# OPT 327-GENERAL PATHOLOGY

**Pathology** is the study and [diagnosis](http://en.wikipedia.org/wiki/Medical_diagnosis) of [disease](http://en.wikipedia.org/wiki/Disease). The word [*pathology*](http://en.wiktionary.org/wiki/pathology) is from [Greek](http://en.wikipedia.org/wiki/Ancient_Greek)  *pathos*, "feeling, suffering"; an, [*-logia*](http://en.wiktionary.org/wiki/-logia), "the study of".  The suffix "path" is used to indicate a disease, e.g. [psychopath](http://en.wikipedia.org/wiki/Psychopath). It is the study of the structure and function of the body in disease just as anatomy is the study of normal structure and physiology the study of the normal function.

Pathology addresses 4 components of disease:

1. Cause/etiology,
2. Mechanisms of development (pathogenesis),
3. Structural alterations of cells (morphologic changes),
4. Consequences of changes (clinical manifestations).

Pathology is further separated into divisions, based on either the system being studied (e.g. veterinary pathology and animal disease) or the focus of the examination (e.g. forensic pathology and determining the cause of death).

General pathology, also called investigative pathology, experimental pathology, or theoretical pathology, is a broad and complex [scientific field](http://en.wikipedia.org/wiki/Science) which seeks to understand the mechanisms of injury to [cells](http://en.wikipedia.org/wiki/Cell_(biology)) and [tissues](http://en.wikipedia.org/wiki/Tissue_(biology)), as well as the body's means of responding to and repairing injury. Areas of study include cellular adaptation to injury, [necrosis](http://en.wikipedia.org/wiki/Necrosis), [inflammation](http://en.wikipedia.org/wiki/Inflammation), [wound healing](http://en.wikipedia.org/wiki/Wound_healing), and [neoplasia](http://en.wikipedia.org/wiki/Neoplasia). It forms the foundation of pathology, the application of this knowledge is used to diagnose diseases in humans and animals.

**BRANCHES OF PATHOLOGY**

Some important branches and sub-branches of pathology include:

**ANATOMICAL PATHOLOGY**

This area of pathology involves the examination of surgical specimens removed from the body (biopsy) to investigate and diagnose disease based on the [gross](http://en.wikipedia.org/wiki/Gross_examination)  [microscopic](http://en.wikipedia.org/wiki/Histopathology), chemical, immunologic and [molecular](http://en.wikipedia.org/wiki/Molecular_pathology) examination of organs, tissues, and whole bodies (autopsy). On examining a biopsy, the following aspects are considered:

* Gross anatomical make up of the sample
* Microscopic appearance of cells
* Chemical signatures in the sample
* Immunological markers present in the cells
* Molecular biology of the cells, organs, tissues and sometimes whole body

Anatomical pathology is itself divided in subspecialties, the main ones being :

**Surgical pathology** - This involves the examination of specimens obtained during surgery such as a breast lump biopsy obtained during mastectomy

**Histopathology** - This refers to the examination of cells under a microscope after they have been stained with appropriate dyes.

**Cytopathology** - In cytopathology, cells that have been shed into bodily fluids or have been obtained by scraping or aspirating tissue are examined. Typical examples include cervical smear, sputum and gastric washings.

**Forensic pathology-**  involves the post mortem examination of a corpse for cause of death using a process called autopsy.

**Dermatopathology** -concerns the study of skin diseases.

**CLINICAL PATHOLOGY**

Clinical pathology is a medical specialty that is concerned with the diagnosis of disease based on the [laboratory](http://en.wikipedia.org/wiki/Medical_laboratory) analysis of body fluids such as blood and [urine](http://en.wikipedia.org/wiki/Urine), and tissues using the tools of [chemistry](http://en.wikipedia.org/wiki/Clinical_chemistry), [microbiology](http://en.wikipedia.org/wiki/Clinical_microbiology), hematology, immunology and molecular pathology.

**Chemical pathology**, also called clinical chemistry, involves the assessment of various components in bodily fluids such as the blood or urine, although for the main part it concerns the analysis of blood serum and plasma.

**Hematology or hematopathology** is the study of the morphology and physiology of

blood. The is concerned with the investigation, diagnosis and monitoring of diseases of

the blood and blood-forming organs.

**Immunology or immunopathology** refers to the study of immune system disorders such as immunodeficiencies, organ-transplant rejection and allergies.

**Molecular pathology**

Molecular pathology is a multi-disciplinary field that focuses on disease at the sub

microscopic, molecular level. Aspects studied may include a mixture of anatomical

pathology, clinical pathology, genetics, molecular biology and biochemistry.

# HEALTH

Health is the level of functional and or metabolic efficiency of an organisms at both the micro (cellular) and macro (social) level. Health is commonly defined as an organisms ability to efficiently respond to challenges (stress) and effectively restore and sustain a state of balance (homeostasis).

Another widely acceptable definition of health is that of WHO. It states that “Health is a state of complete physical, mental, and social well being and not merely the absence of disease or infirmity.

# DISEASE

A disease or medical condition is an abnormality of the body or mind that causes discomfort, dysfunction, distress or death to the person afflicted. It is an abnormal variation in the structure and function in any part if the body or a change in the condition of an organisms complete adaptation to its environment as a result of which the organism suffers from discomfort or disease (dis – ease).

# CAUSES OF DISEASE

1. Congenital/Genetic diseases
2. Acquired Diseases

# Congenital/genetic diseases

Congenital diseases are represented by disease entities that may develop during foetal life as well as those that may arise and manifest themselves clinically during post-natal life. Genetically determined diseases are commonly congenital, although some may present many years after birth e.g. polyposis coli (multiple disease function) which is due to dominant abnormal gene and consists of multiple tumours of the colonic mucosa appearing in adolescent in adult life. Congenital disease may be acquired for example in the transmission of the virus of rubella (German Measles) from mother to foetus during the 1st trimester of pregnancy depending on the stage of foetal development at which infection occurs, it may result in foetal death or involvement of various tissues leading to mental deficiency, blindness, deafness or structural abnormalities of the heart. Mother may also transmit to the foetus various other infections including syphilis and toxoplasmosis with consequent congenital disease.

Ingestion of various chemicals by the mother as in the THALIDOMIDE disaster may induce severe disorder of foetal development and growth of children born to mothers who ingested these chemicals in the 1st trimester of pregnancy.

At other times, the acquired agent or disease may not necessarily be from outside it may be factors that are originating from the mother who during a second pregnancy develops toxic antibodies on their Red blood cells (RBC) transferable to the foetus causing haemolysis of RBC (destruction).

# Genetically determined diseases

Genetically determined diseases are due to some abnormalities of the base sequence in the DNA of the fertilized ovum and the subsequent cells that are derived from it or may be due to reduplication, loss or misplacement of the whole or part of the chromosome. Such abnormalities are often inherited from one or both from parents, the development of an abnormal gene can be provoked by radiation, mutagenic chemical and probably by viruses. In most instances the cause of mutation in Man remains unknown e.g of many condition result from abnormal gene are colour blindness, albinism, sickle cell anaemia, poly posis coli etc. The abnormal gene may be dominant i.e induces an abnormalities inspite of a normal corresponding gene of the other parent. It may be recessive i.e it causes disease only in the absence of a corresponding normal gene.

# Acquired causes of diseases

This is due to effects of some environmental factors. Many factors e.g malnutrition or micro organism. Most diseases are acquired either singly or through the contribution of factors, it is worthy of note that genetic variation of an individual can influence environmental factor in causing acquired diseases. Even in case of infections, there is considerably of individual variation in the severity of the disease e.g of the many individuals who become infected with polio virus most develop immunity without becoming ill, some have a mild illness or some becoming paralysed from the involvement of central Nervous system (CNS). This illustrates the importance of host factors as well as causal agents. The spread of TB is favoured by poor and personal Hygiene, by overcrowding, malnutrition and other various factors. Accordingly disease results not only from exposure to major causal agents, but also from existence of predisposing agent. The other causal agents may be classified as follows

1. Deficiency diseases or disturbances of nutrition
2. Physical agents
3. Chemicals
4. Micro organisms
5. Immunological factors
6. Psychological factors

# Deficiency diseases/disturbances of nutrition

Inadequate diets accounts for poor health in many part of the world. It may take the form of deficiency of either the four classes of food usually high grade protein, of vitamins or elements essential for metabolic processes e.g iron for Haemoglobin production. Often the deficiencies are multiple and complex. Disturbances of nutritions are no means restricted to deficiencies because in the more affluent coutries, obesity due to over eating has become increasingly common with its consequences as high blood pressure and heart disease.

# Physical agents

These include mechanical injury, heat, cold, electricity, Radiation and rapid changes in environmental pressure. In all instances, injury is caused by a high rate of transmission of a particular form of energy to or from the body. Common causes of mechanical injury in Nigeria is (RTA) Road Traffic Accidents, burns etc. Exposure to ionizing radiation is not entirely safe in any dosage. Radiation is beneficial in various diagnostic and therapeutic procedures but any pollution of the environment with radioactive material is potentially harmful to those exposed to it and probably to its subsequent generations.

# Chemical agents

With the use of an ever increasing number of chemical agents as drugs in industries and in the homes, chemically induced injury has become very common. In one extreme are those substances which have a general effect on cells such as cyanide which causes death almost instantaneously with little or no structural changes.

