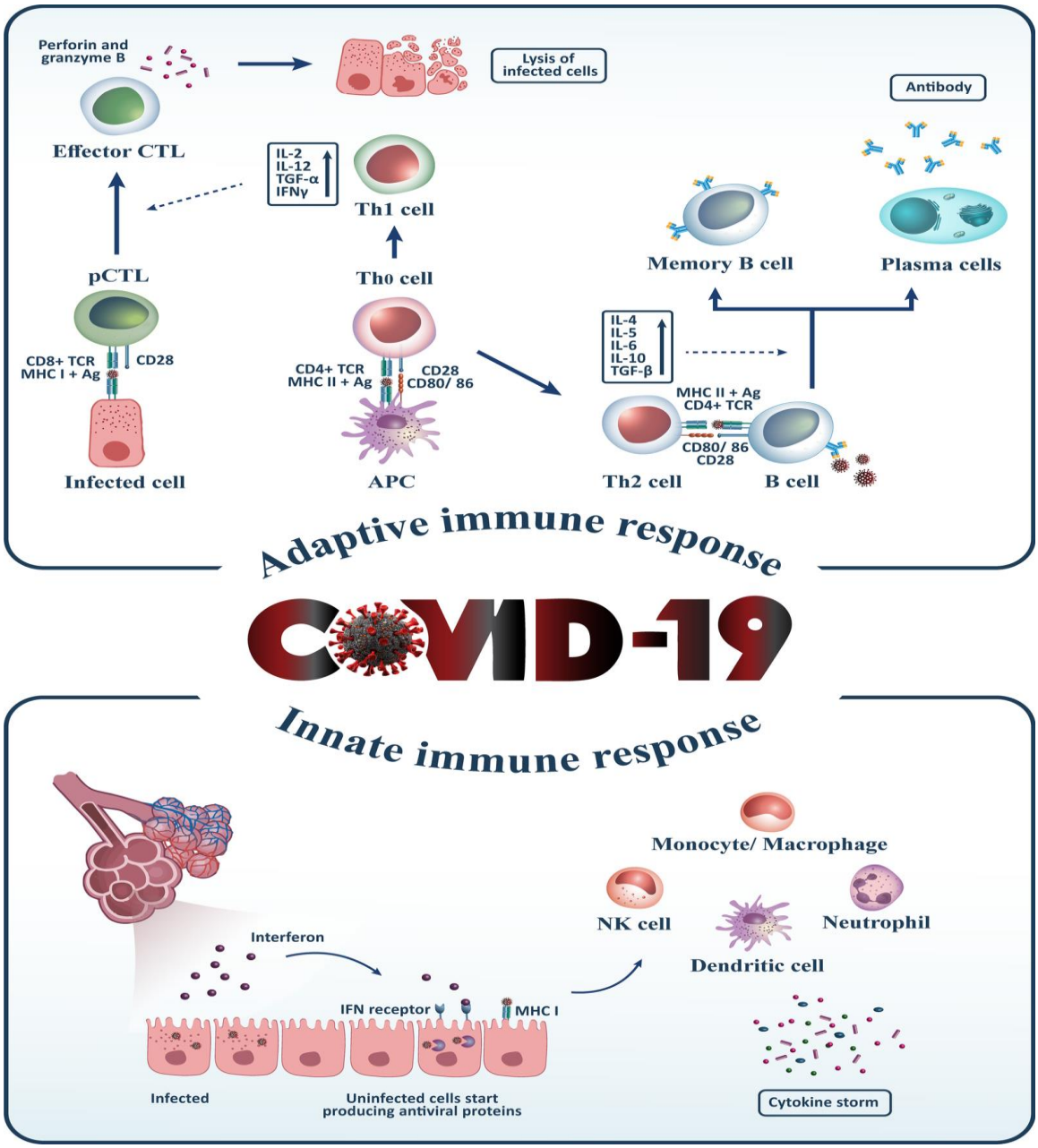
♦ **Suppressor T Cell:** Which inhibit further immune response, i.e., negative feedback mechanism on the immune system?

♦ **Memory T Cells:** This cell remains in the circulation, waiting for re infection with the same microorganism. Then it will divide and give activated T-cell, and the process start again.

Other Elements in the Immune Response

- Complement System: A group of proteins activate each other in a cascade reaction, and regulate chemotaxis, opsonization, and phagocytosis. They also kill microorganisms by forming perforins.

- Plasma proteins: Kinins, coagulation proteins, vasoactive amines, arachidonic acid metabolites & platelet-activating factor are chemical mediator which participates in the immune reactions.



Major Histocompatibility Complex (MHC)

Histocompatibility: It is the degree of similarity and diversity between a donor and a recipient tissue, to determine how much they share the same antigens, so that a graft is accepted or rejected.

HLA and MHC: HLA is gene products of the MHC, which is important in the recognition of self and non-self-antigens. They are inherited from both parents. MHC gene is found on chromosome 6 where genes encode for a group of variable proteins, also known as HLA human leukocyte antigens (firstly discovered on WBCs). Histocompatibility antigens can stimulate an immune response and reject transplants when the donor and recipient are mismatched.

Why are HLA important?

• HLA matching is important in transplantation

• HLA regulate some immune responses

- Virus-infected cells with class I antigen are lysed by CD8+ cells that can recognize the virus-cell complex

- Class II antigens help to induce CD4+ cells

• HLA are associated with a variety of diseases, such as HLA B27 with ankylosing spondylitis, or HLA DR 2, DR3, and DR4 with autoimmune diseases.

MHC composed of class I, and II.

MHC genes products are classified into:

- ***Class I antigens***: are coded by 3 closely linked loci; A, B, and C; (HLA-A, HLA-B, HLA-C) these are present on all nucleated cells& platelets.
- ***Class II antigens*** **:** are in the D region (HLA-DP, HLA-DQ, HLA-DR) and have a narrow distribution (mostly on mononuclear inflammatory cells; macrophages and dendritic cells).
- ***Class III antigen :*** Complement system protein.
- ✓ HLA Antigens are like (finger prints) on the cell surface.

• **Class I Antigens:** MHC antigens Class I, are found in virtually every cell in our body except RBC. Role of Class I Antigens is to protect against intracellular organism such as viruses, and viral antigen are presented on

class I to CD8+ T-cells for recognition and subsequent destruction of the viral infected cells by the cytokine of cytotoxic T-cell.

• **Class II Antigen:** HLA Class II Antigens are synthesized and expressed on the surface of antigen presenting cells (APCs) including, follicular dendritic cells, and Langerhans cells, primarily B lymphocytes and macrophages. CD4+ T-lymphocytes have receptors that interact with class II-peptide complex resulting in T-cell activation once antigen recognition and binding occurs.

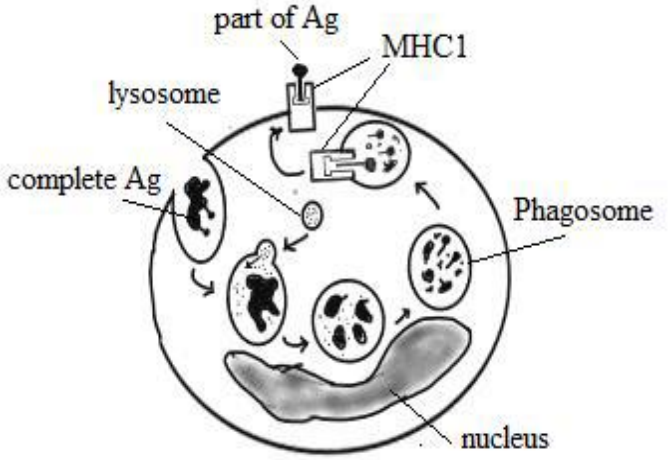


Figure 3: Ags processing and presentation in macrophage

Cell-Mediated Immunity

This is specific type of immunity in which T-cells are specific for a single antigen, and these antigens are recognized by CD4+lymphocyte only if attached to MHC II receptor of antigen presenting cell APCs. At this time APCs secrete IL-1 and CD4+ lymphocyte secrete IL-2, hence further activation of APCs, proliferation and recruitment of antigen-specific TH cells, and TC cells take place, the result of this T cytotoxic cells release perforin to lyses APC cells and damage to the tissue around it (no antibodies in this type of immune response).

Main Cytokines in Cell Mediated Immunity

♦ **Interleukin-1:** Produced by antigen presenting cell when attached to CD4+ cell, its role is to activate TH cell for proliferation and secretion

♦ **Interleukin-2:** Produced by CD4+ cell under the action of IL-1, its role as autocrine and paracrine effects on both CD4+ cell and antigen presenting cell, proliferation and differentiation of B cells, activation of TC cells & NK cells

♦ **Gamma interferon:** One of the innate immune response. It inhibits virally infected cell proliferation and regulate macrophage and antigen presenting cells

♦ **Tumor Necrosis Factor:** Produced from activated macrophages, CD4+ cell. It kills tumor cells; and regulates the immune response, e.g., enhances phagocyte action.

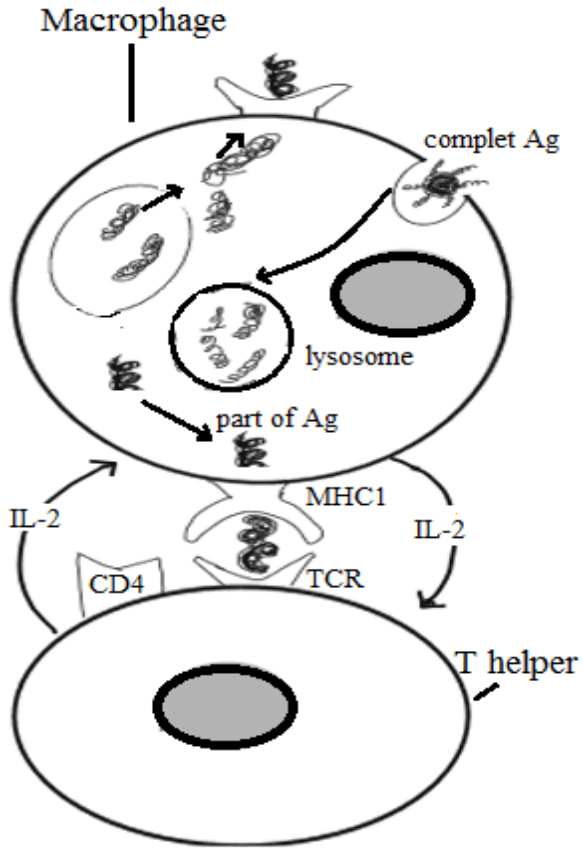


Figure 4: Interaction between Ags presenting cell and T-helper

HYPERSENSITIVITY REACTION

Hypersensitivity reactions are mainly classified into four types:

- Type I: Immediate hypersensitivity reaction
- Type II: Antibody-mediated cytotoxicity reaction
- Type III: Immune complex reaction
- Type IV: Delayed cell-mediated reaction

Hypersensitivity Reactions Type I: Immediately occurring immune response. Takes place within a few minutes after exposure to an antigen (allergen), and always mediated by IgE-bound basophils or mast cells. During the first exposure to the Ags (allergens) there is formation of IgE antibodies which are then fixed to mast cells or basophils and stay as a complex in the circulation.

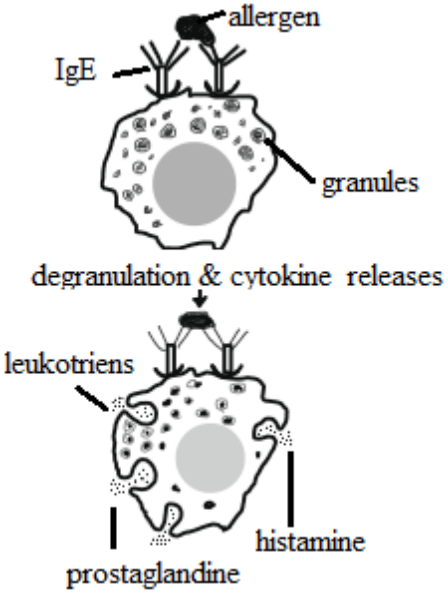


Figure 5: Allergy allergen-IgE-mast cell complex

Mechanisms of Immune Injury

Adverse reactions caused by immune mechanisms are termed hypersensitivity reactions (HSR). HSR classified into four types. Type I, II, and III require the active production of antibody by plasma cells. Type IV is mediated by the interaction of T cells and macrophages.

Type I (anaphylactic) hypersensitivity

Steps in the reaction

- Immunoglobulin E (IgE) antibody production by IgE B cells is stimulated by antigen (Ag). The IgE antibody is then bound to the Fc receptors of mast cells and basophils.
- On subsequent exposure, Ag (allergen) reacts with bound IgE antibody (complement is not involved), resulting in degranulation of mast cells and basophils. This reaction requires bridging (cross-linking) of adjacent IgE molecules on the mast cells surface.

- Degranulation results in histamine release, which increases vascular permeability. Various other substances are produced, many of which are vasoactive or smooth muscle spasm-inducing.
- Chemotactic substances recruit eosinophils, resulting in tissue and peripheral blood eosinophilia.

