NORMAL CELL STRUCTURE

Pathology is a branch of medical science primarily concerning the examination of organs, tissues, and bodily fluids in order to make a diagnosis of disease.

Clinical pathology is a medical specialty that is concerned with the diagnosis of disease based on the laboratory analysis of bodily fluids such as blood and urine, as well as tissues, using the tools of chemistry, clinical microbiology, hematology and molecular pathology.

Pathologists are physicians who specialize in the diagnosis and characterization of disease based on the examination of tissues removed from diseased body parts or biopsy samples. They can also diagnose certain diseases and conditions through the laboratory analysis of various bodily fluids such as the blood, semen, saliva, cervical fluid, pleural fluid, pericardial fluid and ascetic fluid.

Rudolf Virchow (1821–1902) is generally recognized to be the father of microscopic pathology.

What is the Disease? It is the "state in which an individual exhibits an anatomical, physiological, or biochemical deviation from the normal".

Pathology focuses on 3 aspects of disease.

ETIOLOGY: Cause of disease. Environmental agents: • Physical • Chemical • Nutritional Multifactorial: • Infections As Diabetes, • Immunological • Genetic Factors: Cancer • Age • Genes¬Psychological Hypertension

PATHOGENESIS: Mechanisms of development of disease. PathogenesisThe sequence events in the response of thecells or tissues to the etiologic agent, from theinitial stimulus to the ultimate expression of thedisease,"from the time it is initiated to its finalconclusion in recovery or death".

MORPHOLOGY: structural alterations induced in cell and tissues.

Origins of Pathology

The Greek physician Hippocrates, the founder of scientific medicine, was the first to deal with the anatomy and the pathology of human spine. A student of Virchow's, Julius Cohnheim (1839-1884) combined histology techniques with experimental manipulations to study inflammation, making him one of the earliest experimental pathologists. Cohnheim also pioneered the use of the frozen section procedure; a version of this technique is widely employed by modern pathologists to render diagnoses and provide other clinical information intraoperatively.

CELL

The **cell** is the basic structural, functional, and biological unit of all known living organisms. Cells are the smallest unit of life that can replicate independently, and are often called the "building blocks of life". The study of cells is called cell biology. Cells consist of cytoplasm enclosed within a membrane, which contains many biomolecules such as proteins and nucleic acids. Organisms can be classified as unicellular or multicellular. While the number of cells in plants and animals varies from species to species, humans contain more than 10 trillion (10^{13}) cells.Most plant and animal cells are visible only under the microscope, with dimensions between 1 and 100 micrometres. The cell was discovered by Robert Hooke in 1665, who named the biological unit for its resemblance to cells inhabited by Christian monks in a monastery.

CELL DEGENERATION

Defined as deterioration of live cells following injury, but with a possibility of the injured cells to reverse to normal when the injury is removed• Injury is defined as any harmful stimulus that induces disturbance in the homeostasis of cells.

CELL REGENERATION

Cell regeneration is the process of renewal, restoration, and growth that makes genomes, cells, organisms to natural fluctuations or events that cause disturbance or damage. Every species is capable of regeneration, from unicellular bacteria to multicellular humans.

INFLAMMATION

Inflammation is a localized physical condition in which part of the body becomes reddened, swollen, hot, and often painful, especially as a reaction to injury or infection. Inflammation is a protective response that involves immune cells, blood vessels, and molecular mediators. The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair. Inflammation is often characterized by redness, swelling, warmth, and sometimes pain and some immobility.
Inflammation can be classified as either ***acute*** **or** ***chronic***.
Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue.
Prolonged inflammation, known as ***chronic inflammation***, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.
Inflammation is divided into acute and chronic

- Acute is of short duration, primary cell is the neutrophil, characterized by exudation of fluid and plasma proteins.
- Chronic is longer, main cells are lymphocytes and macrophages, proliferation of blood vessels, fibrosis and necrosis.