Many other chemicals such as strong acids and alkali cause local injury accompanied by an inflammation reaction in the tissue exposed to them. A 3rd large group of substances produces a more or less destructive injury within a particular organ or a cell type because of their importance and complex metabolic activities. Hepatocytes are injured by many chemical substances including paracetamol in large dosage and alcohol in high doses.

Specific injures of chemicals are illustrated also by injury of nerves by overdose of barbiturate and lung injury by paraquat (Chemical used for weeding).

**Microorganisms:** These include bacteria, protozoa, lower fungi and viruses. Inspite of the advances in immunization procedures and the extensive use of manmade antibiotics, many important diseases still result from infections by microorganism and the danger of wide spread epidemics e.g of influenza and cholera has been enhanced by air travel. The disease producing capacity of microorganisms depends on their ability to invade and multiply within the host and the possibility of their transmission to other hosts. The features of the disease produced by infection depends on the specific properties of the causal organisms.

# Bacteria

Bacteria brings about harmful effects mainly by the production of chemical compounds termed toxins.

NB: The biological effects of this together with the response of the host determines the features of the disease.

# Viruses

Viruses colonize host cells and have a direct cytopathic effect on the cells. Features of viral diseases depends largely on which cells are colonized, the site of viral replication, the nature of the cytopathic effect and the response of the host.

# Protozoa

Of the protozoa, the malaria parasite is of enormous importance as a cause of chronic ill health in the whole populations.

# Immunological factors

The development of immunity is essential for protection against microbes and parasites. However, this protection which man acquire becomes harmful and causes disease. The immune system does not distinguish between harmful and harmless foreign antigenic materials and an injury may result from immune reactions to either. Such hypersensitivity reactions are numerous and complex, local example include hay fever, asthma and some form of dermatitis while hypersensitivity to many foreign materials including penicillin and other drugs sometimes causes fatal generalized reactions.

# Psychogenic factors

The mental stresses imposed by conditions of life particularly in technologically advanced communities are probably largely responsible for three important and overlapping groups of diseases.

1.Acquired Mental disease such as SCHIZOPHRENIA and depression for which no specific structural or biochemical basis has get been found.

2.Disease of addiction particularly to alcohol, various drugs and tobacco. These results in their own complication e.g alcohol predisposes to liver damage and causes various neurological and mental disturbances while cigarette smoking is the major cause of lung cancer and chronic bronchitis. It is also concerned with peptic ulceration and coronary artery disease (Psychosomatic disease)

3.The third group of disease is Heterogenous and include peptic ulcer, high blood pressure and coronary artery disease.

In these three important conditions, anxiety, overwork and frustration appears to be the causal factors although their modes of action are obscure.

## PATHOLOGICAL PROCESSES

## The cell

The cell is the functional unit of all tissues, it has the capacity to perform individually all the essential life functions within the various tissues of the body. The constituent cells exhibit a wide range of specialization which are nevertheless merely amplifications of one or more of the fundamental cellular processes.

Mammalian cells have an extraordinary range of morphological forms yet all cells conform to a basic model of cell structure. All metabolism of the body are carried out and regulated by the cells of the tissue. Cells are active participants in their environment constantly adjusting function and structure to accommodate changing demands in extra cellular stress.

All disturbances of function and structure in disease are due to cellular abnormalities and the phenomena of a particular disease are brought about by a series of cellular changes. It is important to know the pathway of mechanism through which the cells are damaged because their damage gives rise to disease.

Pathological processes are of a dual nature consisting firstly of the changes of the injury induced by a causal agent and secondly of reactive changes which are often closely similar to physiological processes. If death is rapid as for example, in cyanide poisoning, there may be little or no structural changes of either type. In many instances, where cell injuries persist without killing the cell, the cytological changes are complex and those due to injuries often cannot be distinguished from those due to reaction. In order to facilitate the understanding of pathological processes, it is helpful to group together those which have common causal factor and as a consequence exhibit similarities in their structural changes e.g bacterial infections have certain features in common and may with advantage be further sub divided into acute and chronic infections. The features and behavior of neoplasms (tumours) are sufficiently similar to classify most tumours into two categories:

1. Benign (localized tumours) found within the tissue and is not life threatening
2. Malignant (this evades the entire body and is life threatening).

From old, the central problem of pathology is injury to the cell. The study of cellular damage starts as a microscopic disruption of individual components of each cell, progressively reaching a macroscopic level at the level of the tissues and organs. During the process of cellular disruption, there is disruption of biochemical, biophysical and anatomic structure of the cell. At a time the cell is undergoing these stages following injury, a series of analysis can be carried out which can help to stop or eliminate the injury.

### CAUSES OF CELL INJURIES

Cell injuries can be caused by genetic and acquired factors

### Oxygen depletion

Hypoxia or O2 deficiency interferes with aerobic respiration and it is an extremely importance factor among causes of cell injury and death, while ischaemia is the most common cause of hypoxia. Oxygen deficiency can also result from inadequate oxygenation of blood as in pneumonia or reduction of O2 carrying capacity of the blood as in anemia or carbon dioxide poisoning.

**Chemical agents**

Any chemical agent can cause injury to the cell even glucose or salt if sufficiently concentrated in the cell can cause injury to the cell. Oxygen at sufficiently high partial pressure is highly toxic. Agents commonly known as poison cause severe damage at cellular level by altering membrane permeability, osmotic homeostasis and can culminate in the death of the whole organism. Other potentially toxic agents are encountered daily in our environment, this include air pollutant, insecticide, carbon monoxide (co), asbestos, ethanol e.t.c Even therapeutic drugs can cause cell or tissue injury in susceptible patients.

**Infectious agents:**

Organisms that cause infections include viruses, bacteria, fungi, protozoa, helminth (parasitic worms). These have diverse ways of causing cellular injuries.

**Immunological reactions**

Although the immune system defends the body against foreign materials, immune reaction intended or incidental can result in cell and tissue injuries. Anaphylaxis to a foreign protein or a drug is a typical example.

**Nutritional imbalances**

Nutritional deficiency remains a major cause of cell injury. Protein calorie insufficiency among under priviledged population is an obvious example. Specific vitamin deficiencies are very common in developing and also developed nations. Excesses of nutrition are also important causes of morbidity and mortality e.g obesity markedly increases the risk of type II diabetes. All over, diets rich in animal fats are strongly indicated in the development of atherosclerosis (deposit of fat)

**Physical agent:**

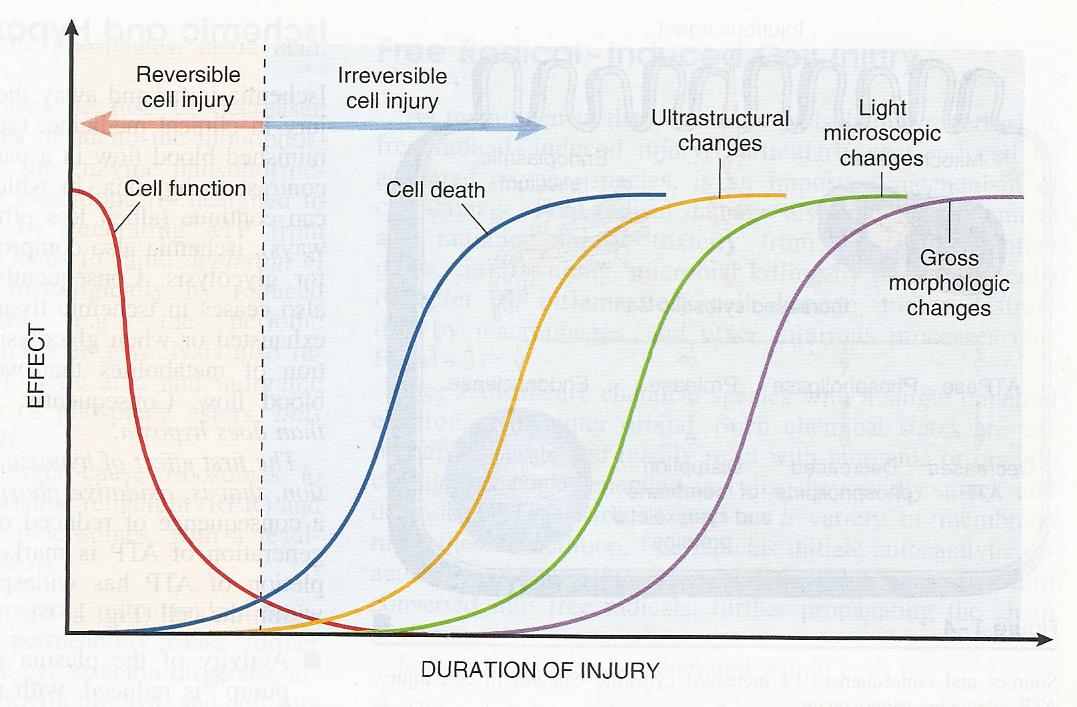
Trauma, extreme temperature, radiation, electric shock, sudden changes in atmospheric pressure, all have wide ranging effect on cells.

### Genetic defect

Genetic defect may result in pathologic changes e.g down syndrome, sickle cell diseases e.t.c.