Clinical examples

- Allergic or atopic reactions, such as seasonal rhinitis (hay fever), allergic asthma, or urticaria.
- Systemic anaphylaxis (anaphylactic shock) is a potentially fatal reaction, characterized by the rapid onset of urticaria, bronchospasm, laryngeal edema, and shock after exposure to offending antigen.
- Hereditary angioedema is caused by deficiency of C1 esterase inhibitor; serum C4 is low and other complement components such as C3 are consumed.

Type II (Cytotoxic) hypersensitivity

1- Complement-fixing antibodies reacts directly with antigens that are integral components of the target cell. The interaction of complement with the cell surface results in cell lysis and destruction. Serum complement is characteristically decreased.

The Ags involved are usually localized to tissue basement membranes or blood cell membranes.

Clinical examples include autoimmune hemolytic anemia, hemolytic transfusion reaction, and hemolytic disease of the newborn (erythroblastosis fetalis), in which the antigens are components of red blood cell membranes; and Goodpasture syndrome (antiglomerular basement membrane antibody), in which the pulmonary alveolar and glomerular basement membranes are affected.

Pemphigus vulgaris caused by Abs against desmosomal protein that lead to disruption of epidermal intercellular junction.

2- Antibody-dependent cell mediated cytotoxicity (ADCC)

Antibody react directly with integral surface antigens of targeted cells.

The free Fc portion of the Ab molecule reacts with the Fc receptor of a variety of Cytotoxic leukocytes, most important NK cells. Other leukocytes, including monocytes, neutrophils, and eosinophils, also bear Fc receptors and can participate in ADCC.

The target cells are killed by the Fc receptor-bound Cytotoxic leukocytes. Complement is not involved.

3- Antibody-mediated cellular dysfunction

In some cases, Abs directed against cell surface receptors impair or dysregulate function without causing cell injury or inflammation. Thus, in myasthenia gravis, Abs against acetylcholine receptors in the motor end plates of skeletal muscles impair neuromuscular transmission with resultant muscle weakness. Conversely, Abs can stimulate cell function. In Graves disease, Abs against the thyroid stimulating hormone receptor stimulate thyroid epithelial cells and result in hyperthyroidism.

Type III (Immune complex) hypersensitivity

• Is mediated by the deposition of Ag-Ab (immune) complexes, followed by complement activation and accumulation of polymorph nuclear leukocytes.

• Immune complexes can involve exogenous Ags such as bacteria and viruses or endogenous Ags such as DNA

• Immune complexes are most often removed by cells of the mononuclear phagocyte system without adverse effect. Pathologic immune complexes either form in the circulation and subsequently deposit in the tissues or form at extracellular sites where Ag has been planted (in situ immune complexes).

• Immune complex-mediated injury can be systemic when complexes are formed in the circulation and are deposited in multiple organs or localized to particular organs (e.g., kidneys, joints, or skin) if the complexes are formed and deposited in a specific site.

• The mechanism of tissue injury is the same regardless of the pattern of distribution; the immune complexes bind complement, which is highly chemotactic for neutrophils,. The neutrophils release lysosomal enzymes, resulting in tissue damage, which can also result from other substances released by neutrophils, including prostaglandins, kinin, and free radicals.

• Immune complexes can also cause platelet aggregation and activate Hageman factor (factor XII) ; both of these reactions augment the inflammatory process and initiate microthrombi formation that contribute to the tissue injury by producing local ischemia.

• During the active phase of the disease, consumption of complement decreases the serum levels.

Clinical Example: Glomerulonephritis, rheumatoid arthritis, serum sickness, subacute bacterial endocarditis, systemic lupus erythematosus, arthus reaction.

Type IV (cell-mediated) hypersensitivity

1- Delayed hypersensitivity

* Is exemplified by the tuberculin reaction, a localized inflammatory reaction initiated by the intracutaneous injection of tuberculin and marked by proliferation of lymphocytes, monocytes, and small numbers of neutrophils, with a tendency toward cellular accumulations about small vessels (perivascular cuffing). Induration (hardening) results from fibrin formation.

* Is also exemplified by contact dermatitis, which may result from either delayed hypersensitivity or direct chemical injury to the skin.

* Involves the interaction of the T cell receptor of CD4+ lymphocytes with Ag, presented by macrophages, and with HLA class II antigens on macrophages, resulting in stimulation of antigen specific CD4+ memory T cells.

a. On subsequent contact with Ag, the CD4+ T memory cells proliferate and secrete cytokines.

b. IL-2 and other cytokines secreted by the CD4+ T cells recruit and stimulate the phagocytic activity of macrophages.

2- T- cell-mediated cytotoxicity

Is direct CD8+ T cell-mediated killing of target cells (typically tumor cells or virus-infected cells)

a. Target cell HLA class I Ags recognized as self Ags are also required

b. Specific target cell Ag is recognized by the T cell receptor of CD8+ lymphocytes.

c. Two principle mechanisms of Cytotoxic T lymphocyte killing have been demonstrated: 1- perforin-granzyme-dependent killing and 2- Fas-Fas ligand dependent killing.

d. Cytokines are not involved.

IMMUNODEFICIENCY

Can be classified according to the deficient type of cells i.e., T or B lymphocyte or combined deficiency, and according to the etiology whether primary or secondary deficiency.

Primary Immune Deficiencies: A group of diseases caused by intrinsic genetic or congenital defects, primary immune deficiencies occurs in various cell lineages, affecting different sets of cells/molecules. As indicated below.

B-cell Deficiencies: affecting B cells including the following:

- Bruton's Disease: Congenital X-linked infantile hypogammaglobulinemia. Pre-B cells do not mature into B-lymphocytes hence reduce immunoglobulins production.

- Transient Hypogammaglobulinemia of Infancy: Occurs in infancy as a transient finding

- Immunoglobulin Deficiency with Normal or High IgM: Other classes of immunoglobulins are reduced.

- Common Variable Immunodeficiency: Presents with low IgG. young adult presents with pyogenic infections.

- Selective IgA Deficiency: The most common form of primary immunodeficiency. B-cell count is normal but IgA is not synthesized or secreted. Presents as recurrent or opportunistic GI and respiratory tract infections.

T-cell Deficiencies: Affecting T cells, including the following:

- DiGeorge's Syndrome: Results from defect in thymic development that prevent normal development and thymic education of T cells. DiGeorge syndrome varies with the severity and may be accompanied by abnormal development of embryological related tissues (aorta, face and jaw, and

parathyroid glands), due to abnormal embryogenesis of 3rd and 4th pharyngeal pouches.

- Chronic Mucocutaneous Candidiasis: Disorder of T-lymphocytes characterized by chronic infection with Candida that are limited to the mucosa, skin, and nails.

Combined B &T-cell Deficiencies: Both T and B lymphocytes are affected including the following:

- Severe Combined Immunodeficiency (SCID): Due to adenosine deaminase deficiency. resulting in accumulation of deoxyadenosine, a toxic substance to lymphocytes so impairing both cellular and humeral responses. It results in absence of B-cell & T-cells, and failure in antigen presentation. It has two variants, autosomal recessive, and X-linked form (the most common form of SCID).

- Wiskott-Aldrich Syndrome: Genetic defect leading to depletion of T-lymphocytes, macrophages, and platelets from the body. Clinically presents as severe eczema, thrombocytopenia, and recurrent infections with defective T-cell function resulting in failure of T-cell, and macrophage functions and with normal or high immunoglobulin and good response to protein antigens, but not to polysaccharide antigens.

Secondary Immune Deficiencies: These are acquired conditions caused by chronic diseases, and environmental factors such as drugs, cancer, malnutrition, and infection e.g., acquired immunodeficiency syndrome (AIDS), HIV-1 and HIV-2, associated with complete loss of cellular immunity as a result of reduction of CD4+ T- lymphocytes. Clinically presents as asymptomatic, immune exhaustion, opportunistic infections, and malignancies e.g., Kaposi's sarcoma, B-cell lymphomas.

AUTOIMMUNE DISEASES

Important Terminology in autoimmune diseases:

- Tolerance: Defined as failure of the immune system to respond to specific types of Ags, so the body immune system can tolerate them. Normally only self -Ags should be tolerated.

- Central Tolerance: A process that occurs in the primary lymphoid organs (bone marrow and thymus) during the early development of B and T cells to eliminates all T and B lymphocyte that are formed against body antigens

(self Ags). In addition, called education of lymphocyte to know what is self, and what is non-self Ag (desensitization of self-antigen).

 Peripheral Tolerance: Results from mechanisms that inactivate or eliminate B and T-cells in the circulation to create a state of immune anergy for both self and non-self-antigens.

 Anergy: Hypo-responsiveness (inactivation of B and T cells). It occurs when naïve lymphocytes bind via their receptors ("first signal") but fail to receive the second signals provided by T cells for B cells and APCs that are necessary for activation.

Organ and non-organ Specific Autoimmune Diseases:

Some diseases, such as systemic lupus erythematosus and rheumatoid arthritis, are multi systemic and affect several body organs simultaneously, (non-organ specific). Others, such as Hashimoto's thyroiditis and Sjögren's syndrome, affect specific tissues or organs so called organ specific autoimmune disease.

TISSUE TRANSPLANTATION

This process depends on histocompatibility antigens i.e., MHC class I and II molecules of the major histocompatibility complex (MHC). The genetic match of (similarity/disparity) between the donor and the host is a very important factor in determining the likelihood of a successful transplant.

Immunology of Tissue Transplantation: A host can recognize transplanted tissue as foreign, and start an immune response against any histocompatibility antigen not encoded within its own cells. The host immune system recognizes peptide fragments presented only by both MHC class I or II molecules. The recognition of foreign histocompatibility antigens and the activation of T cells against them involve a process that is very similar to those involved in the initiation of responses against antigens derived from infectious organisms. Immune reaction from the host against the transplanted tissue is called graft rejection. On the other hand, immune reaction from the transplanted tissue against the host called graft versus host reaction.

Complications of Tissue Transplantation: include the following

1- Tissue rejection:

- Chronic Rejection: This is the slowest and the least severe type of transplant rejection, (occurs after three months). chronic rejection is a typical situation in which the donor and recipient differ slightly in MHC classes.

- Acute Rejection: Occurs much sooner after graft emplacement than does chronic rejections (e.g., two to four weeks) due to incompatibility between the host and the donor.

- Hyper-acute Rejections: These are the most rapid type of rejections. They are initiated and completed within a very few days of graft emplacement, usually before the grafted tissue or organs can establish connections with the recipient vasculature, and occur when major incompatibility between the host and recipient are found.

- Second Set Rejection: These types of grafts that are rejected more rapidly when repeated in a recipient who rejected the same type of graft on a previous occasion.

Pathology of Graft Rejection: Pathogenesis depends on development of delayed type hypersensitivity reaction, and cytotoxic T lymphocyte responses, directed against histocompatibility antigens, which have been detected as incompatible in both acute and chronic rejections. Steps can be taken to inhibit the ability of the immune system to attack the engrafted tissues using immune regulating medication.

2- Graft-versus-host Disease (GVHD):

This reaction develops from blood transfusion, or bone marrow transplantation, when the immune system of the donor (graft) attacks the recipient (host) tissue. Responsibility for this is attributed to T-lymphocyte present in the implanted bone marrow or blood. However, the risk of developing GVHD can be minimized by removing T cell from the bone marrow prior to its infusion.

INTRODUCTION

Introduction

Literally translated, Pathology is the science of suffering, i.e., (Logos = science), (pathos = suffering). While, scientifically Pathology is defined as the study of structural and functional abnormalities at the level of cells, tissues, organs, and the study of systemic effect of diseases and how to reach the diagnosis of these diseases, i.e., It is the science behind the cure and it is a discipline that bridges the clinical practice and basic science. General pathology is a tool through which you can understand the systemic pathology.

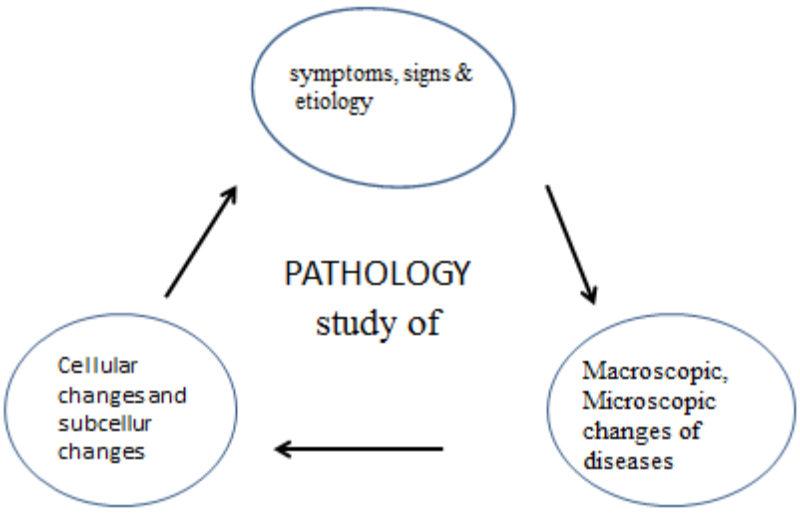


Figure 1: Definition of pathology:

To study pathologic changes you need to have good knowledge of basic medical sciences, especially cellular structures, histology, and blood cells. Pathology explains a disease by studying the following five aspects etiology, pathogenesis, morphological changes, functional, molecular alterations, & clinical signs and symptoms.