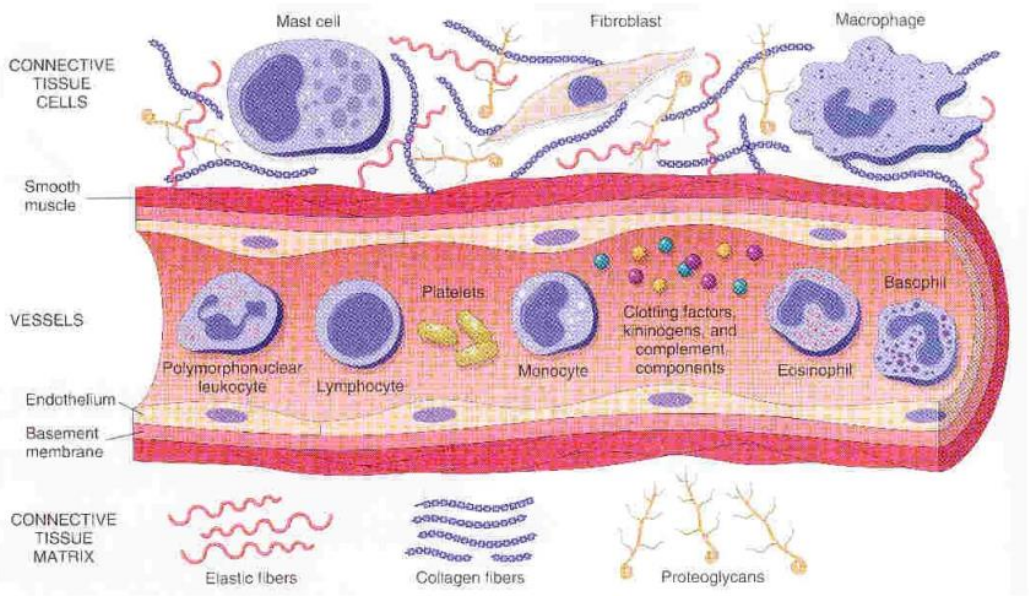
Vascular and cellular responses of both acute and chronic are mediated by chemical factors derived from cells and plasma and triggered by the inflammatory stimulus. Necrotic cells, themselves, release these chemical. These are called **chemical mediators of inflammation.** Inflammation stops when the injurious stimulus is removed.
Acute inflammation has three major components:

- Alteration in vessels leading to increased blood flow to the area.
- Structural changes in microvessels that allow plasma protein and WBCs to leave the circulation.
- Emigration of WBCs from vessels so they can accumulate at the site of injury.

Vasodilatation occurs resulting in **increased blood flow to the area**. New capillary beds open up.

This is followed by slowing of the circulation that is brought about by increased permeability. Fluid moves into the extravascular space, the blood becomes thicker and thus moves more slowly. At this point the blood is more viscous; there are higher concentrations of RBCs in the vessels. We call this stasis.
When stasis occurs the WBCs start to move toward the periphery of the vessel. This is call **margination** or **pavementing**.
The acute inflammation is increased vascular permeability leading to **edema**.
How does excess fluid get out of the vessels?

- Endothelial gaps. Gaps are do to endothelial contraction mediated by histamine, bradykinin, leukotrienes, substance P and others.
- Direct endothelial injury by burns, lytic bacterial infections.
- Delayed prolonged leakage beginning after a delay of 2 to 12 hours. Usually caused by thermal injury, radiation and certain bacterial toxins. An example is a late occurring sunburn.
- Leukocyte-mediated endothelial injury. Seem mostly in the kidneys and lungs and is related to a hypersensitivity reaction.
- Leakage from new blood vessels which have lots of receptors for chemical mediators.



Cellular Events

- Margination, cells have to adhere to vessels. There are adhesion receptors and chemical mediators that allow this to happen. There are genetic disorders where people can not make adequate adhesion factors; these people can not mount a normal inflammatory response.
- Transmigration
- Migration, leukocytes emigrate to the site of injury by a process called chemotaxis. Chemotactic factors can be both endogenous and exogenous. Bacterial products are the most common exogenous factors. Endogenous agents include components of compliment, leukotrienes and cytokines. Chemotactic factors stimulate locomotion.

Phagocytosis is the ability of the WBC to recognize the pathogen, form an attachment, engulf it and kill it. Various chemical mediators are important in this function. Bacterial killing is accomplished mostly by an oxygen-dependent mechanism. Killing can also occur by the release of granules from the lysosomes.