GENERAL PRINCIPLES RELEVANT TO MOST FORMS OF CELLULAR INJURY

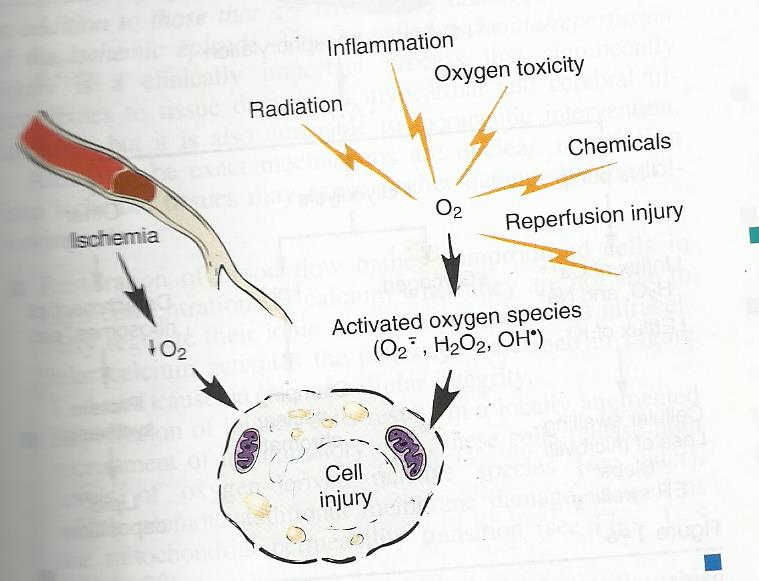
1. The cellular response to injurious stimuli depends on the type of injury, its duration and its severity. Thus low doses of toxins or a brief duration of ischaemia may lead to reversible cell injury where as larger toxin doses or longer ischaemia intervals may result in irreversible injury and cell death.
2. The consequences of an injurious stimulus depend on the type, status (nutritional), adaptability and genetic makeup of the injured cell. The same injury has vastly different outcome depending on the cell type, thus striated skeletal muscles in the leg accommodate complete ischaemia up to 2-3 hrs without irreversible injuries where as cardiac muscle dies only after 20-30 mins. The nutritional status can also be very important as a glycogen replete hepatocyte will tolerate ischaemia much better than one that has just burned its last glucose molecule.
3. Four intracellular systems are particularly vulnerable in cellular injury.
   1. Cell membrane integrity
   2. ATP generation
   3. Protein synthesis
   4. Intergrity of the genetic apparatus.
4. The structural biochemical components of a cell are so integrally connected that regardless of the initial locus of Injury, multiple secondary effects rapidly occurs.
5. Cellular function is lost far before cell death occurs and the morphological changes of cell injury or death lag far behind both loss of cellular function and cell death.



Schematic diagram demonstrating the relationship between cellular function, cell death and Morphological changes.

Note that cells may become rapidly non-functional after the onset of injury, although they are still viable with potentially reversible damage. The longer duration of injury may eventually lead to irreversible injury and cell death.

### GENERAL BIOCHEMICAL MECHANISM OF CELL INJURIES



**The role of oxygen in cell injury**

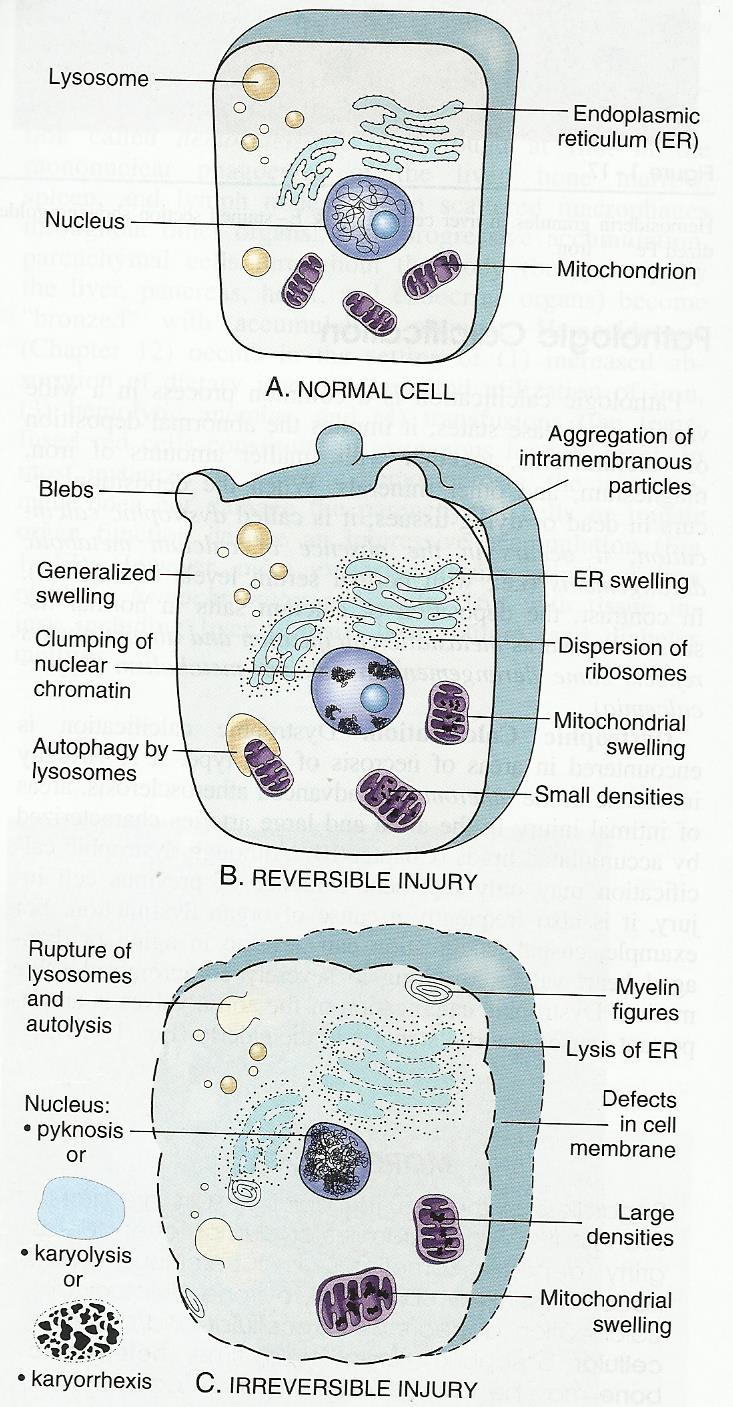
1. **ATP Depletion:** The high energy phosphate of Adenosine Triophosphate (ATP) are critical for virtually every process in the cell. A loss of ATP synthesis results in rapid shutdown of most critical homeostatic pathways.
2. **Loss of calcium homeostasis:** Ischaemia or toxins allow a net influx of extracellular calcium across the plasma membrane followed by the release of calcium in the intracellular stores. Increased cytosolic calcium in turn activates a variety of phospholipases (promoting membrane damage).
3. **Free radicals:** Examples are superoxide, anions, hydroxyl radicals and peroxides. Free radicals are partially reduced activated oxygen species. They cause liquid peroxidation and other harmful effect on cell structures.
4. **Defective membrane permeability:** A loss of membrane barriers leads to a breakdown of concentration gradients of metabolites necessary to maintain normal metabolic activities. The plasma membrane may be directly damaged by certain bacterial toxins etc.
5. **Mitochondria damage:** Mitochondrial intergrity is critical for cell survival. Mitochondria ends up as targets of most types of injury.

### REVERSIBLE AND IRREVERSIBLE CELLULAR INJURIES

Cellular damage can be divided into 2 groups (1) Reversible injuries or cellular degeneration and (2) Irreversible cellular injuries or cell death.

### Reversible injuries or cellular degeneration

Reversible injury is when a particular pathological change can be reversed such that it returns back to its original normal state. E.g cardiac muscle suffering from Ischaemia for a short period of time causes reversible injury to cardiac muscle cells, so that ATP production is sustained via anaerobic respiration, but if ischaemia is prolonged, then it will lead to irreversible injury where the pathological change is permanent and will lead to cell death. Reversible injury is a lesser form of cellular damage in which the functions important for the economy of the cells are diminished and or lost but in which integrated vital functions such as respiration, membrane permeability are still possible.



Schematic representation of the ultrastructural features of a normal cells (A) and those changes seen in reversible (B), and irreversible (C), cell injury.

In reversible injury, the pathological change can be reversed to its original state either by treatment of the symptom or by removing the external stimuli causing the injury.

### Irreversible cellular injuries or cell death

In irreversible cellular damage, the pathological change has advanced to a stage that is permanent and will lead to cell death. Death of cells occurs in two ways: 1 Necrosis and 2. Apoptosis.

**NECROSIS**

Necrosis is cell death or irreversible cellular injury, they are changes produced by enzymatic digestion of dead cellular elements. Necrosis is the most common form of cell death. It describes the process of cell death due to external stimulus. It occurs as a consequent to irreversible cell injury leading to cell death. It is always associated with an inflammatory process, we can expect cells such as neutrophils, macrophages e.t.c. to be present when observed under the microscope. For necrosis to take place, there is disintegration of vital functions of the cells, tissues organs beyond a reversible state. Whether anatomically or functionally, necrosis is recognizable.