Etiology: Etiology of a disease means the cause of the disease, if the cause is known, it may be of primary or secondary type, and when the cause is unknown, it is called idiopathic etiology. Additionally, there is another category, genetic or acquired etiology (infectious, nutritional, chemical, physical, etc., are acquired types).

Pathogenesis: Means the mechanisms through which pathological and clinical manifestations of diseases take place.

Morphological Changes: The morphological changes refer to the structural alterations at the level of cells, tissues, and organs of the whole body. Which occur following the mechanisms. Those changes seen by the naked eyes are called gross changes or macroscopic findings & those seen under the microscope are called microscopic changes. Both the gross & the microscopic morphological changes may be specific to that disease or non-specific ones. Therefore, these morphological changes must be detected by the pathologist for the final diagnosis the diseases, then the treating doctor can choose the proper way of treatment accordingly. In addition, the morphological changes will lead to functional alterations to produce the clinical signs &symptoms of the disease. The morphologic changes in the organ influence the normal functions of that organ, by doing so; they determine the clinical features (symptoms and signs), course, and prognosis of the disease. In summary, pathology studies: etiology, pathogenesis, morphological changes, clinical features, diagnosis and prognosis of all diseases.

CHAPTER 1

CELL PATHOLOGY AND CELL ADAPTATION

CELL INJURY

Homeostasis (Steady State): Normal cell is confined to a relatively narrow range of functions and structures by its genetic reprogramming to handle normal physiologic demands. The cells react to adverse stress by one or more of the following:

- Adaption (new homeostasis).
- Reversible cell injury.
- Irreversible cellular injury leading to cell death.

Causes of Cell Injury:

1-Hypoxia: Decrease of oxygen supply, it is the most common cause of cell injury, usually occurs because of ischemia (loss of blood supply), which occurs for example, when arterial wall develop atherosclerosis or thrombotic occlusion. The most common cause of hypoxia is due to inadequate oxygenation, for example in cardio-respiratory failure, anemia or after poisoning with carbon monoxide (CO).

2-Chemical Agent: The list of chemicals that may cause cell and tissue injury includes:

- Poisons (arsenic, cyanide, mercuric salts... etc.)
- Air pollutants.
- Insecticides and herbicides uses .
- Alcohol and narcotic drugs.
- Variety of therapeutic drugs and even oxygen in high concentrations.

3-Physical Agent: Many forms of physical energy can give rise to cell and tissue injury, such as mechanical trauma, extremes of temperature, sudden changes in atmospheric pressure, electromagnetic energy, radiation and electric shock, the most important and frequently in clinical practice are mechanical forces (car accidents). Changes in atmospheric pressure and hypothermia are relatively uncommon causes of injury, but hyperthermia (burns) encountered more often. Radiation injury, also have assumed importance as potential causes of injuries.

4-Infectious Agent: Viral, bacterial, fungal and parasitic infections.

5-Immunological Agent: Loss of self-tolerance (Autoimmune diseases), antigen antibody precipitate, and atopic allergy.

6-Genetic Defect: Like sickle cell anemia, Down's syndrome …etc.

7-Intracellular Substance Accumulation: Deposition and accumulation due to excess of substances like pigments, fat, protein... etc.

8-Nutritional Imbalances: Nutritional deficiency continues to be a major cause of cell injury. Protein-calorie deficiencies- chiefly among underprivileged population deficiencies of specific vitamins, nutritional excesses have become important in cell injury among over privileged population (excess in lipids-predispose to atherosclerosis, obesity, diabetes mellitus).

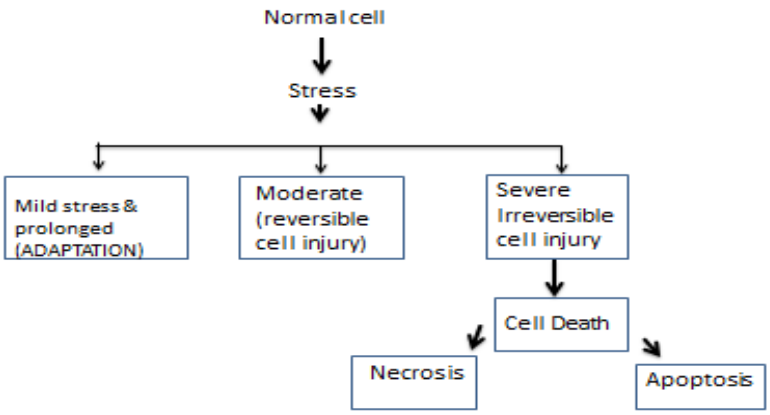


Figure 2: Outcome of cell injury

Mechanisms of Cell Injury

Mechanisms of cell injury include mainly three points

1-Hypoxia &ATP Depletion: hypoxia resulted in abnormal metabolism associated with the following changes:

- Reduce phosphorylation hence ATP production.
- Increase anaerobic glycolysis.
- Increase lactic acidosis.
- Decrease pH (cellular acidosis).

The sequel of the above mention disorders include clumping of chromatin, loss of ribosome, and intracellular influx of water.

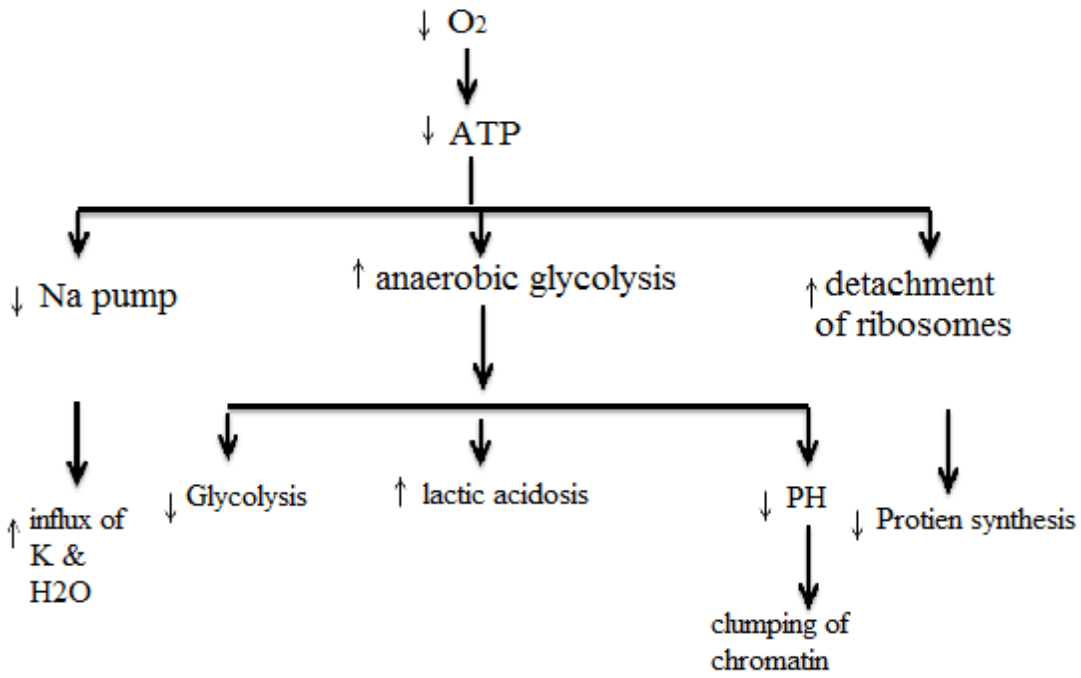


Figure 3: Reduce ATP in cell injury & effect of hypoxia

2-Formation of Free Radicals: Like superoxide O-3, hydrogen peroxide H2O2, hydroxile group OH- those lead to damage of cell membranes with loss of Na, K, and influx of Ca++, energy dependent sodium pump slows down. The normal activity of the sodium pump keeps the intracellular

concentration of potassium (K+) significantly high. Failure of active transport through the cell membrane causes accumulation of sodium (Na+) and water within the cell, and potassium out of the cell.

3-Increase of intracellular calcium: Release of Free (Ca++) from intracellular stores (mitochondria and ER) with activation of different enzymes (protease, endonuclease, phospholipase).

Outcome of Cell Injury

1- **Recovery of Cells:** In cases of reversible injuries, restoring full structure and functions may take place.

2- **Cell Adaptation:** includes atrophy, hypertrophy, hyperplasia, and metaplasia.

3- **Cell Death:** Occurs by necrosis or apoptosis in cases of irreversible cell injury.

4- **Inflammation:** Occurs after cell death and necrosis, in acute and chronic forms

5- **Tissue Repair:** Include cell regeneration and fibrosis, after inflammation to fill the gap.

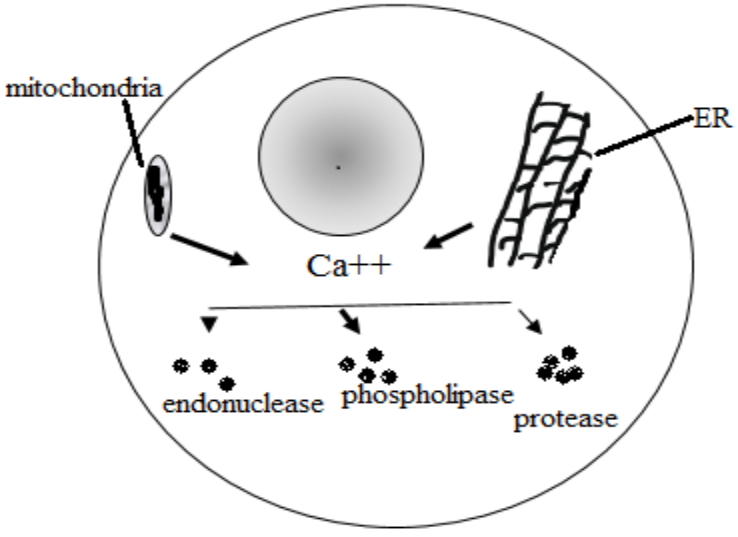


Figure 4: Increase cytoplasmic calcium in cell injury

Morphological Changes in Cell Injury

The effect of injury depends on the type, duration, and severity of injury, thus short ischemia may induce reversible injury, while more prolonged ischemia might lead to irreversible injury, ultra structural changes, light microscopic or gross changes and ultimately cell death. The following factors influence the severity of injury, hence the reversibility.

 Type of Injurious Agent: For example hypoxia results in impairment of aerobic respiration, disrupts the energy-dependent sodium pump and in loss of ionic and fluid balance (hydropic changes) while other agents induces the calcium release and activate the enzymes.

 Time Factor: Morphological changes of cell injury become apparent only after some critical time.

 Cell Susceptibility to Injury: Reactions of the cells to pathologic stimuli depend on the type of the cell. Also, the consequences of cell injury depend on the type, state and adaptability of the cell.

Reversible Cell Injury

Denotes pathologic changes that can be reversed when the stimulus is removed and the cellular injury has been mild. Cell injury is reversible only up to a certain point; otherwise, it will be irreversible.

Changes in reversible cell injury

 Loss of microvilli

 Blebs formation

 Swelling of endoplasmic reticulum, & mitochondria.

 Clumping of chromatin.

 Accumulation of substances (inclusion).

All of the above-mentioned changes are only reversible if oxygenation was restored. Events during reversible cell injury are called degeneration.

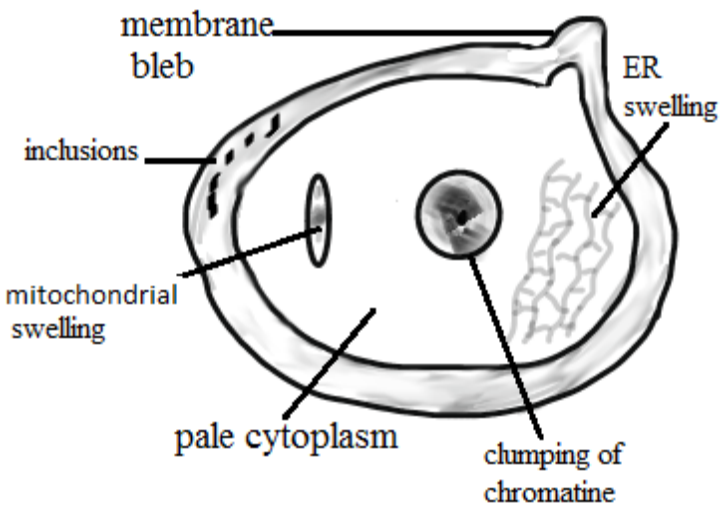


Figure 5: Reversible changes in cell injury

Degeneration

Defined as deterioration of cells following injury, but with a possibility of returning to normal when the injury is removed, Deterioration of cells is evaluated in terms of morphological changes that occur inside or outside the cells. Morphological changes that occur in the cells following injury involve accumulation of metabolites inside the cell, one of these metabolites is water following hypoxic injury, other metabolites known to accumulate inside cells after injury include Protein, Carbohydrates and Lipids.