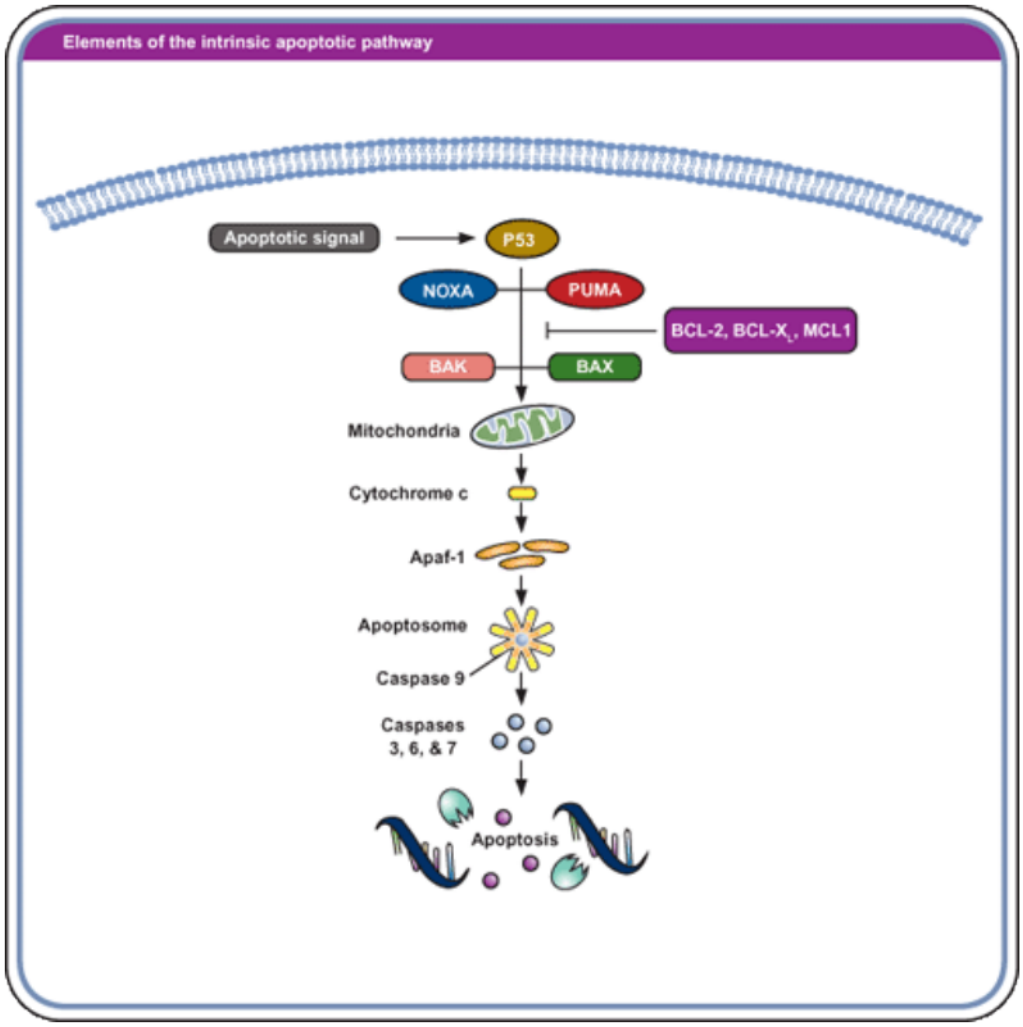
APOPTOSIS

Apoptosis definition: A form of cell death in which a programmed sequence of events leads to the elimination of cells without releasing harmful substances into the surrounding area. Apoptosis plays a crucial role in developing and maintaining the health of the body by eliminating old cells, unnecessary cells, and unhealthy cells. The human body replaces perhaps one million cells per second. When apoptosis does not work correctly, cells that should be eliminated may persist and become immortal.
German scientist Karl Vogt was first to describe the principle of apoptosis in 1842. In 1885, anatomist Walther Flemming delivered a more precise description of the process of programmed cell death. In Greek, apoptosis translates to the "falling off" of leaves from a tree.

Activation mechanisms
The initiation of apoptosis is tightly regulated by activation mechanisms, because once apoptosis has begun, it inevitably leads to the death of the cell. The two best-understood activation mechanisms are of are the intrinsic pathway (also called the mitochondrial pathway) and the extrinsic pathway. The *intrinsic pathway* is activated by intracellular signals generated when cells are stressed and depends on the release of proteins from the intermembrane space of mitochondria. The *extrinsic pathway* is activated by extracellular ligands binding to cell-surface death receptors, which leads to the formation of the death-inducing signaling complex (DISC).
A cell initiates intracellular apoptotic signaling in response to a stress, which may bring about cell suicide. The binding of nuclear receptors by glucocorticoids, heat, radiation, nutrient deprivation, viral infection, hypoxia and increased intracellular calcium concentration, for example, by damage to the membrane, can all trigger the release of intracellular apoptotic signals by a damaged cell. A number of cellular components, such as poly ADP ribose polymerase, may also help regulate apoptosis.
Before the actual process of cell death is precipitated by enzymes, apoptotic signals must cause regulatory proteins to initiate the apoptosis pathway. This step allows those signals to cause cell death, or the process to be stopped, should the cell no longer need to die. Several proteins are involved, but two main methods of regulation have been identified: the targeting of mitochondria functionality, or directly transducing the signal via adaptor proteins to the apoptotic mechanisms.
An extrinsic pathway for initiation identified in several toxin studies is an increase in calcium concentration within a cell caused by drug activity, which also can cause apoptosis via calcium binding protease calpain.
Intrinsic pathway
The mitochondria are essential to multicellular life. Without them, a cell ceases to respire aerobically and quickly dies. This fact forms the basis for some apoptotic pathways. Apoptotic proteins that target mitochondria affect them in different ways. They may cause mitochondrial swelling through the formation of membrane pores, or they may increase the permeability of the mitochondrial membrane and cause apoptotic effectors to leak out. they are very closely related