### Functional identification of necrosis

This is associated with analysis of the product particularly lytic enzyme released from cellular cytoplasmic contents. This enzyme acts as a biochemical index of cell death. Morphologically, necrosis is represented from the naked eye inspection by whitish discoloration of the affected area followed by a yellowish discoloration and softening which is synonymous with when the lytic enzyme comes into play.

### Patterns of necrosis in tissues or organs

As a result of cell death, the tissues or organs display certain macroscopic changes.

(1) **Coagulative necrosis**: This is the most common pattern in necrosis, it occurs in almost all organs, outline of dead cells are maintained and the tissue is firm.

(2)**Liquifactive (colliquative) necrosis**

The dead cells undergo disintegration and the affected tissue is liquefied, this results in action of powerful hydrolytic enzymes, example is cerebral infarction. It also occurs as a result of bacteria or fungi infection and it involves complete breakdown and digestion of the dead cell.

(3) **Caseous necosis:** It is a form of coagulative necrosis, it is found typically in the center of tuberculotic lesion, grossly the necrotic area appears soft and white resembling cheese material and therefore is called cheese-like necrosis.

(4**) Gangrenous necrosis:** It is typically secondary to ischaemia and superimposed infection eg necrosis of distal limbs usually foot and toes in diabetics

(5**)Fat necrosis:** This is encountered in adipose tissues due to the action of lipases. It is most commonly seen in acute pancreatic necrosis in which pancreatic enzymes cause fatty deposit throughout the abdomen.

**Morphology of necrosis**

1. The digestive action of enzymes may show breakdown of membrane walls or organelles especially endoplasmic reticulum.

**(2) Nuclear Changes:**

* 1. Pyknosis: The nucleus progressively shrinks and becomes transformed to a dense and small wrinkled mass of chromatin
  2. Karyolysis: Chromatin undergoes progressive dissolution and eventually disappears
  3. Karyorrhexis: This is another form of fragmentation of chromatin which occurs by mitosis. The nucleus of a dead cell completely disappears in 1 to 2 days.

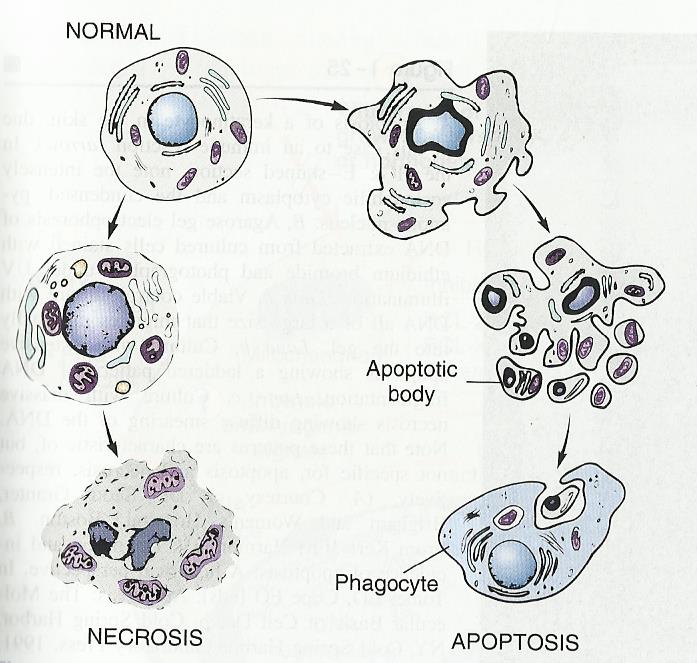
APOPTOSIS:

Apoptosis is programmed cell death. It is a vital process that helps to eliminate unwanted cells and it is an internally programmed series of events affected by dedicated gene products. There are instances that certain cells are needed only for a short period of time and then regarded as useless or detrimental to the process involved, thus they indulge themselves in a suicide programme causing minimal injury to the surrounding tissues. Apoptosis serves several vital functions and is seen under various settings

1. During development for removal of excess cells during embryogenesis
2. To maintain cell population in tissues with high turnover of cells such as skin, bowels etc.
3. To eliminate immune cells after cytokine depletion and auto reactive T. cells in developing thymus.
4. To remove damaged cells by viruses
5. To eliminate cells with DNA damage by radiation, cytotoxic agents etc.
6. Hormone dependent involution e.g. ovary endometrum, breast
7. Cell death in Tumours

### Morphology of apoptosis

* 1. Shrinkage of cells
  2. Condensation of nuclear chromatin peripherally under nuclear membrane
  3. Formation of apoptotic bodies by fragmentation of the cells and nuclei
  4. Phagocytosis of apoptotic bodies by adjacent healthy cells or phagocytes
  5. Unlike necrosis, apoptosis is not accompanied by inflammation reaction thus hindering microscopic recognition.



**SOMATIC DEATH**

Somatic death is the death of the body as a whole. It occurs when respiration and heart activity stop. (Cessation of breathing and cardiac arrest) although individual cells and even tissues may continue to live for short periods. Soon, characteristic changes begin to make their appearance in the dead bodies.

**Signs of somatic death**

1. Cessation of [breathing](http://en.wikipedia.org/wiki/Breathing)
2. [Cardiac arrest](http://en.wikipedia.org/wiki/Cardiac_arrest) (no [pulse](http://en.wikipedia.org/wiki/Heart_rate))
3. Loss of response to stimuli
4. Cessation of the circulation
5. [**Pallor mortis**](http://en.wikipedia.org/wiki/Pallor_mortis) **:**  Paleness which happens in the 15–120 minutes after death
6. [**Algor mortis**](http://en.wikipedia.org/wiki/Algor_mortis) **:** This is the reduction in body temperature following death. This is generally a steady decline until matching ambient temperature
7. [**Livor mortis**](http://en.wikipedia.org/wiki/Livor_mortis) **:** This is a reddish discoloration of the dependent parts of the body due to the sinking of the blood from gravity, combined with a breaking down (haemolysis) of the red blood cells.
8. [**Rigor mortis**](http://en.wikipedia.org/wiki/Rigor_mortis)**:** This ismuscular rigidity due to chemical changes in the muscle. The stiffness begins in 4 hours or more and passes off in 3 days. The limbs of the corpse become stiff and difficult to move or manipulate
9. [**Decomposition**](http://en.wikipedia.org/wiki/Decomposition) **:** This is reduction into simpler forms of matter, accompanied by a strong, unpleasant odor.

### CELLULAR ADAPTION TO INJURY

As cells encounter physiologic stress, or pathologic stimuli, they undergo adaptation, achieving a new steady state and preserving viability. The principal adaptive responses are:

(i) Atrophy

1. Hypertrophy
2. Hyperplasia
3. Metaplasia
4. Dysplasia

If the adaptive capability is exceeded cell injury develops. These physiological adaptations usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators e.g the enlargement of the breast and induction of lactation and pregnancy.

Pathologic adaptation often shares the same underlining mechanisms but they allow the cells modulate their environment and ideally escape injury. Thus cellular adaptation is a state that lies between the normal unstressed cell and the injured overstressed cell.

**ATROPHY**

Shrinkage in the size of the all by the loss of cell substance, when a sufficient number of cells involved, the entire tissue or organ diminishes in size becoming atrophic. Although atrophic cells may have diminished function, they are not dead.

Atrophy represents a retreat by the cell to a smaller size at which survival is still possible. A new equilibrium is achieved between cell size and diminished blood supply, nutrition and trophic stimulation.

#### Causes of atrophy

1. Decreased workload e.g immobilization of a limb to permit healing of a fracture
2. Loss of innervation
3. Diminished blood supply
4. Inadequate nutrition
5. Loss of endocrine stimulation
6. Ageing

### Physiologic atrophy

Morphologically by naked eye inspection, atrophy is seen as reduction in size of an organ e.g a normal adult heart that is supposed to weigh 250-350g, when it undergoes atrophic changes can weigh as little as 100g. Most physiologic atrophies are related to age, with advancement in age, there is reduction in physiologic activities. The cells and tissues undergo degenerative changes. Examples of physiological atrophy are (1) Cardiac atrophy (2) Testicular atrophy (3) Atrophy of the uterus and ovary during menopause due to loss of endocrine stimulation (4) Physiologic atrophy of the breast.

### Pathologic atrophy

These are particularly resulting from diseased entities that include:-

1. Neoplastic conditions, particularly malignant neoplasia (cancer)
2. Immobilization and sedentary activities
3. Inability of the body’s regulation of hormonal system.

**Neoplastic condition:** In the case of neoplastia (cancer), atrophy results from general disbalance or disorganization of organs by the activities of stubborn uncontrollable cells that are proliferating and multiplying. Each system is unable to carry out its function and this result in a multiple organ failure and the overall effect is known as a state of CACHEXIA

**Atrophy resulting from immobilization and sedentary activities**: This can be best seen with people with bone fracture because of their inability to utilize their skeletal muscle. The skeletal muscle undergoes progressive reduction in size i.e decreased work load. Sometimes this type of atrophy can result in excessive compression of a large organ from its neighbour e.g a uterus with fibroid can cause pressure atrophy changes in the bladder and large intestine.