Degeneration involving intracellular accumulation of water:

Cell swelling: This is the earliest morphological change that occurs whenever the plasma membrane is injured. It is characterized by swelling of the cell due to distention with water. It is readily observed by light microscopy in epithelial and endothelial cells stained with H&E the cytoplasm of affected cells appear pale Types of changes involving accumulation of water:

a- **Cloudy swelling:** This is a synonym term to cell swelling, initially used by one of the founding fathers of Pathology Rudolph Virchow, who described swollen unstained cells.

b- **Hydropic degeneration:** This is the advanced stage of cell swelling, characterized by appearance of either one large clear vacuole (ballooning degeneration) or multiple vacuoles (vacuolar degeneration).

Degeneration involving intracellular accumulation of carbohydrates:

Glycogen degeneration: in cases of excess glucose in blood (hyperglycaemia), and become glycogen and stored in hepatocytes additionally in cases of glycogen storage diseases. Glycogen in histopathologic section stain purple with a special stain called periodic acid Schiff (PAS).

Degeneration involving intracellular accumulation of protein:

Occurs in cases of alpha-1 antitrypsin deficiency and in alcoholic liver disease (mallary bodies). It has the following morphologic types.

a) Hyaline droplet degeneration: This is defined as accumulation of excess protein droplets inside cells, which stain in H&E homogeneous-glassy-eosinophilic color.

b) Zenkers degeneration/Waxy degeneration/Zenkers necrosis: The condition is named after Friendrich Zenker. It is a form of severe hyaline degeneration in skeletal muscle caused by toxins in severe infections e.g. typhoid. Grossly, the muscles appear pale and friable due to coagulation of sarcoplasm proteins. Microscopically the muscles are swollen with loss of cross striation and show a hyaline appearance and necrosis.

Degeneration involving accumulation of lipid inside cells:

Accumulation of excess lipids inside the cells is called Fatty change it will be discussed later.

Extracellular Accumulation of Metabolites:

The metabolites that accumulate outside the cells and induce degenerative changes are hyaline, fibrinoid, amyloid, uric acid, cholesterol and calcium, the corresponding degenerative changes resulting from each are Hyalinization, Fibrinoid/fibrinous degeneration, Amyloidosis, Gout,

atherosclerosis and calcification correspondently. The degenerative change arising from deposition of calcium is called metastatic calcification

a- Hyalinization: deposition of hyaline material outside the cell. Common sites where hyalinization occurs include: Walls of arteries, following damage of endothelial cells, Glomeruli, following damage of glomeruli and Bowman`s capsule, Renal tubules, in the form of hyaline casts formed due to crystallization of leaking protein on the renal tubules walls.

b- Fibrinoid/Fibrinous degeneration: This is a degenerative change in which there is accumulation of a homogeneous eosinophilic material that resembles fibrin in walls of arteries or connective tissue.

c- Amyloidosis: Amyloidosis is a term used to refer to extracellular deposition of a group of chemically abnormal proteins.

Irreversible Cell Injury

Denotes pathologic changes that are permanent and causes cell death, they cannot be reverse to normal state. For example, if the blood supply to the heart muscles is cut off for 10-15 minutes, the myocardial cells experience injury but it can recover to normal function. However, if the blood flow is cutoff for longer period the myocardial fiber dies and necrosis occurs. Irreversible injury is marked by severe mitochondrial vacuolization and density formation, extensive damage to plasma membranes, detachment of ribosomes from the granular endoplasmic reticulum (ER). Injury to lysosomal bodies leads to leakage of lysosomal enzymes into the cytoplasm. There is no universal agreed biochemical point of no return.

Events in Irreversible Cell Injury: the following two events take place in irreversible cell injury

 ATP Depletion: As a result of mitochondrial dysfunction lack of oxidative phosphorylation, ATP is depleted and production of energy is reduced

 Cell Membrane Damage: The earliest phase of irreversible injury is associated with functional and structural defects in cell membranes, a great

deal of evidence indicates that cell membrane damage is a central factor in the pathogenesis of irreversible injury, intact cell membranes are essential to the maintenance of normal cell permeability and volume, loss of membrane integrity causes massive influx of calcium from the extracellular space, resulting in mitochondrial dysfunction, activation of intracellular enzymes, and denaturation of proteins.

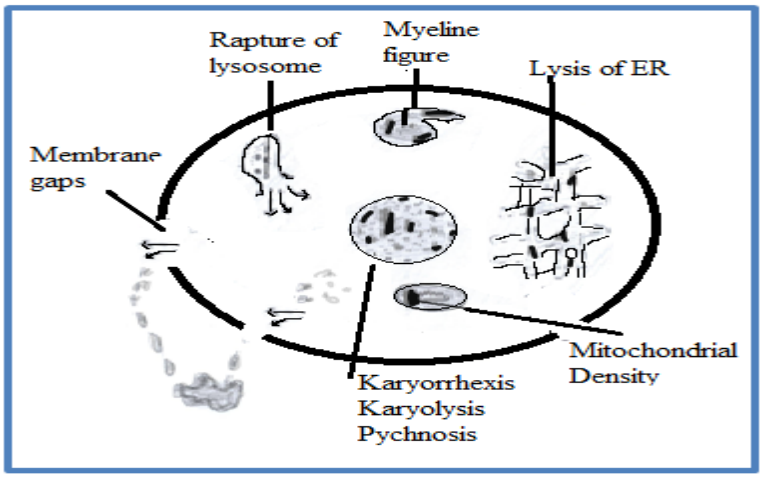


Figure6: Irreversible changes in cell injury

Sub-cellular Alteration in Irreversible Cell Injury

Effects of injurious agents on organelles and cellular components varies, some forms of cell injury affect particular organelles and have unique manifestations, e.g.

1-Autophagy: In nutritional deprivation, cellular organelles are enclosed in dead vacuoles that fuse with lysosomes, the organelles are digested but in some cases indigestible remnants form a pigment called lipofuscin, autophagy is thought to be a survival mechanism in times of nutrient deprivation, such that the starved cell lives by eating its own contents, in this process, intracellular organelles and portions of cytosol are first sequestered from the cytoplasm in an autophagic vacuole formed from ribosome-free regions of the rough endoplasmic reticulum (RER). The vacuole fuses with lysosomes to form an autophagolysosome, and the cellular components are digested by lysosomal enzymes.

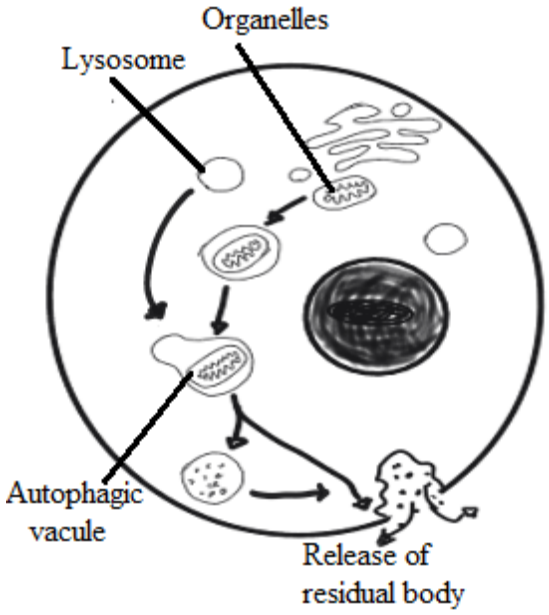


Figure 7: Autophagy

2-Hypertrophy of Smooth Endoplasmic Reticulum: Cells exposed to toxins that are metabolized in the smooth endoplasmic reticulum (SER) show hyper trophy of the ER, a compensatory mechanism to maximize removal of the toxins especially in the liver .

3- Mitochondrial Alterations: Changes in the number, size, and shape of mitochondria are seen in diver se adaptations and responses to chronic injury.

4- Cytoskeletal Alterations: Some drugs and toxins interfere with the assembly and functions of cytoskeletal filaments or result in abnormal accumulations of filaments

Examples of degenerative condition due to accumulation of substances

These are some examples include fatty changes, calcification, amyloidosis, pigment accumulations

1-Fatty changes: Defined as accumulation of excess lipids inside the cells. It occurs mostly in the liver and occasionally in the kidney and heart. The cause of accumulation of lipids inside hepatocytes is interference in any of the metabolic pathways of lipid metabolism. in this change cells have been

damaged and become unable to metabolize fat adequately, small vacuoles of fat accumulate and become dispersed within the cytoplasm, mild fatty change may have no effect on cell function; however more severe fatty change can impair cellular function. In the liver. The enlargement of hepatocytes due to fatty change may compress adjacent bile canaliculi, leading to cholestasis. Depending on the cause and severity of the lipid accumulation, fatty change is generally reversible. Accumulation of fat within the organs occurs in cases of malnutrition, obesity, DM, alcohol abuse, and CCl4 poisoning.

2-Calcification: Define as Intracellular or extra-cellar deposition of calcium salts in an organ or a tissue, it can be metastatic or dystrophic calcification.

Dystrophic Calcifications This is a common pathologic process in a wide variety of disease; it implies the abnormal deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals. When the deposition occurs in dead or dying tissue called dystrophic calcification; it occurs in the absence of calcium metabolic disorders (i.e., with normal serum levels of calcium), in contrast, the deposition of calcium salts in normal tissues is known as metastatic calcification and almost always reflects some derangement in calcium metabolism (hypocalcaemia). It should be noted that while hypocalcaemia is not a prerequisite for dystrophic calcification, it can exacerbate it. The main differences between the two types are shown in the below table.

Character	Dystrophic calcification	Metastatic calcifications
Type of tissue	In dead tissues	In living, healthy tissues
Ca++ level	Normal level	High level
Site of deposition	Areas of necrosis (Atheroma, granuloma, etc.) Intracellular or extra- cellular	Healthy tissues, kidney, heart, lung, Intracellular or extra-cellular

Table: Comparison between dystrophies and metastatic calcification

3-Amyloidosis: Amyloidosis refers to the extracellular deposition of fibrillary misfolded proteins in various organs.

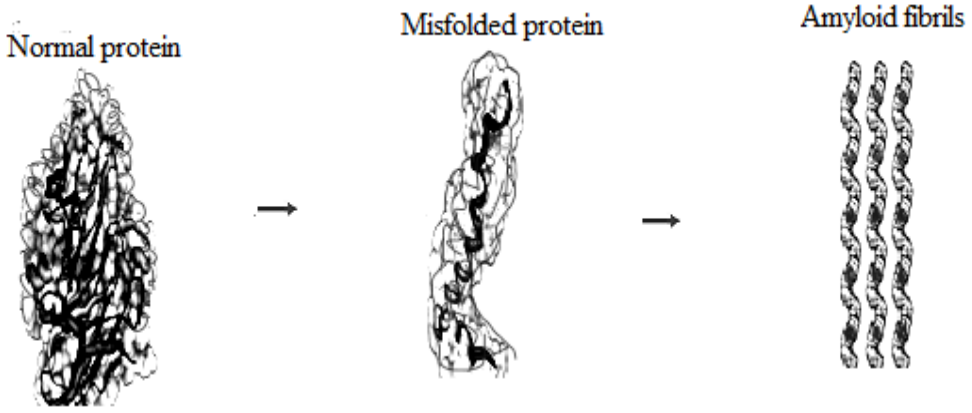


Figure 8: Misfolded protein and Amyloid

Pathogenesis: It is associated with miss-folding of proteins, which are deposited as fibrils in extracellular tissues and interfere with normal function of tissues and organs; it is either due to normal protein that is produced in excess amount or mutant proteins that are prone to misfolding.

Classification of Amyloidosis: According to the type of fibril amyloidosis is categorized into the following subtypes.

a- AL (Amyloid Light Chain Protein): Define as fibrils from light chains produced by plasma cells, and are made up of complete immunoglobulin light chains, amino-terminal fragments of light chains, or both of them. It is associated with proliferation of plasma cells in multiple myeloma or any monoclonal proliferation of B lymphocyte.

b- AA (Amyloid-Associated Proteins): Fibrils derived from a serum precursor called SAA (serum amyloid-associated protein) that is synthesized in the liver during inflammation; thus, long-standing inflammation leads to elevated SAA levels, and ultimately the AA form of amyloid deposits.

4-Pigments Accumulation: Pigments are colored substances that are either indigenous (melanin, lipofuscin, heamochromatosis), or exogenous pigments like carbon, asbestoses…etc.

1- Exogenous Pigment: The most common exogenous pigment is carbon from coal dust, and air pollutant of urban life. When inhaled it is phagocytosed by alveolar macrophages and transported through lymphatic channels causing anthracosis or coal workers'pneumoconiosis.

2-Endogenous Pigments: Include lipofuscin, melanin, and haemosiderin. Lipofuscin: "wear -and-tear pigment"is an insoluble. brown to yellow granular intracellular material that accumulates in a variety of tissues (particularly the heart, liver , and brain) as a sign of age and atrophy. It is not injurious to the cell, but is important as a marker of past free-radical injury, the brown pigment when present in large amounts are called brown atrophy. Melanin: This is an endogenous, brown-black pigment produced in melanocytes and acts as a screen against harmful ultraviolet radiation, adjacent basal keratinocytes in the skin can accumulate the pigment, as can dermal macrophages. Haemosiderin: this is a hemoglobin-derived granular pigment that is golden yellow to brown and accumulates in tissues when there is a local or a systemic excess of iron, more extensive accumulations of iron are seen in hereditary haemochromatosis with tissue injury including liver, heart fibrosis, and diabetes mellitus.