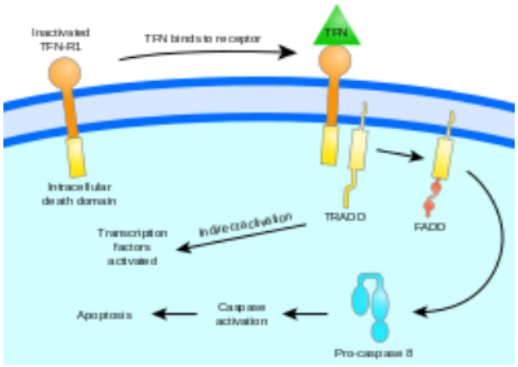
to intrinsic pathway, and tumors arise more frequently through intrinsic pathway than the extrinsic pathway because of sensitivity.There is also a growing body of evidence indicating that nitric oxide is able to induce apoptosis by helping to dissipate the membrane potential of mitochondria and therefore make it more permeable.Nitric oxide has been implicated in initiating and inhibiting apoptosis through its possible action as a signal molecule of subsequent pathways that activate apoptosis.

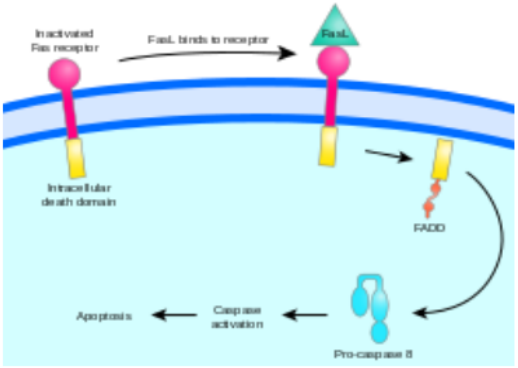
Mitochondrial proteins known as SMACs (second mitochondria-derived activator of caspases) are released into the cell's cytosol following the increase in permeability of the mitochondia membranes. SMAC binds to *proteins that inhibit apoptosis* (IAPs) thereby deactivating them, and preventing the IAPs from arresting the process and therefore allowing apoptosis to proceed. IAP also normally suppresses the activity of a group of cysteine proteases called caspases,which carry out the degradation of the cell, therefore the actual degradation enzymes can be seen to be indirectly regulated by mitochondrial permeability.



Cytochrome c is also released from mitochondria due to formation of a channel, the mitochondrial apoptosis-induced channel (MAC), in the outer mitochondrial membrane, and serves a regulatory function as it precedes morphological change associated with apoptosis.

Extrinsic pathway





Overview of TNF and Fas signaling in apoptosis

Two theories of the direct initiation of apoptotic mechanisms in mammals have been suggested: the *TNF-induced* (tumour necrosis factor) model and the *Fas-Fas ligand-mediated* model, both involving receptors of the *TNF receptor* (TNFR) family coupled to extrinsic signals.

TNF path

TNF-alpha is a cytokine produced mainly by activated macrophages, and is the major extrinsic mediator of apoptosis. Most cells in the human body have two receptors for TNF-alpha: TNFR1 and TNFR2. The binding of TNF-alpha to TNFR1 has been shown to initiate the pathway that leads to caspase activation via the intermediate membrane proteins TNF receptor-associated death domain (TRADD) and Fas-associated death domain protein (FADD). cIAP1/2 can inhibit TNF-α signaling by binding to TRAF2. FLIP inhibits the activation of caspase-8. Binding of this receptor can also indirectly lead to the activation of transcription factors involved in cell survival and inflammatory responses.[32] However, signalling through TNFR1 might also induce apoptosis in a caspase-independent manner.[33] The link between TNF-alpha and apoptosis shows why an abnormal production of TNF-alpha plays a fundamental role in several human diseases, especially in autoimmune diseases.