**Inability of the body’s regulation of hormonal system**. Atrophy in the last stage can result in the improper regulation or hormonal imbalance in which the target organ adapts itself by reduction in size e.g. when there is an imbalance between progesterone and oestrogen, some women react by having atrophy of both ovaries.

### HYPERTROPHY

This means increase in the size of the cell and consequently and increase in the size of the organ. In pure hypertrophy there are no new cells just bigger cells enlarged by increased synthesis of structural protein and organelles. Hypertrophy can be caused by:

* Increase functional demand
* Specific hormonal stimulation

Hypertrophy can be physiologic or pathologic

**Physiologic hypertrophy:** It results from conditions that demand increase in metabolic activity of tissues and organs and sometimes to over reaction to some types of hormonal production e.g skeletal muscle reaction to excessive exercise by an increase in oxygen consumption for their metabolic processes.

In such condition, there is an excessive muscular hypertrophy eg the weight lifters can develop their rippled physique only by hypertrophy of individual skeletal muscle induced by an increased workload. Another example is the massive hypertrophy of the uterus during pregnancy which occurs as a consequence of oestrogen stimulation.

### Pathologic hypertrophy

An example of pathologic hypertrophy is seen in cardiac enlargement that occurs with hypertension or aortic valve disease. The heart which must contract against increased pressure achieves a weight of about 700 – 1000g. Another example is enlargement of residual viable cardiac myocytes after myocardial infarction. In this case, hypertrophy compensate for death of neighbouring cells due to ischaemia.

In some conditions in which there is imbalance of hormonal functions with advancement of age, some target organs respond by increase in size e.g. an imbalance between oestrogen and testosterone causes benign hypertrophy of the prostate.

### Hyperplasia

It constitutes an increase in the number of cells in an organ or tissue. Hypertrophy and hyperplasia are closely related and often develop concurrently in tissues so that both may contribute to an overall increase in organ size e.g. the gravid uterus (pregnant uterus). Hyperplasia can be pathologic or physiologic.

### Physiologic hyperplasia

1. **Hormonal hyperplasia**: this is exemplified by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy.
2. **Compensatory hyperplasia**: This is hyperplasia that occurs when a portion of the tissue is removed or diseased e.g. when a liver is partially resected, mitotic activity in the remaining cells begin as early as 12 hrs later eventually restoring the liver to its original state.

##### Pathologic hyperlasia

Most forms of pathologic hyperplasia are instances of excessive hormonal stimulation or the effect of growth factor on target cells.

Hyperplasia of the endomentrum is an example of hormonally induced hyperplasia. If the balance between oestrogen and progesterone is disturbed resulting in excess of oestrogen, hyperplasia of endometrum may result. The patient presents with abnormal uterine bleeding. Endometrial hyperplasia is considered a forerunner of endometrial carcinoma.

Pathologic hyperplasia constitutes a fertile soil in which cancerous proliferation may eventually arise, thus patients with hyperplasia of the endometrum are at increased risk of developing endometrial cancer.

##### Metaplasia

This is cellular adaptation whereby cells sensitive to a particular stress are replaced by other cell types better able to withstand the adverse environment.

Epithelial metaplasia is exemplified by the squamous change that occurs in the respiratory epithelium of habitual cigarette smokers. The normal ciliated, columnar epithelia cells of the trachea and bronchi are focally or widely replaced by stratified squamous epithelia cells.

Vitamin A deficiency may also induce squamous metaplasia in the respiratory epithelium. Presumably, the more rugged stratified squamous epithelium is able to survive under circumstances that the more fragile specialized epithelium would not tolerate.

**Dysplasia**: The term refers to either epithelial or mesenchymal cells that have undergone proliferation and a typical cytogenic cell alterations involving cell size, shape and organization. The dysplastic cells are characterized by increased mitotic activities. It is considered a forerunner of cancer.

# INFLAMMATION

Inflammation is a complex reaction in vascularized connective tissue as a result of cell injury. It is a protective response intended to eliminate the initial cause of cell injury as well as necrotic cells and tissues resulting in the original insult. Inflammation accomplishes its protective mission by diluting, destroying or otherwise neutralizing harmful agents e.g microbes or toxins. It then sets into motion the events that eventually heal and reconstitute the site of injury. The inflammatory responses has many players, these include:

1. **Circulating cells:** These are bone marrow derived polymorphonuclei leucocytes (neutrophils), monocytes, eosinophils, lymphocytes, basophils and platelets.
2. **Circulating proteins:** This includes clotting factors, kininogenes and complement components largely synthesized by the liver.
3. **Vascular Wall Cells:** This includes endothelial cells in direct contact with the blood as well as the underlining smooth muscle cells that impart tone to the vessels.
4. **Connective tissue Cells:** This includes mast cells, macrophages, lymphocytes and fibroblasts.
5. **Extracellular Matrix:** This includes fibrous structural protein e.g collagen and elastin, gel forming proteoglycans and adhesive glycol proteins:-

There are two types of inflammation, acute and chronic inflammation. Acute inflammation is of relatively short duration lasting from a few minutes up to a few days, and it is characterized by fluid, plasma protein extrusion. Sources of acute inflammation include infection (bacteria, viral, parasitic) and microbial toxins.

Chronic inflammation is of a longer duration (days to years) and it is typified by influx of mononuclear cells, lymphocytes macrophages and plasma cells with associated vascular proliferation and scaring. Causes include viral infections, chronic infections, persistent injury and autoimmune response.

**NOTE:** These two forms of inflammation can overlap.

**ACUTE INFLAMMATION**

This is the immediate and early response to injury, designed to deliver leukocytes to site of injury. Acute inflammation has two major components:-

(1) **Vascular changes**:- Vasodilatation and increased vascular permeability. Alterations in vessel caliber that results in increased blood flow and structural changes that permit plasma protein to leave the circulation

**(2) Cellular events:-**

(a) Cellular recruitments and – emigration of leucocytes from the microcirculation and accumulation in the site of injury.

(b) Cellular activation - margination, adhesion – chemotaxis and activation.

**Vascular changes**: These cascade of events in acute inflammation is integrated by local release of chemical mediators.

**Chemical mediators of inflammation**

**Local mediators:-** Vasoactive amines e.g.

**(a) Histamine**:- It is widely distributed in tissues particularly mast cells, also present in circulating basophils and platelets. Histamine causes arteriolar dilatation and is the principal mediator of the immediate phase of increased vascular permeability.

**(b) Serotonin**: It has effects similar to histamine and found primarily within platelets.

**(c) Lysosomal Enzymes:-** This includes prostaglandins, nitric oxide, cytokines.

**Systemic mediators:**-

**(1) Kinin System:** **e.g.** Bradykinin. Like histamine, Bradykinin causes increased vascular permeability, arteriolar dilatation and bronchial smooth muscle dilatation. It causes pain when injected into the skin.

**(2) Coagulation/fibrinolysis system**

**(3) Anaphylatoxins**

**(4) Membrane attack complex**

**Phases of acute inflammation**

Generally, acute inflammatory pathways consist of a number of inter-dependent phases:-

(1) Alternative phase

(2) Exudation phase

(3) Reparative phase

**Alternative phase**:- This phase of inflammatory process includes the tissue reaction which occurs in the interval between injury and appearance of exudative phase. The phase is of short duration and almost not clinically and directly observable. The tissue changes which occur are retrogressive in nature. As a result of this tissue changes, certain chemical substances are released into the injured area and this includes vaso active amines, polypeptides etc. The chemical substances alter the hydrogen ion concentration and the osmolarity of microcirculation and act directly on the microcirculation to initiate the exudative phase of the inflammatory process.

**Exudative phase:** This is a vascular reaction characterized by the formation of an exudate which is a protein rich fluid of high specific gravity. The fluid that is initially formed during this type of reaction contains a little number of cells and almost completely lacks proteins and is referred to as transudate. The exudative phase is responsible for the five (5) cardinal signs of acute inflammation. Four (4) cardinal (macroscopic signs) signs of acute inflammation were described by Celsius. Galen actually added the 5th sign which is loss of function.

1. Redness - Rubor
2. Heat - Calor
3. Pain - Dolor
4. Swelling - Tumour
5. Loss of function – function laese

**Redness** (Rubor): This is a central dull area at the site of injury as a result of dilatation of vessels (venules and capillaries) which were acted on directly by chemical substances released in the area. Bright red halo surrounding the site of injury and dilatation of arteriole outside the injured area are observable.

**Heat** (Calor): The vascular dilatation is associated with increased rate of flow and volume of blood into the injured area. The injured area when on the exposed body surface is at lower temperature than the interior of the body in which the blood flows, thus the tissue in the body in the injured area becomes warmer than the adjacent areas.

**Pain (Dolor):** This probably results from a combination of factors acting alone or together on nerve endings in the injured area. Some of these factors are pressure caused by the exudates in the tissue, released serotonin and of bradykinin into the tissue and altered tonicity and osmolarity.

**Swelling (Tumour):** Swelling of the injured area is due to accumulation of exudates in the injured tissue. Increased vascular permeability is the basis for the exudates. The increased vascular permeability allows initially fluids and colloids and later cells from the lumen of the microcirculation to enter into the interstitial compartments.

**Loss of function** **(Function laese)**: Decreased function of inflamed area is usually caused by a reflex inhibition of muscle movement associated with pain and mechanical disability produced by swelling.