CELL DEATH

It is a loss of biological activities and change architecture of the cell as a result of irreversible injury; death is one of the most crucial events in the evolution of disease in any tissues or organs.

Two Types of Cell Deaths: Necrosis and apoptosis, which differ in their morphology, physiology, mechanisms, and roles in diseases.

NECROSIS

Definition: Necrosis is the death of a group of cells in a living tissue and complete lyses of these cells by their own enzymes (autolysis) or other enzymes from recruited inflammatory cells, like neutrophils, macrophages,etc. (heterolysis). Necrosis is the major pathway of cell death in many commonly encountered injuries, such as those resulting from ischemia, exposure to toxins, various infections, and trauma. The term

necrosis was first used by morphologists referring to a series of changes that accompany cell death, largely resulting from the degrading action of enzymes in lethally injured cells. Necrotic cells are unable to maintain membrane integrity, and their contents often leak out.

Morphological Types of Necrosis: There are several morphological distinct patterns of tissue necrosis, which may provide clues about the underlying cause, these patterns include

1- Coagulative Necrosis: Coagulative necrosis is a form of necrosis in which the component cells are dead, but the basic tissue architecture is preserved for several days, the affected tissues take on a firm texture, denaturation of cell structural proteins and enzymes without lyses of cell membrane nor organelles (cellular structure is preserved), enzymes are denatured and so block the proteolysis of the dead cells; as a result, an eosinophilic, anucleate cell may persist for days or weeks. Ultimately, the necrotic cells are removed by phagocytosis i.e., infiltrating leukocytes digest the dead cells by the action of their lysosomal enzymes. coagulative necrosis is mostly a characteristic of infarcts that occur in hypoxic injury of any solid tissues, i.e. liver , heart, kidney, except the brain.

2- Liquifactive Necrosis: Cell death and fluid formation, occurs in pyogenic bacterial infection, and ischemic injuries in the brain, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest ("liquefy") the tissue. Also for obscure reasons, the hypoxic death of cells within the central nervous system often evokes liquifactive necrosis. Whatever the pathogenesis complete digestion of the dead cells, result in transformation of the tissue into a liquid viscous mass. If the process was initiated by acute inflammation, the material is frequently creamy and yellow and is called pus.

3-Gangrenous Necrosis: A type of coagulative ischemic necrosis plus bacterial infection, the term gangrene is still commonly used in clinical practice. It is usually applied to the lower leg, that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers, when bacterial infection is superimposed, and coagulative necrosis are

modified by the liquifactive action of the bacteria and the attracted leukocytes (so called wet gangrene) but gangrenous necrosis may be dry, wet, or gas gangrene which is commonly found with clostridia infection.

4- Caseous Necrosis: Caseous necrosis is encountered most often in foci of tuberculous infection. The term "Caseous"(cheese like) is derived from the friable yellow-white appearance of the area of necrosis. On microscopic examination, the necrotic focus appears as a collection of fragmented or lost cells with an amorphous granular appearance, unlike coagulative necrosis, the tissue architecture is completely obliterated and cellular outlines cannot be seen. Caseous necrosis is often enclosed within a distinctive inflammatory border; this characteristic is known as a granuloma.

5-Fat Necrosis: Occurs in fatty tissues in cases of acute pancreatitis and breast trauma, Fat necrosis, commonly found in an areas of fat destruction, typically results from release of activated pancreatic lipases into the tissues of the pancreas and the peritoneal cavity, this occurs in an emergency case known as acute pancreatitis, in this disorder, pancreatic enzymes that have leaked out of acinar cells and ducts liquefy the membranes of fat cells in the peritoneum.

6-Fibrinoid Necrosis: This is a special form of necrosis usually seen in immune reactions involving the blood vessels. This pattern of necrosis is prominent when complexes of antigens and antibodies are deposited in the walls of arteries. Deposits of these "immune complexes, "together with fibrin that has leaked out of vessels, resulted in a bright pink and amorphous appearance in H&E stains, called "fibrinoid "(fibrin-like) by pathologists in immunologically mediated diseases (e.g., polyarteritis nodosa).

Mechanisms of Necrosis: In irreversible cell injury, the following steps take place::HOLOGYMADE

1-ATP Depletion And Mitochondrial Damage: ATP depletion →failure of energy-dependent functions → irreversible injury → necrosis and leakage of proteins.

2-Calcium Release: Influx of calcium from intracellular stores leads to activation of enzymes that damage cellular components and may also trigger further enzyme activation and rapture of lysomes **.**

3-Accumulation of Reactive Oxygen Species: Oxygen free radicals result in covalent bonds modification of cellular proteins, lipids, nucleic acids**.**

4-Increased Permeability of Cellular Membranes: This may affect cytoplasmic, lysosomal, and mitochondrial membranes; typically culminates in necrosis by letting substances freely move in and out of the cell.

Morphological Recognition of Necrosis: Necrosis can be detected in H&E stains by the following findings,

 Cytoplasm Eosinophilia: Redness of the cytoplasm in H&E stains due to release of RNA from the nucleus.

 Karyolysis : Dissolution of nuclear chromatin.

 Karyorrhexis: Fragmentation of nuclear chromatin.

 Pyknosis: Condensation of nuclear chromatin.

Fate of Necrosis (Outcome) The outcome of necrosis after an inflammatory period may be one of the followings,

 Resolution: Restoring of normal tissue function and structure.

 Organization: Replacement of the necrotic tissue by granulation tissue and fibrosis

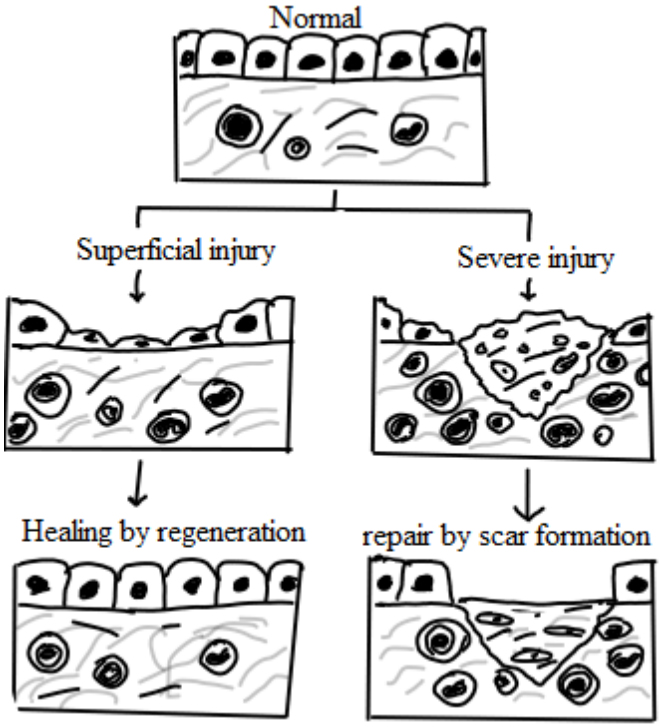
 Calcification: Dystrophic calcification due to precipitation of calcium salts.

HEALING AND REPAIR

Inflammation and healing are closely intertwined; but repair is discussed here as a separate entity. Repair of injuries is intimately associated with the inflammatory response. The healing process begins early in the inflammatory process and results in repair of the injury by replacement of dead or damaged cells with healthy ones. The body uses two distinct processes in repair:

-Regeneration: It is the replacement of injured tissue with cells of the same type,

-Fibrosis: Defined as a replacement of damaged tissue by fibrous connective tissue. Most injuries are repaired by a combination of these two processes; it is most advantageous for repairs to occur by regeneration because this will restore the organ to normal functioning capabilities.



Healing by regeneration &scar formation

Regeneration: Repair by regeneration is governed by several factors including the regenerative capacity of the cells involved and the severity of the injury.

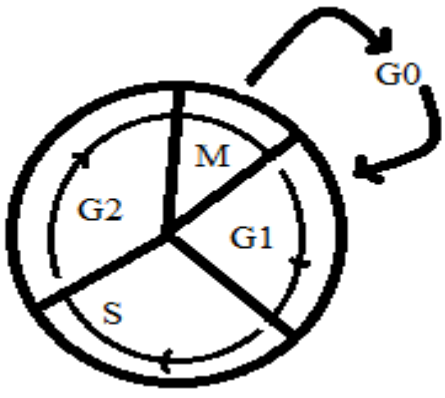
Based on their regenerative capabilities, cells of the body are divided into three groups (labile cells, stable cells, and permanent cells).

a- Labile Cells: In a proliferative state throughout life, to replace cells that are continually being destroyed continuously and rapidly replaced, examples: surface epithelium of the skin, gastrointestinal tract, genitourinary tract, hematopoietic cells. These cells heal by regeneration.

b- Stable Cells: Stable cells are cells that divide only when needed, they spend most of the time in the quiescent (G0 phase) of the cell cycle, but can be stimulated to enter the cell cycle when needed., examples include: liver , proximal tubules of the kidney, and endocrine glands, endothelium, smooth muscle and mesenchymal cells such as fibroblasts, osteoblasts, & chondroblasts. These cells can heal by regeneration.

c- Permanent Cells: These are cells that are incapable of division, some portions of these cells may be restored as in CNS neurons, the cells themselves do not regenerate, and also regeneration does not occur in skeletal and cardiac muscle. Injuries in organs or tissues composed of permanent cells will be repaired by fibrosis, while injuries in organs composed of labile or stable cells are repaired either by regeneration or by a combination of regeneration and fibrous tissue formation, the extent of the injury is a major factor in determining which of this to occur. The scaffolding provided by stroma and basement membranes is so important structure in the haeling by regeneration. However, if these structures are also damaged, then repair by fibrous replacement becomes more likely.

Cell cycle and control of regeneration: normal cell cycle is composed of G1 (gap1), S (DNA synthesis), G2 (gap2), and M (mitosis) phases, in addition of resting stage called G0.



cell cycle

Regeneration is controlled by stimulatory and inhibitory factors for the cell cycle; stimulation is a two-stage process:

a- Initiation: in initiation, cells in resting phrase (G0) are primed for progression to cell division; initiation is brought about by tissue-specific growth factors such as Epidermal Growth Factor (EGF), and Platelet Derived Growth Factor (PDGF).

b- Potentiation: It means stimulation of cells, which have already been primed by the appropriate initiator to enter S phase of cell cycle. Nonspecific growth factors such as insulin, hydrocortisone, and growth hormone are the main stimulators.

Repair by Connective Tissue (Fibrosis):

This type of repair predominates when injuries occur in tissues formed largely of permanent cells or when the injury results in extensive damage to stromal framework and supporting connective tissues. In these situations, the injured tissue is replaced by fibroblastic cells, usually in a form of granulation tissue, which eventually results in the formation of a scar. Granulation tissue formation is early in the inflammatory process. Fibroblasts and vascular endothelial cells star t to proliferate, and sometimes this begins as early as 24 hours after injury. By three to five days, a specialized type of tissue appears that is known as granulation tissue. This specialized tissue is composed of proliferating fibroblasts and newly formed blood vessels. The process resulting in the development of these newly formed blood vessels is called angiogenesis or neovascularization. This process is important in healing, and involved in the progressive growth of parenchymatous tumors. It occurs in four basic steps:

Enzymatic degradation of the basement membrane of the parent vessel, migration of endothelial cells toward the angiogenic stimulus, proliferation of endothelial cells, maturation of endothelial cells and organization into capillary tubes.

Mechanisms Involved in Repair: The mechanisms regulating repairs are becoming better understood and the more important features involved in it include:

- Growth factors,
- Cell to cell and cell to matrix interactions.
- Extracellular matrix synthesis and collagenization.

These processes, at least in part, are mediated by a series of low molecular weight polypeptides referred to as **growth factors**.

These growth factors have the capacity to stimulate cell division and proliferation. Some of the factors, known to play a role in the healing process, are briefly discussed below.

Sources of Growth Factors:
Following injury, growth factors may be derived from a number of sources such as:
1.Platelets, activated after endothelial damage,
2. Damaged epithelial cells,
3. Circulating serum growth factors,
4. Macrophages, or
5. Lymphocytes recruited to the area of injury
The healing process ceases when lost tissue has been replaced. The mechanisms regulating this process are not fully understood. TGF-β acts as a growth inhibitor for both epithelial and endothelial cells and regulates their regeneration.
The summary of molecular control shown below

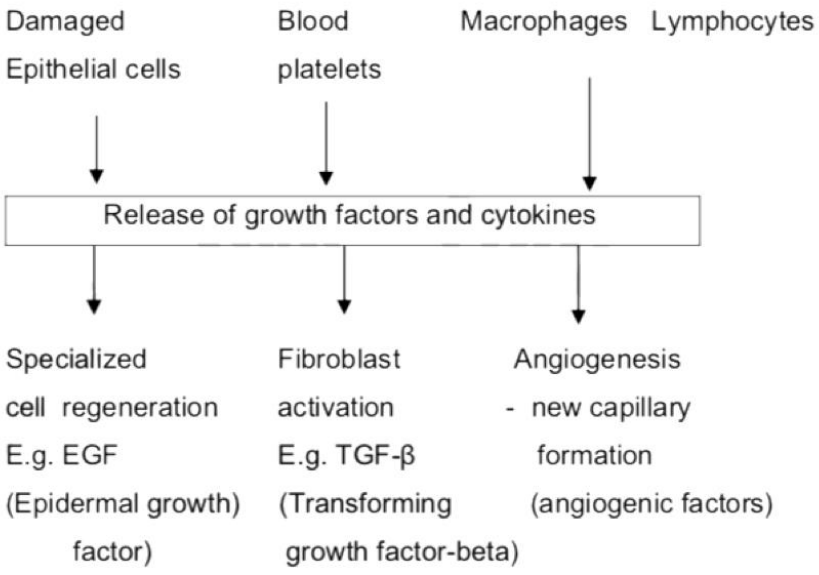


Diagram showing sources of growth factors and their effect.

Factors Affects Healing Process

1-Local Factors: Infection, poor blood supply, foreign bodies like sutures remnants, movement, and exposure to ionizing radiation delay wound healing, while exposure to ultraviolet light facilitates healing. Type, size and location of injury all of these are localized factors influencing healing process.

2-Systemic Factors:

a- Age: Wound healing take place rapid in the young and slow in aged and debilitated people

b- Nutrition: Deficiency of protein, vitamin C, and zinc delays the wound healing process

c- Systemic infection: Delays healing, administration of large doses of glucocorticoids delays the healing process.

d- Uncontrolled diabetics : Diabetics are more prone to develop infections and hence delayed healing.

e- Hematologic abnormalities: Defect of neutrophil functions, neutropenia and bleeding disorders slow wound healing.

Healing process has different phases in different tissues, these are some example of healing process in special tissues.

Wound Healing

Wound healing is a complex and dynamic process. The physiology of the normal wound healing occurs through the following phases (haemostasis, inflammation, granulation and maturation).

a- Haemostasis Phase: A process in which fibrin mesh strengthens the platelet aggregate into a stable haemostatic plug, then platelets secrete cytokines such as platelet-derived growth factor (PDGF), which is recognized as one of the first factors secreted in initiating subsequent steps. Homeostasis occur within minutes of the initial injury unless there are underlying clotting disorders.

b- Inflammatory Phase: Inflammation is the second stage of wound healing presents as erythema, swelling, and warmth often associated

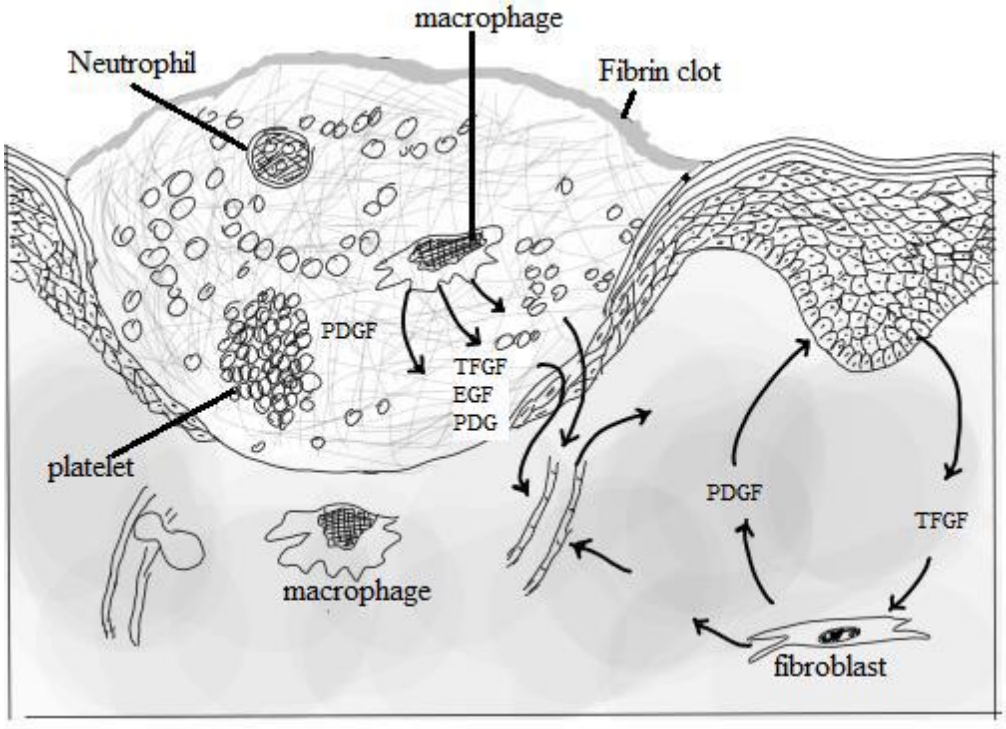
c- Proliferative Phase: Proliferation of granulation tissues start approximately four days after wounding and usually lasts up to day 21 in acute wounds depending on the size of the wound.

d- Remodeling or Maturation Phase: Remodeling can take up to two years after wounding and explains why apparently healed wounds can break down so dramatically and quickly if attention is not paid to the initial causative factors.

Wound Healing by First Intention (Primary Union)

This type of healing occurs when there is no contamination of the wound, and the edges of the wound are approximated, thus closing the wound. The best example of this situation is the surgical incision where contamination of the wound is minimized and the wound is closed by suturing, once the wound is sutured, the incision space fills with blood, which contains fibrin and blood cells and which subsequently clots, the surface of this clot becomes dehydrated and forms a scab. Within 24 hours, neutrophils appear at the edges of the incision and the epithelium at the edges of the incision begins to proliferate, it migrates under the scab and forms a thin continuous

epithelial layer. By 72 hours, macrophages are usually the most numerous inflammatory cells and granulation tissue starts to develop, collagen fibers are present but do not bridge the incision site, the epithelial cells continue to proliferate under the scab and the epidermal covering over the incision becomes thicker. By day 5, the incision space is filled with granulation tissue and collagen fibers begin to bridge the incision, the epidermis returns to its normal thickness and keratinized architecture. During the second week, there is continued accumulation of collagen fibers and proliferation of fibroblasts, inflammatory cells, edema disappears, and the process of blanching begins. By the end of one month, a connective tissue scar is devoid of inflammatory cells and is covered by an intact epidermis.

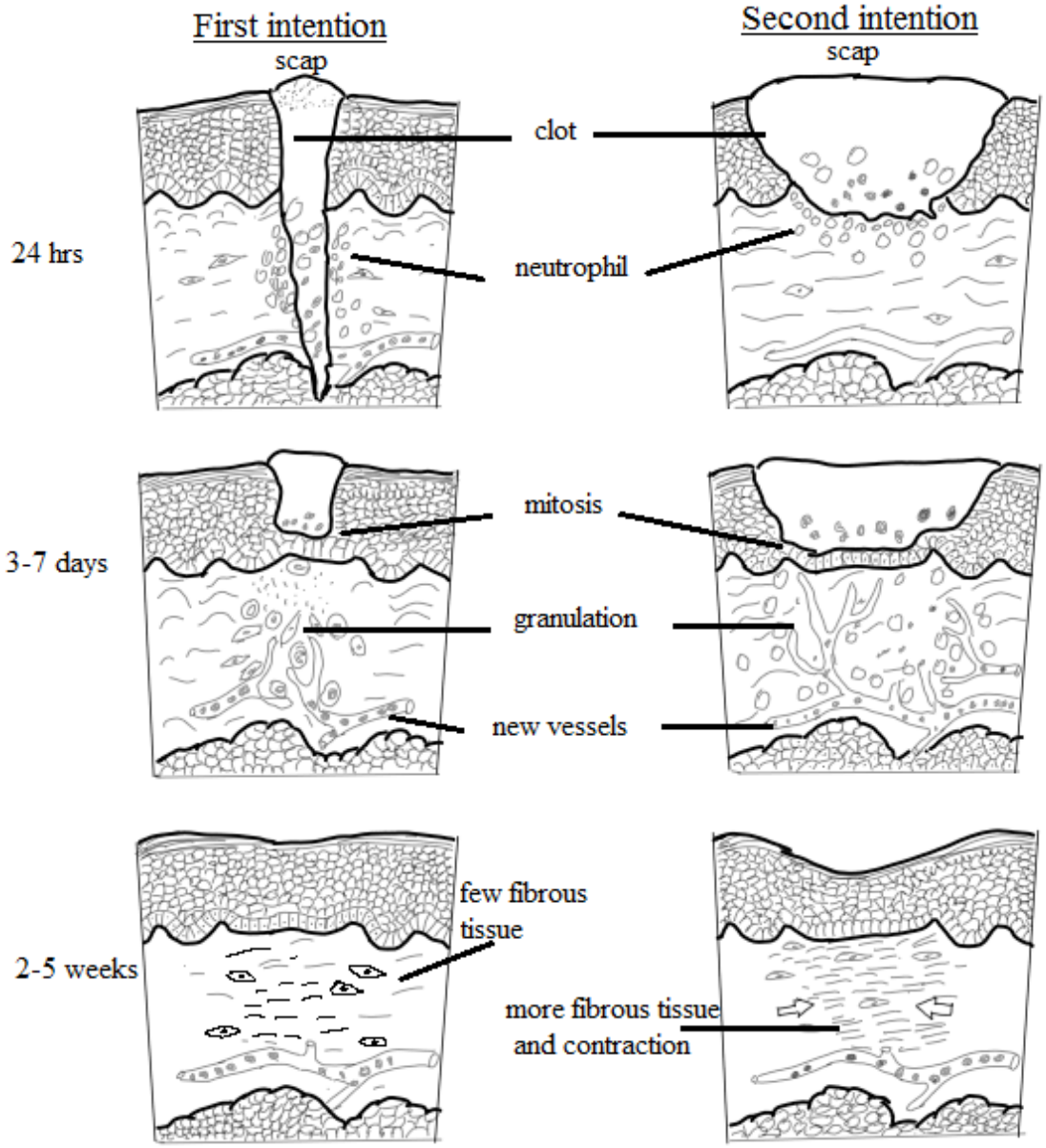


Inflammatory phase of healing Day 3

Wound Healing by Second Intention (Secondary Union)

This type of healing occurs when injuries result in more extensive loss of tissues, such as with infarction, inflammatory ulceration, and large surface wounds. In these situations, due to the large tissue defects, repair by regeneration is minimal and the defect is filled with granulation tissue. Second intention healing differ from first intention healing in several ways, first the greater injury induce a more intense inflammatory response. Secondly, much more granulation tissue is formed, and thirdly wounds that are repaired by second intention healing undergo a phenomenon known as "wound contraction" whereby specialized granulation tissue fibroblasts

called myofibroblasts contract and dramatically reduce the size of the wound.



Healing first and second intention

Complications of Wound Healing

a- Excessive Scar Formation: Excessive granulation is characterized by the formation of a mass of granulation tissue protruding from the wound and prevents re-epithelialization. Such excesses are commonly refer red to as "proud flesh".

b- Keloid Formation: Keloid formation also refers to an aberration of wound healing resulting in the formation of large bulging scars, but it differs from excessive scar in that it is caused by excessive

collagenization of the wound and not excessive formation of granulation tissue, this phenomenon is a common problem in darker people.

c- Wound Rupture: Failure of fusion of the two ends of the wound, or nonunion of bone fracture.

d- Epidermoid Cyst: Implantation of epidermal cells, giving rise to keratin filled cyst known as epidermoid cyst.

e- Infection: Bacterial infection and pus discharge may take place if a wound is contaminated.

f- Weak Scars Formation: Failure to close the wound.

Bone Healing

Neurons Healing

WHITE BLOOD CELLS DISORDERS

Neutropenia (agranulocytosis)

It is low neutrophil count less than 1500 cells/ µL of blood. Agranulocytosis is severe neutropenia with neutrophil counts less than 200 cells/µL of blood.
Causes: idiopathic, reaction to a drug (chemotherapeutic agents), inherited syndromes, viral or bacterial infections and bone marrow neoplasms.
The major effect of this condition is an increased susceptibility to infections. Vital signs may show a rapid pulse, increased respirations, and hypotension, in addition to fatigue, fever, malaise, and extreme weakness. Oral infections are common and very severe. Periodontal disease in these individuals is very aggressive and painful.
Treatment focuses on using antibiotics to prevent infections and boosting the production of neutrophils by administering drugs that contain colony-stimulating factor. Neutropenia caused by cancer chemotherapy is eliminated once the treatments are completed.

Cyclic neutropenia: a specific form of inherited neutropenia characterized by drops in neutrophil numbers that occur on a regular basis of every 21- 30 days and last for about 3-6 days.