Effects of inflammation and their major mediators:-

1. Vasodilatation

2. Vascular permeability

3. Chemotaxis

4. Fever

5. Pain, Tissue damage

**Outcome of acute inflammation**

Although the consequences of acute inflammation are modified by the nature and intensity of the injury, the site and tissue affected and the ability of the host to mount a response, acute inflammation generally has three (3) outcomes:

**(i) Resolution:** This involves neutralization or removal of chemical mediators. Neutralization of vascular permeability and cessation of leukocytes emigration with subsequent death of estravasated neutrophils thus there is restoration of histologic and functional normalcy. Resolution results from limited or short lived injury with minimal tissue damage.

**(2) Scarring or Fibrosis:** This results from injuries with substantial tissue destruction or when inflammation occurs in tissues that do not regenerate. Due to extensive underlying tissue destruction, the only outcome is scarring.

**(3) Progression to chronic inflammation**

This may follow acute inflammation, although the signs of chronic inflammation may be present at the onset of injury. Chronic inflammation may be followed by regeneration of normal structure and function but may lead to scarring.

**Functions of exudate**

1. To limit the extent of tissue damage

2. It helps to dilute the toxins in the tissue

**Clinical information about inflammation**

1. Clinically inflammation is represented by the nomenclature “ITIS” but at other times some traditional nomenclature are used e.g. pneumonia

2. Acute inflammation occurs generally in tissues that are well vascularized and they present with fever and pain.

3. Chemical reactions and their product can be investigated either by the study of the blood or tissue exudate.

**Systemic effects of inflammation**

1. Fever (pyrexia) – high temperature

2. Malaise – general feeling of illness

3. Anorexia – loss of appetite

4. Somnolence – feeling sleepy

5. Leukocytosis – increased white blood cell.

**Reparative Phase**: Repair begins almost as soon as the inflammatory changes have started and involves several processes including cell proliferation, cell differentiation and extra cellular matrix deposition. Repair involves two main processes

1. Regeneration of injured tissue by parenchyma cells of the same type.

2. Replacement by connective tissue (fibrosis) resulting in a scar.

Commonly tissue repair (healing) involves a combination of both processes.

**1. Regeneration of injured tissue by parenchyma cells of the same type :**

The cells of the body are divided into 3 groups on the basis of their regenerative capacities and their relationship to the cell cycle.

**Labile cells**: These are continuously dividing and continuously dying cells e.g. heamatopoetic cells in the bone marrow and majority of surface epithelia cells including the stratified squamous epithelia of the skin, columnar epithelia of GIT, uterus etc.

**Stable cells :** These have low level replicating capacity in their normal state but are capable of undergoing rapid division in response with injury e.g. parenchyma of most solid glandular tissues including liver, kidney, pancreas as well as endothelia cells lining blood vessels.

**Permanent cells**: These are considered to be terminally differentiated and non-proliferative in post natal life. The majority of neurons and cardiac muscles cells belong to this category. Thus, injury to brain or heart is irreversible and results to only scar formation since the tissue cannot proliferate.

Cell growth and differentiation are dependent on extra cellular signals derived from

(a) Soluble chemical mediators e.g. polypeptide growth factor circulating in the serum or produced locally by cells.

(b) Extra cellular matrix (ECM) Component of ECM:-

(i) Fibrous structural proteins that confer tensile strength e.g. collagen and elastin.

(ii) Water hydrated gel that enhance lubrication e.g. proteoglycans

1. Adhesive glycoprotein that connect the matrix element onto another and to other cells e.g. fibrorectin and laminin

**2. Replacement by connective tissue**:

Severe or persistent tissue injury with damage to both the parenchyma cells and to the stroma frame work leads to a situation in which repair cannot be accomplished by parenchyma regeneration alone. Under these conditions repair occurs by replacement of the non-regenerated parenchyma cells with connective tissue. There are 4 general components of this process:

1. Formation of new blood vessels (Angiogenesis)
2. Migration and proliferation of fibroblasts
3. Deposition of Extra Cellular Matrix (ECM)
4. Maturation and reorganization of the fibrous tissue (remodeling)

**WOUND HEALING**

Wound healing is a complex but generally orderly process. The events are orchestrated by interplay of soluble growth factors and extracellular matrix (ECM) and physical factors. Wound healing is regarded as the basis for all surgical procedure.

**Types or forms of wound healing**

(1) Healing by 1st intention or primary union e.g. is a healing of a clean uninfected surgical incision approximated by surgical sutures. Epithelial regeneration predominates over fibrosis in this form of healing. The narrow incisional phase rapidly fills with fibrin clothed blood. The hydration at the surface produces a scab to cover and protect the healing repair site. The final product is a clean and organized tissue.

(2) Healing by secondary intention:- This form of healing occurs when cells or tissue loss is more extensive as in infarction, inflammatory, ulcerative, and abscess formation of large wounds. It involves a more complex reparative process. Restoration of parenchyma cells alone cannot restore the original cell architecture as a result, there is an extensive in growth of granulation tissue from the wound margin, followed by accumulation of ECM and scarring.

**Factors affecting wound healing**

**Local factors**

(a) Blood supply: A good blood supply gives rise to good wound healing

(b) Superimposed infection:- This gives rise to poor wound healing. Infection prolongs the inflammation phase of healing process and potentially increases the local tissue injury.

(c) Presence of foreign body eg fragments of steel, glass or bone, this gives rise to poor wound healing as they impede the healing process.

(d) Mobility of tissues: A well mobilized tissue heals faster than immobilized tissue.

(e) Aging process: Healing is faster in children than in adult.

(f) Type of tissue (complete repair can only be seen in labile and stable cells). Injury to tissues composed of permanent cells must inevitably result in scarring. Such is the case with the healing of myocardial infarction.

**Systemic factors**

(i) Nutritional factors: A poor nutritional status will give rise to a poor wound healing. Protein deficiency and particularly Vit. C deficiency inhibits collagen synthesis and retard healing.

(2) Physiological conditions: Physiological conditions of individuals in particular immunological status – Immunodeficient individual of primary or acquired nature have poor wound healing.

(3) Endocrine deficiency: Reduction in most endocrine secretions gives rise to poor wound healing e.g. deficiency of adrenal gland in the production of ACTH gives rise to poor wound healing.

**Complications of wound healing**

(1) **Keloid formation**: This is an abnormal formation of healing particularly found in negroid race. There is accumulation of exuberant amounts of collagen which can give rise to prominent raised scars known as keloid.

(2) **Hypertrophy tissue**: This is an abnormal production of extra strengthened collagen fibre.

**(3) Exuberant granulation (proud tissue):** They contain few vascular tissues, chronic inflammatory cells and collagen fibres. This is where a healing wound generates excessive granulation tissue that protrudes above the level of the surrounding skin. The outgrowth of new capillaries and connective tissue cells from the surface of an open wound is called a granulation tissue.

**CHRONIC INFLAMMATION**

Chronic inflammation can be considered to be inflammation of prolonged duration weeks to months, years) in which active inflammation, tissue injury and healing proceed simultaneously. Chronic inflammation is characterized by:-

(1) Infiltration of mononuclear cells (macrophages, lymphocytes and plasma cells).

(2) Tissue destruction – largely directly by inflammatory cells.

(3) Repair involving new vessel proliferation and fibrosis.

Chronic inflammation may progress from acute inflammation, this transition occurs when the acute response cannot be resolved either because of the persistence of the injurious agent or because of interference in the normal process of healing. Although the injurious agent mediating chronic inflammation may be less noxious than those that cause acute inflammation, the overall failure to resolve the process may lead to substantially more long term injury.

Chronic inflammation arises in the following settings.

1. Viral infections
2. Persistent microbial infections
3. Prolonged exposure to potential toxic agent
4. Auto immune disease e.g. rheumatoid arthritis

If the condition causing acute inflammation is not resolved, the inflammation may pass to a longer term chronic phase. Also, some pathogens by their nature tend to directly provoke chronic rather than acute inflammation. Many of the features of acute inflammation continue as the inflammation becomes chronic, including increased blood flow and increased capillary permeability. Accumulation of white blood cells also continues, but the composition of the cells changes. Neutrophils quickly enter the infected tissue, and these short-lived cells predominate initially. However, soon macrophages and lymphocytes begin to be recruited. The sequence by which they bind to cell adhesion molecules and pass through the endothelium is the same as for neutrophils. Thus, the primary cells of chronic inflammation are macrophages and lymphocytes.

Chronic inflammation is distinguished from acute inflammation by the absence of cardinal signs such as rubor, calor, dolor, tumor, active hyperemia, fluid exudation and neutrophilic emigration. It is distinguished from acute inflammation by its long duration, which permits a manifestation of immune response.

**Histologic hallmarks of chronic inflammation are:**

1. Infiltration of affected tissue by macrophages, lymphocytes and plasma cells

2. Proliferation of fibroblasts and myofibroblasts and proliferation of small blood vessels, together known as formation of *granulation tissue*

3. Most cases of chronic inflammation are accompanied by an increase in amount of connective tissue, referred to as *fibrosis*, or production of scar

**Types of chronic inflammation**

1. Chronic specific or non specific reactions

A chronic specific reaction is usually associated with known cause or isolated micro organism e.g. chronic peptic ulcer and it sometimes overlaps into chronic granulomatous reaction.