Reactive Leukocytosis

An increase in the number of WBCs due to inflammation, microbial and infectious diseases such as infectious mononucleosis and Cat-scratch disease.
Infectious mononucleosis is also known as glandular fever and kissing disease, it is an acute, self-limited disease of adolescents and young adults that is caused by Epstein-Barr virus (EBV), a member of the herpesvirus family. The disease often results in fever, sore throat, enlarged lymph nodes in the neck, and tiredness. Most people recover in two to four weeks; however, feeling tired may last for months. The liver or spleen may also become swollen. Rest and enough fluids are keys to recovery.

Cat-scratch disease or felinosis is a bacterial infection caused by *Bartonella henselae* bacteria. It occur after scratches from cats. The most common symptoms include fever; enlarged, tender lymph nodes that develop 1–3 weeks after exposure; and a scab or pustule at the scratch site.
Diagnosis: serologic testing and the distinctive morphologic changes in the lymph nodes (Follicular Hyperplasia).

Lymphoma

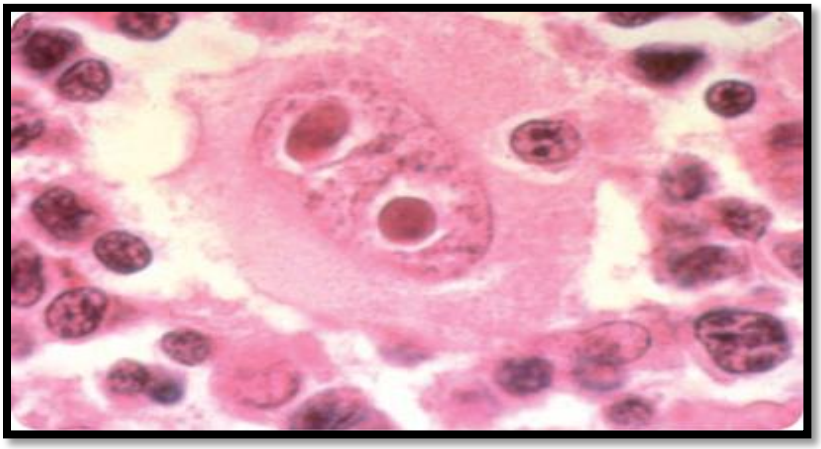
It is a group of lymphocyte malignancies. Hodgkin's lymphoma, a malignancy involving an atypical form of B cell, Non-Hodgkin's lymphomas include neoplasms associated with B cells, T cells, and natural killer cells.

Hodgkin's Lymphoma (Hodgkin Disease)

The etiology of Hodgkin's lymphoma is unknown but several risk factors exist: with the Epstein-Barr virus infection, immunosuppression, human immunodeficiency virus (HIV), and genetic factors.
Hodgkin's lymphoma is characterized by the presence of an abnormal B lymphocyte within the tumors called a Reed-Sternberg cell, it starts in a single lymph node in the upper body and then spreads to the adjacent nodes. The nodes most commonly affected are the cervical, supraclavicular, axillary, inguinal, and retroperitoneal. Spread of Hodgkin's lymphoma usually progresses in a systematic manner, moving from the original node to the next in the chain. Advanced Hodgkin's lymphoma can spread to any organ of the body (spleen, bone marrow, lungs, digestive tract, and liver). As the disease progresses, the individual becomes highly susceptible to infections because of the immune system dysfunction. Organs begin to shut down due to the increasing numbers of cancer cells that block their normal function and death occurs.
Clinical Characteristics: Asymmetric enlargement of one or more lymph nodes without reason.
Significant weight loss, fever, extreme night sweats, pruritus (itchiness), and fatigue.

Significant Microscopic Features: Presence of the Reed-Sternberg cell in tissue.

Treatment depends on the severity of the disease, the most common treatment is a combination of chemotherapy and radiation therapy.



Non-Hodgkin's lymphoma

It is a group of malignant neoplasms that arise from B (85%), T lymphocytes and natural killer (15%). The risk factors including:

1. Chromosomal mutations
2. Advancing age
3. Celiac diseases
4. Exposure to radiation or chemotherapy
5. Autoimmune disorders
6. Bacterial infection with Helicobacter pylori associated with mucosa-associated lymphoid tissue lymphomas in the gastric mucosa. (MALT lymphoma)
7. Viral infection: HIV infection, Hepatitis B and C, Human herpesvirus-8 (HHV-8), Epstein-Barr virus, and human T cell lymphoma virus (HTLV-1).

Clinical Characteristics: non-tender lymphadenopathy that fixed to the surrounding tissues. Bones may be affected by tumors. Oral lymphoma can

cause loss of alveolar bone, tooth mobility, swelling, pain, paresthesia, and pathologic bone fractures.

Significant Microscopic Features: the tumor cells varies with each type of lymphoma.

Treatment depends on the type of non-Hodgkin's lymphoma and the stage of the disease. Radiation therapy and Chemotherapy are effective.

BURKITT'S LYMPHOMA

A very aggressive form of non-Hodgkin's lymphoma which affects children and young adults more often than older adults, the lesion appears in the maxilla or the mandible or as a mass in the abdomen, with or without bone marrow involvement. Burkitt lymphoma is highly associated with translocations involving the MYC gene on chromosome 8 that result in overexpression of the MYC transcription factor. There are three types of the disease:

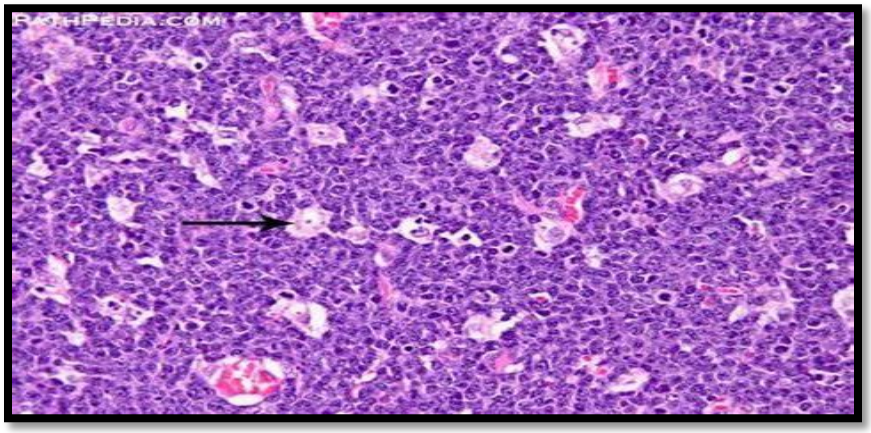
(1) Endemic type: found in Africa associated with the Epstein-Barr virus

(2) Sporadic type: seen in North America and Europe

(3) Burkitt's lymphoma associated with immunodeficiency.

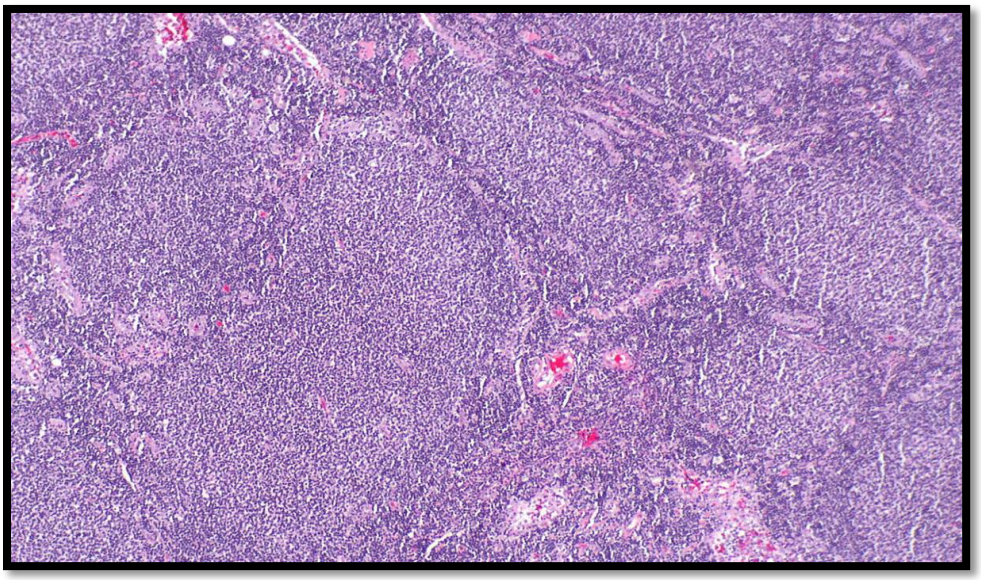
The oral manifestations are rapidly expanding bone lesions that quickly deform the face and loosening of the affected teeth; intense chemotherapy is used for treatment however death occurs shortly after the diagnosis.

Diagnosis of Burkitt lymphoma by examine the lymph node, the tumor cells and their nuclei are uniform, with high level of mitotic activity and prominent nucleoli. The "starry sky" pattern produced by interspersed normal macrophages.



Follicular Lymphoma

It is a common tumor of the adult NHLs, 85% of follicular lymphomas have a characteristic (14;18) translocation that fuses the BCL2 gene on chromosome 18 to the IgH locus on chromosome 14. It usually manifests as painless, generalized lymphadenopathy and bone marrow involvement. It is not curable disease (therapy with cytotoxic drugs).

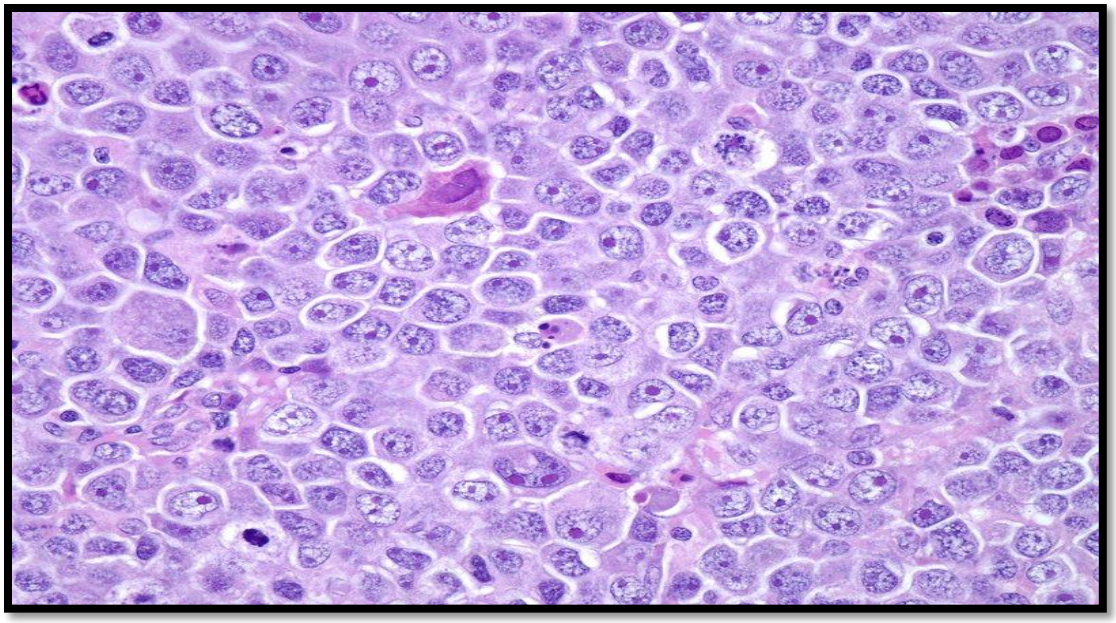


Mantle Cell Lymphoma

It is an aggressive tumor of NHLs and occurs mainly in men older than 50 years of age. It occurs as (11;14) translocation that fuses the cyclin D1 gene to the IgH locus lead to overexpression of cyclin D1, which you will stimulates growth by promoting the progression of cells from the G1 phase to the S phase of the cell cycle.

Diffuse Large B Cell Lymphoma

It is the most common type of lymphoma in adults, accounting for approximately 35% of adult NHLs. It includes several subtypes that share an aggressive natural history. 30% of tumors have a (14;18) translocation involving the BCL2 gene that results in overexpression of BCL2 protein. The remaining tumors have mutations, such as translocations involving the MYC gene and BCL6.



Oral manifestations of lymphoma appear as a soft tissue mass in the Waldeyer's ring area, in the lymphoid tissues found at the base of the tongue, or hard palate or in the major and minor salivary glands. The lesions may, or may not, be ulcerated. It may present as an ill-defined radiolucency, expansion and perforation of the cortical plate, tooth mobility, pain, paresthesia, and pathologic bone fractures.

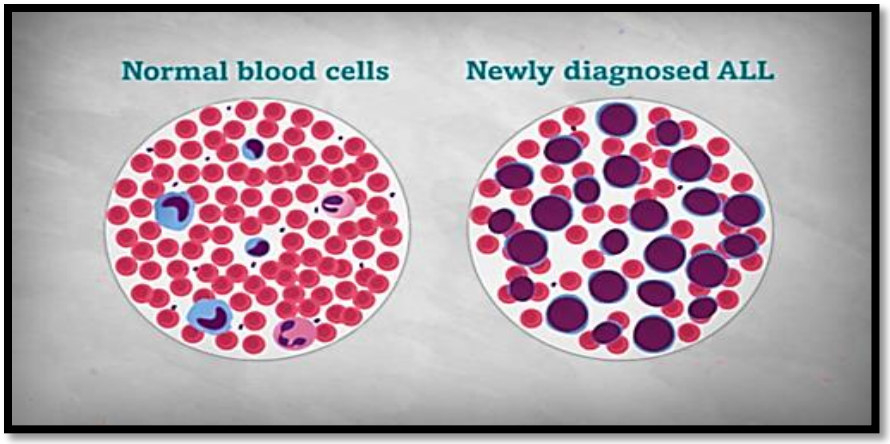
Extraoral examination for signs of lymphadenopathy should be performed for every patient when they present for dental appointments, any patient who presents with indurated, nontender, fixed nodes should be referred immediately to a physician for further diagnosis.

Leukemia

Leukemia is a group of malignant neoplasms involving leukocytes. Two basic classifications for this disorder involve cells that are derived from a lymphoid or from a myeloid progenitor cell. Further classification identifies whether the disease is acute or chronic. There are four main types of acute and chronic leukemia:

• Acute lymphoblastic leukemia (ALL) • Chronic lymphocytic leukemia (CLL)

• Acute myeloblastic leukemia (AML) • Chronic myelogenous leukemia (CML)



Etiology of leukemia is unknown, risk factors include exposure to radiation, certain chemicals, previous exposure to chemotherapeutic drugs, and some genetic syndromes.

The acute forms of leukemia usually present with symptoms within days to several weeks of the start of disease activity where there is an overgrowth of blastic cells (cells that fail to mature).

The chronic forms exhibit a more gradual progression of the disease, the cells produced do not respond to the body's regulation mechanism of proliferation, high numbers of the white cells are produced, increasing the viscosity (thickness) of the blood and causing an infiltration or overflow of the excess white blood cells into the organs and tissues that normally contain leukocytes. In addition, the cells that are produced are malignant cells that do not function normally and therefore do not fulfill their role in protecting the body against infection.

The symptoms of leukemia are:

1. Anemia (fatigue, pallor, etc.)
2. Infection (fever, night sweats)
3. Thrombocytopenia (epistaxis, petechiae, bruising)
4. Increased metabolism of the cancer cells (weight loss)
5. Bone marrow expansion (bone pain)
6. Infiltration of the liver, spleen, and lymph nodes by leukemic cells, causing enlargement of these organs.
7. Leukemic infiltration of the skin can cause pruritus.

8. Infiltration of the central nervous system can cause headache, nerve dysfunction, nausea, vomiting, and sometimes seizures.
9. Hyperviscosity of the blood caused by leukocytosis causing infarcts and vessel rupture in the lungs, brain, and other organs.

Chronic leukemia may be present for years without being noticed and may only be discovered while performing routine blood work.

Oral findings in all types of leukemia include:

1. increased gingival or periodontal infections
2. increased gingival bleeding, unexplained petechiae or purpura in the oral soft tissues
3. gingival enlargement due to leukemic infiltrate, pateints seek dental care prior to medical care because of the rapid decline in oral health.

The clinician must investigate any case of gingival or periodontal inflammation or infection that does not respond to normal interventions, especially if other systemic manifestations, such as fever, weight loss, or night sweats are present. Patients should be referred to their physician for further evaluation.

Elective dental care would not be appropriate during periods when bleeding is excessive or white cell counts are low. Consultation with the oncologist should precede any dental or dental hygiene care.

Treatment and Prognosis: aggressive chemotherapy and bone marrow and peripheral blood stem cell transplantations.

Multiple myeloma

It is a malignant neoplasm of plasma cells (the cells responsible for producing all of the body's immunoglobulins). Acquired genetic abnormalities involving translocation of genetic material from a number of different chromosomes to chromosome 14 which regulates the formation of

immunoglobins. The genetic abnormalities have been linked to environmental radiation, such as nuclear accidents, and with the accumulation of genetic errors with cellular aging.

The risk of genetic tendency of this disease is higher within first-degree relatives (mother, father, sisters, and brothers).

The manifestations of this disease are caused by excessive production of an abnormal immunoglobin called M-protein, a decreased production of all other immunoglobulins, and results in immunosuppression. The malignant plasma cells also stimulate osteoclastic activity with resultant bone resorption, pathological fractures, and bone pain. In multiple myeloma an abnormal protein called Bence Jones protein is eliminated through the kidney. Bence Jones protein is toxic to the kidney and accumulates in the tubules, eventually causing renal failure. The most common causes of death are severe infection or renal failure.

There are two other forms of the disease:

(1) solitary plasmacytoma: a single area of bone destruction, usually in the vertebrae, ribs, or pelvis. It is rarely seen in the oral cavity. Some 30-75% of these cases progress to multiple myeloma.

(2) extramedullary plasmacytoma: Plasma cell tumors that are found in soft tissues, (80%) are found in the upper respiratory tract and the oral environment, tumors present as exophytic red masses that may or may not eventually ulcerate. Progression to multiple myeloma is rare in these individuals.

Some of the abnormal immunoglobulins created by this disease combine to form amyloid that is deposited in tissues throughout the body such as in the heart, lungs, or kidneys, where it interferes with normal functioning and causes tissue enlargement. It is very common to see amyloid accumulation in the tongue results in macroglossia.

Distinguishing Characteristics: The “punched-out” radiographic lesions are characteristic of this disease.

Significant Microscopic Features: Bone marrow samples that contain over 30% plasma cells indicate this disease.

Treatment and Prognosis: chemotherapy. The mean survival rate for treated multiple myeloma is 3 years, untreated it is 6 months.

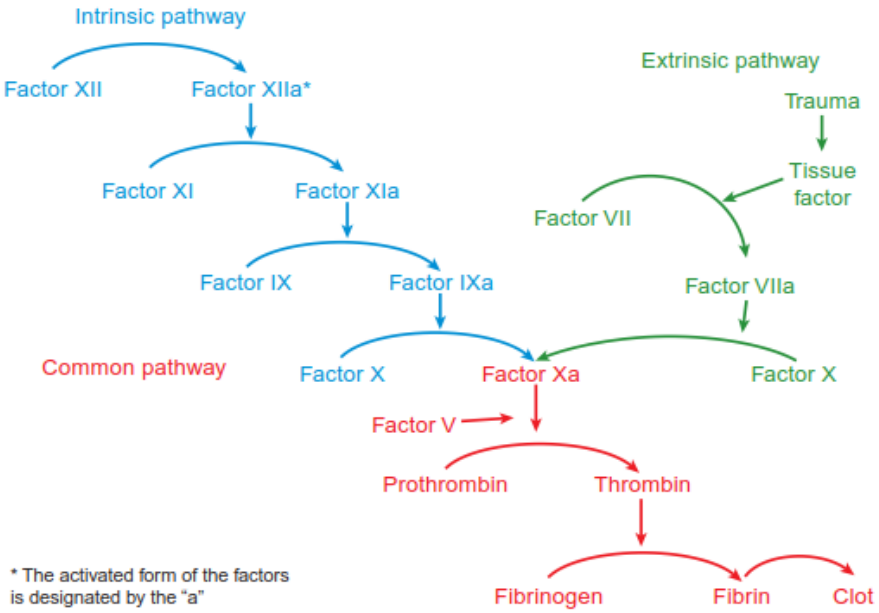
Hemostasis

It is the process of prevented blood loss from injury depends on the platelets and circulating coagulation factors. Platelets are created from megakaryocyte which is derived from the pluripotential stem cells. There are 12 numbered coagulation factors found in the blood plasma and produced by the liver.

Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue factor
Factor IV	Calcium
Factor V	Proaccelerin
Factor VII	Proconvertin
Factor VIII	Antihemophilic factor
Factor IX	Plasma thromboplastin
Factor X	Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor

The coagulation cascade consist of a series of inactive enzymes, once the first enzyme (coagulation factor) in the series is activated, it initiates the next in a series of reactions in which the product of the last reaction is the initiator of the next reaction. The end result of the coagulation cascade is thrombin that converts fibrinogen into fibrin. Fibrin forms the substance of a blood clot.

It is important to realize that a defect at any point in the cascade or in the substances that initiate the cascade can result in malfunction of the clotting system and uncontrolled blood loss.



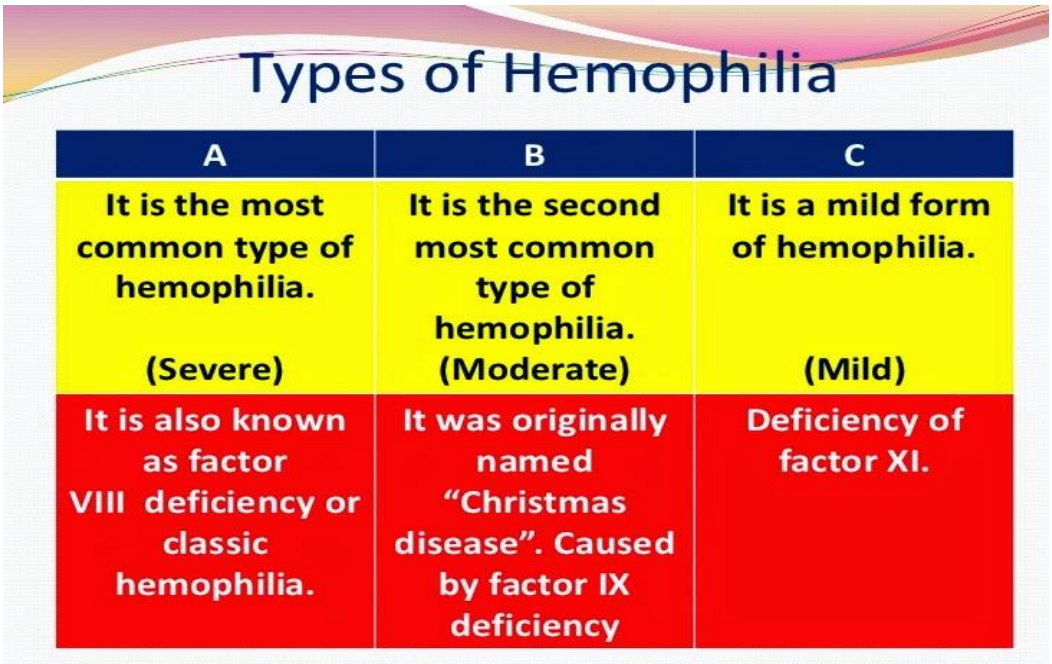
Hemophilias

It is a group of bleeding disorders (inherited genetic disorders) that associated with a deficiency or defect in one of the factors in the coagulation cascade which results in defective clot formation.

Hemophilia A: is an inherited genetic disorder caused by missing or defective Factor VIII protein. Hemophilia A is carried by the X chromosome. It is inherited in an X-linked recessive manner. As such, two hemophilia-carrying X chromosomes must be inherited for the disease to be active in women, but only in one X chromosome for men.

Hemophilia B: is an inherited genetic disorder caused by missing or defective Factor IX clotting protein. It is also carried in the X chromosome, in an X-linked recessive manner.

Hemophilia C: is an inherited genetic disorder caused by missing or defective Factor XI clotting protein. The disease was first recognized in 1953 in patients who experienced severe bleeding after dental extractions.



von Willebrand disease is associated with defective or inadequate levels of von Willebrand factor that lead to inadequate platelet adhesion to sites of injury.

Acquired bleeding disorders (bleeding disorders that are not genetic, but develop during life) are often associated with liver disease, because almost all of the coagulation factors are manufactured in the liver. If the liver is not functioning correctly, then the coagulation factors will not be produced effectively. Vitamin K is essential for appropriate clotting to take place. Normally, vitamin K is produced by the bacteria living in our intestines, so that it is almost impossible to have a deficiency. However, anything that disrupts or destroys the normal intestinal flora (bacteria), such as long term use of broad spectrum antibiotics, might cause a deficiency of vitamin K and produce an acquired bleeding disorder.

Thrombocytopenia

It occurs when the platelet count drops below 100,000/mm3 in blood, it usually occurs as a sequela of another condition; Aplastic anemia, chemotherapy, radiation therapy, and some drugs (thiazide diuretics, ibuprofen, tamoxifen, phenytoin, and ranitidine).

Alcohol abuses are at risk for developing this disorder because alcohol has the potential to suppress platelet production. Immune thrombocytopenia purpura (ITP) is caused by the destruction of platelets by antibodies that the immune system creates. ITP is associated with leukemia, HIV infection, and systemic lupus.

Clinical Characteristics:

- Petechial hemorrhages in the skin of the lower extremities and oral mucosa.
- Bruising, purpura, epistaxis, heavy menstrual flow, gingival and gastrointestinal bleeding, and retinal hemorrhages.

Dental Implications: patient refers to a physician for evaluation and platelet levels should be determined by blood tests prior to dental therapy, if excessive bleeding occurs during dental treatment, used local hemostatic measures.

The treatment depends on the suspected cause, eliminating the drug if it is drug associated, if it caused by cancer treatments usually resolves with the termination of treatment. ITP is treated with transfusions of platelets, steroids to inhibit the production of antibodies, and intravenous immunoglobulin infusions.