Non specific chronic reaction is caused by organisms that are usually multiple, and specific organisms are impossible to be isolated or demonstrated.

1. Chronic granulomatous inflammatory reaction

Granulomatous inflammation is a distinct type of chronic inflammation. It is marked by the formation of [granulomas](http://www.britannica.com/EBchecked/topic/241892/granuloma), which are small collections of modified macrophages called epithelioid cells and are usually surrounded by lymphocytes. Granulomas often contain giant, or Langerhan cells that form the coalescence of epithelioid cells. A classic example of granulomatous inflammation is tuberculosis, and the granulomas formed are called tubercles. Granulomas also typically arise from fungal infections, and they are present in [schistosomiasis](http://www.britannica.com/EBchecked/topic/527459/schistosomiasis), [syphilis](http://www.britannica.com/EBchecked/topic/578770/syphilis), and rheumatoid arthritis.

Granuloma formation does not always lead to eradication of the causal agent which is frequently resistant to killing or degradation but effectively “wall off” the offending agent and is therefore a useful defense mechanism.

According to the mechanism, granulomatous inflammation may be: immune type (tuberculosis, sarcoidosis) and non-immune type (foreign body reaction).

Classification of granulomatous inflammation, according to the etiology :

1. Infectious granuloma :
   * 1. Bacterial e.g. Mycobacterium tuberculosis (Koch bacillus) – Tuberculosis, mycobacterium leprae - Leprosy
     2. Parasitic e.g. Toxoplasma gondii – Toxoplasmosis

c. Fungi (Candida albicans) - Candidiasis

1. Foreign body granuloma

Other inflammatory agents are materials foreign to the body that cannot be removed by [phagocytosis](http://www.britannica.com/EBchecked/topic/454919/phagocytosis) or enzymatic breakdown. These include substances that can be inhaled, such as silica dust, and materials that can gain entry to wounds, such as metal or wood splinters.

III Unknown etiology granuloma eg Sarcoidosis

**MORPHOLOGIC PATTERNS OF ACUTE AND CHRONIC INFLAMMATION**

The severity of the inflammatory response, its specific cause and the particular tissue involved can all modify the basic morphologic patterns of acute and chronic inflammation. Such patterns frequently have clinical significance.

**Morphology**

1. **Serous inflammation**

This is characterized by the outpouring of a watery relatively protein poor fluid called EFFUSION. This effusion depending on the site of the injury could be from the serum or from the secretions of cells lining the peritoneal, pleural and pericardial cavities. A good example of serous effusion is the skin blister resulting from a burn or viral infection.

1. **Fibrinous inflammation**

This occurs as a result of more severe injuries with a resultant greater vascular permeability allowing larger molecules (specifically fibrinogens) to pass the endothelial barriers. Fibrinous exudates may be degraded by fibrinolysis and the accumulated debris may be removed by macrophages resulting in restoration of the normal tissue structure. It may also result in the in growth of fibroblasts and blood vessels leading to scarring if not completely removed.

1. **Suppurative (purulent) inflammation**

This is manifested by the presence of large amounts of purulent exudates (pus) consisting of neutrophils, necrotic cells and edema fluid. Certain organisms eg staphylococcus are more likely to induce this localized suppuration and therefore referred to as pyogenic organisms. Focal collections of pus are called abscess.

1. **Ulcerative inflammation**

This refers to a site of inflammation where an epithelial surface has been necrotic and eroded often with associated sub epithelial acute and chronic inflammation. This can occur as a result of toxic or traumatic injury to the epithelial surface.

# HYPERTENSION

Hypertension is a sustained elevated blood pressure (BP) (systolic pressure of 140mmHg or greater and or diastolic pressure of 90mmHg or greater).

Hypertension or high B.P means high pressure in the arteries. High BP does not mean excessive emotional tension, although emotion tension and stress can temporarily increase BP. Normal BP is below 120/80mmHg. BP between 120/80 % 139/89 is called pre-hypertension. BP. of 140/90 or above is considered high BP.

The systolic BP represents the pressure in the arteries as the heart contracts & pumps blood into the arteries while the diastolic pressure represents the pressure in the arteries as the heart relaxes after the contraction. The diastolic pressure therefore reflects the minimum pressure to which the arteries are exposed. Whereas, it was previously thought that diastolic blood pressure elevations were a more important risk factor than systolic elevations it is now known that for individuals older than 50yrs of age systolic hypertension represents a greater risk.

# Types of hypertension

There are 2 major types of hypertension and 4 less frequently found types. The 2 major types are:

1. Primary or essential hypertension: also known as benign or idiopathic.
2. Secondary hypertension
3. other types:
   1. Malignant hypertension
   2. Isolated systolic hypertension
   3. White coat hypertension
   4. Resistant hypertension

# Primary hypertension

Primary hypertension is the most common type of hypertension diagnosed in about 95% of cases. Essential hypertension has no obvious or identifiable cause. It usually has its onset in the 20’s – 30s and it affects males more than females.

# Secondary hypertension

Five to ten (5-10) percent of all hypertensive cases have an identifiable cause; Removal of cause does not guarantee normal pressure. This may be caused by:

1. Kidney damage or impaired kidney function. (This accounts for most secondary forms of hypertension)
2. Tumours or over activity of the adrenal gland.
3. Thyroid dysfunction
4. Medication e.g recreational drugs, oral contraceptives, corticosteroids, drinks & food.
5. Pregnancy related conditions.

# Malignant

This is the most severe form of hypertension and is severe and progressive. It rapidly leads to organ damage. Unless properly treated, it is fatal within 5 years for the majority of the patients. Death usually comes from heart failure, kidney damage or brain haemorrhage. However, aggressive treatment can reverse the condition and prevent its complications. It is becoming relatively rare and isn’t caused by cancer or malignancy.

# Isolated systolic hypertension

In this case, the systolic BP is consistently above 160mmHg & the diastolic below 90mmHg. This may occur in older people and results from the age related stiffening of the arteries. The loss of elasticity in arteries like the aorta is mainly due to arteriosclerosis, the western life style and diet is believed to be the root cause.

# White coat hypertension

This is a.k.a anxiety induced hypertension it means BP is only high when tested by a health professional. If confirmed with repeated readings outside of the clinical setting or a 24 hour monitoring device, it doesn’t need to be treated. However, regular follow up is recommended to ensure that persistent hypertension has not developed. Life style changes like more exercise, less salt & alcohol intake, no nicotine and weight lost are recommended. A low fat, high fibre diet with increased fruits (vegetables will be beneficial).

# Resistant hypertension

If BP cannot be reduced to below 140/90mmHg despite a triple drug regime, resistant hypertension is considered.

# Pathophysiology of essential hypertension

Essential hypertension develops from renal system dysfunction. The kidney is a filtering organ that retains vital blood components & excrete excessive fluid. If too much fluid is retained BP rises and if too little fluid is retained BP decreases. Arterial pressure within the renal artery. trigger a feedback loop. The kidney excretes sodium which osmotically draws fluid into the excretory system in a process called pressure diuresis . This causes a decrease in blood fluid volume and arterial pressure. As pressure within the renal artery decreases, the kidney reflexly secrets an enzyme called renin. This enzyme causes the formation of a protein called angiotensin I which directly stimulates the kidneys to retain Na & fluid. Angiotensin I is converted in the lungs via the enzyme angiotensin converting enzyme (ACE) to angiotensin II. Angioensin II is a potent vasoconstrictor which increases total peripheral vascular resistance & hence elevates B.P.

As BP elevates, the whole system begins again with pressure diuresis. In healthy individuals, the feedback loop maintains a constant BP with only minor fluctuation. In patients with essential hypertension the feedback fails and the result is higher than normal level of pressure within the renal artery necessary for pressure diuresis to occur.

# Risks or Predisposng factors for development of hypertension

The likely causes or predisposing factor are;

1. Increased reactivity of resistant vessels & resultant increase in peripheral resistance
2. A sodium homeostatic effect. In essential hypertension the kidneys are unable to excrete appropriate amount of Na at any given BP, as a result sodium & fluid are retained and the BP increases.

**Other Causes;**

1. **Age.** B.P tends to rise with age possibly as a result of decreased arterial compliance.
2. **Genetics**: History of hypertension ends to run in families. The closest correlation exists between siblings rather than parent and child. It is also possible that environmental factors common to members of same family also has a role to play in the development of hypertension.
3. **Environment:** Mental & physical stress increase BP. Removing the stress may not necessarily return the BP to normal.
4. **Na+ intake**: The salt study has confirmed a strong relation between hypertension, stroke & salt intake. Reducing salt intake in hypertensive individuals lowers BP.
5. **Alcohol**. This is the most common cause of hypertension in the young. It affects about 1% of the population. However, small amount of alcohol decrease BP, large amounts increases BP. If alcohol consumption is reduced; Blood pressure falls over several days to normal.
6. **Weight**: Obese patients have a higher BP. Up to 30% of hypertension is attributable in part or wholly to obesity. If a patient loses weight, BP falls in untreated patients, a weight loss of 9kg has been reported to produce a fall of BP of 19-18mmHg. Weight reduction is the most important non pharmacological measure available.
7. **Race**. Caucasians have a lower BP than black populations living in the same environment, Black population living in rural Africa have a lower BP than those living in town. Black populations are genetically selected to be salt retainers & so are more sensitive to an increase in dietary salt intake.

# RISKS OR COMPLICATIONS OF HYPERTENSION

* 1. **Ocular complications:** Systemic hypertension can affect the retinal, choroidal and optic nerve circulations. A variety of retinal vascular changes can be seen in hypertensive patients. This depends in part on the severity and duration of the hypertension. Hypertension is manifested in the eye as both hypertensive retinopathy & hypertensive ocular complications.
  2. **Coronary heart disease**: Excess work load on the heart leads to the development of congestive heart disease, coronary heart disease or both often causing death as a result of heart attack. Coronary heart disease is the leading cause of death in hypertensive patients. Ventricular hypertrophy occurs as a result of increased cardiac output in the face of systemic vascular resistance. Eventually, the heart is unable to maintain this constant output and the hypertrophied muscle outstrips it O2 supply.
  3. **Cerebrovascular disease**: The high pressure frequently ruptures major blood vessels in the brain followed by blood clotting and death of major portion of the brain. This is cerebral infarct (clinically this called stroke). Depending on the part of brain involved, a stroke can cause paralysis, dementia, blindness or multiple other serious brain disorders. Cerebrovascular disease is a serious complication of hypertension and hypertension is the leading cause of stroke.
  4. **Renal failure**: Very high pressure always almost causes multiple haemorrhages in the kidneys producing many areas of renal destruction and eventually kidney failure, coma and death.
  5. **Atherosclerosis and arteriosclerosis**: High BP plays a significant role in the development of these. High BP reduces elasticity of vessels allowing lipids to deposit in the form of atheromas which in turn leads to thrombus formation and possible emboli formation. This impedes blood flow and leads to ischaemic disease.

# DIABETES MELLITUS

This is the most common endocrine disorder. It is defined as a group of disorders that exhibit a defective or deficient insulin secreting process, glucose underutilization and hyperglycaemia. It is a chronic disorder of carbohydrate, fat and protein metabolism.

Possible systemic signs and symptoms include:

* Polyurea ( increased frequency of urination)
* Polydipsia (increased thirst)
* Polyphagia (increased appetite)
* Glyosurea (deposition of glucose in urine)
* Weakness (asthenia)
* Weight loss
* Nephropathy.

Heredity usually plays a major role in the development of diabetes mellitus. Obesity also plays a role in development of clinical diabetes.

### Classificaiton

**Type I** – This was formally known as insulin dependent diabetes mellitus. It is also known as juvenile onset or ketone prone diabetes mellitus. It usually begins at age 20 or less and it is defined by an absolute lack of insulin caused by a reduction in the B cell mass of the pancreas. This may be the result of auto immune processes and may involve genetic susceptibility. Approx 10% of diabetic cases are type I.

**Type II-** Was formally known as non insulin dependent diabetes mellitus (NIDDM). Sometimes referred to as adult onset diabetes mellitus. It usually begins after age 40 and a multi factorial disease that may involve improper insulin secretion, malfunctioning insulin and or insulin resistance in peripheral tissues. Approximately 90% of diabetic cases are type II. While there is a strong genetic component to developing this form of diabetes, there are other risk factors, the most significant of which is obesity. There is a direct relationship between the degree of obesity and the risk of developing type II diabetes and this holds true in children as well as adults. Two metabolic defects characterize type II diabetes. (1) Derangement in insulin secretion that is delayed or that is insufficient relative to the glucose load. (2) inability of peripheral tissues to respond to insulin (insulin resistance).

### Pathophysiology of diabetes mellitus

The pancrease plays a primary role in glucose metabolism by secreting the hormones insulin and glucagon. The islet of Langerhans secrete insulin and glucagon directly into the blood. Insulin is a hormone essential for proper metabolism of glucose and for maintenance of proper blood-glucose levels. Inadequate secretion of insulin or inadequate structure or function of insulin or its receptors results in impaired metabolism of glucose, other carbohydrates, proteins and fats. This is characterized by hyperglycaemia and glycosurea.

Hyperglycaemia is the most frequently observed sign of diabetes. Following a meal, glucose is absorbed into the blood. In response to increased blood levels, insulin is secreted causing rapid uptake, storage of glucose by the tissues of the body. Elevated glucose levels results in the formation of sorbitol (sugar alcohol). Since sorbitol cannot readily diffuse through the cell membranes, cell edema and changes in function can result. An additional complication of hyperglycaemia is non-enzymatic glycosylation. This is the binding of excess glucose to the amino group of proteins in the tissues.

In addition, some special pathophysiological occur in diabetes mellitus that are not so readily apparent;

**Glycosurea**  (presence of glucose in the urine).

Whenever the quantity of glucose entering the kidney tubules in the glomerular filterate rises above a critical level, a significant proportion of the excess glucose cannot be re-absorbed and instead spills into the urine. This occurs when the blood-glucose concentration is above 180mg/dl, a level that is called the blood threshold for the appearance of glucose in urine.

**Dehydrating effect of elevated blood glucose level of diabetes mellitus:**

A significant effect of the elevated glucose is dehydration of the tissue cells because glucose does not diffuse easily through the pores of the cell membrane, and the increased osmotic pressure in the ECF causes osmotic transfer of water out of the cells.

**Acidosis & Coma in diabetes –** In diabetes there is a shift from carbohydrate to fat metabolism. When the body depends almost entirely on fat for energy, the level of the keto acid in the body fluids may rise. All of these extra acids obviously is likely to result in acidosis.

**Physiologic basis of signs and symptoms of diabetes mellitus.**

Polyurea, polydipsia, glycosurea, polyphagia, asthenia, weight loss, nephropathy are the earliest symptoms of diabetes.

Polyuria is due to the osmotic diuretic c effect of glucose in the kidney tubules.

In turn, polydipsia is due to dehydration resulting from polyuria.

The failure of glucose utilization by the body causes weight loss and the tendency towards polyphagia.

The asthenia apparently also is caused mainly by loss of body protein.

### Ideal blood glucose values

Normal blood glucose level – 80-120mg/dl

* 1. Before meal – 72 – 126 mg/dl (4-7mmol/L)
  2. 90 mins after a meal – 180mg/dl.(less than 10mmol/L)
  3. At bed time – 144 mg/dl (8mmol/L)

# Clinical tests for diabetes mellitus

Diabetes mellitus can be tested for in many ways:

**Urinalysis** – is a rapid method of testing grossly for diabetes mellitus. laboratories examine the urine specimen primarily for 2 components, glucose and ketones.

The presence of glucose in the urine indicates insulin dysfunction meaning the body is not adequately converting the b/d-glucose into energy or storage materials and hence dumps it out via the renal system. Ketones represent end product of fatty acid metabolism. In most patients ketones are formed in the liver and are completely metabolised so that only negligible amounts are present in the urine. When the body is unable to use carbohydrate as an energy source, fat becomes the predominant body fuel and ketones are then formed.

Presence of ketones in the urine represent a significant problem and advanced disease.

2 **Blood testing**

* **Fasting blood sugar (FB**S)
* **Random plasma glucose (RPG)**

Most often, blood testing is the definite method of diagnosing diabetes mellitus and the preferred way of monitoring therapy.

The most common screening method is the **Fasting blood sugar test.** This test measures the level of blood glucose in the blood for a minimum of 8 hrs after food intake. Normal values for FBS are 110 mg/dl and those with values between 110-126 mg/dl are said to have impaired fasting glucose and should be suspects for diabetes. Those with values > 126mg/dl on 2 or more separate occasions may be diagnosed with diabetes mellitus.

**Random Plasma glucose (RPG)-** This is the measurement of serum glucose level at other times when the patient has not fasted. RPG values of 200mg/dl or greater measured on 2 or more separate occasion when diabetes symptoms are present indicates a diagnosis of the disease.

**Oral glucose tolerance test (OGTT)** – OGTT begins with the patient fasting for 8 hours and then drinking a syrupy beverage with glucose load equivalent to 75g. 2hrs after infesting the liquid, serum glucose is measured. Normal values for the OGTT are 140mg/dl or less. Findings between 140 and 200mg/dl indicate impaired glucose tolerance and those greater than 200mg/dl are consistent with diabetes

4. **Glycosylated haemoglobin (HBAic) Test** – This refers to the end product of glucose binding with the Hb within RBC. This is a natural occurrence in all individuals. However in uncontrolled diabetic patients, there are much higher levels of ambient glucose in the blood and hence higher levels of glycosylated Hb. Unlike urine testing or FBG which are essentially spot checks glycosylated Hb yields an assessment of blood sugar control over a1-3 mths period. It is very valuable for monitoring patients compliance and effectiveness of therapy.

# Ocular complications of diabetes mellitus

1. Large Changes in Refraction – This may be the first sign of diabetic disease often myopic or hyperopic shifts are created as the lens swells secondary to sorbitol effects resulting in large refractive changes in what are otherwise noted as stable eyes.
2. Cataracts – The cataracts may mature quickly but have been documented to regress once sugar levels are stabilized.
3. Retinopathy – is a common eye complication among people with diabetes. It is a leakage of damage blood vessels in the retina and collapse or deterioration of blood vessels. The risks of retinopathy greatly increase, when the patients FBG is above 116mg/dl