Fas path

The fas receptor First apoptosis signal (fas) – (also known as *Apo-1* or *CD95*) binds the Fas ligand (FasL), a transmembrane protein part of the TNF family.[30] The interaction between Fas and FasL results in the formation of the *death-inducing signaling complex* (DISC), which contains the FADD, caspase-8 and caspase-10. In some types of cells (type I), processed caspase-8 directly activates other members of the caspase family, and triggers the execution of apoptosis of the cell. In other types of cells (type II), the *Fas*-DISC starts a feedback loop that spirals into increasing release of proapoptotic factors from mitochondria and the amplified activation of caspase-8.[34]

Common components

Following *TNF-R1* and *Fas* activation in mammalian cells a balance between proapoptotic (BAX, BID, BAK, or BAD) and anti-apoptotic (*Bcl-Xl* and *Bcl-2*) members of the *Bcl-2* family is established. This balance is the proportion of proapoptotic homodimers that form in the outer-membrane of the mitochondrion. The proapoptotic homodimers are required to make the mitochondrial membrane permeable for the release of caspase activators such as cytochrome c and SMAC. Control of proapoptotic proteins under normal cell conditions of nonapoptotic cells

is incompletely understood, but in general, Bax or Bak are activated by the activation of BH3-only proteins, part of the Bcl-2 family.

Caspases Caspases play the central role in the transduction of ER apoptotic signals. Caspases are proteins that are highly conserved, cysteine-dependent aspartate-specific proteases. There are two types of caspases: initiator caspases, caspase 2,8,9,10,11,12, and effector caspases, caspase 3,6,7. The activation of initiator caspases requires binding to specific oligomeric activator protein. Effector caspases are then activated by these active initiator caspases through proteolytic cleavage. The active effector caspases then proteolytically degrade a host of intracellular proteins to carry out the cell death program.

Caspase-independent apoptotic pathway also exists a caspase-independent apoptotic pathway that is mediated by AIF (apoptosis-inducing factor)

Once cytochrome C is released it binds with Apoptotic protease activating factor – 1 (*Apaf-1*) and ATP, which then bind to *pro-caspase-9* to create a protein complex known as an apoptosome. The apoptosome cleaves the pro-caspase to its active form of caspase-9, which in turn activates the effector *caspase-3*.

MAC also called "Mitochondrial Outer Membrane Permeabilization Pore" is regulated by various proteins, such as those encoded by the mammalian Bcl-2 family of anti-apoptopic genes, the homologs of the *ced-9* gene found in *C. elegans*.[28][29] *Bcl-2* proteins are able to promote or inhibit apoptosis by direct action on MAC/MOMPP. Bax and/or Bak form the pore, while Bcl-2, Bcl-xL or Mcl-1 inhibits its formation.

ATROPHY

Atrophy is a decrease in size of a body part, cell, organ, or tissue. The term implies that the atrophied part was of a size normal for the individual, considering age and circumstance, prior to the diminution.

Atrophy also can be defined as gradual loss of muscle or flesh usually because of disease or lack of use of any organ or body parts.

Types of Atrophy & Their Symptoms

Atrophy is a catch-all term used to describe a number of different conditions. For instance, two rare forms of atrophy are:

- **Glandular atrophy** occurs when the glands of the body atrophy due to the extended use of steroids or other drugs, lack of proper nutrition, disease, or hormonal imbalances.
- **Vaginal atrophy** occurs in post-menopausal women when their vaginal walls thin. It's believed to occur because reproduction is no longer biologically necessary.

However, there are three more common types of atrophy - skeletal muscle, spinal muscle, and multiple system.

Skeletal Muscle Atrophy

First, there is **skeletal muscular atrophy**. This type results in the wasting of muscle or a loss of muscle tissue and can be categorized into two types.

1. Disuse atrophy: This type is caused by a lack of physical activity ('use it or lose it') and can usually be reversed with exercise and proper nutrition.
2. Neurogenic atrophy: This type is caused by an injury or disease that affects the nerves connected to a muscle. It usually appears more suddenly and is more serious than disuse atrophy. It can be caused by Lou Gehrig's disease, Guillain-Barre syndrome, neuropathy, polio, immobilization, spinal cord injuries, and arthritis, among other things.

Both types of skeletal muscular atrophy cause muscle weakness and a decrease in strength as well as reduced mobility or movement. Some types may occur naturally as a part of aging.
Treating skeletal muscular atrophy can be done with:

- **Exercise** to help rebuild the muscle
- **Physical therapy**, especially in patients with limited mobility
- **Ultrasound therapy**, which uses sound waves to treat the affected area
- **Surgery** to correct **contracture deformity**, a condition in which the muscles, skin, or connective tissues are too tight, preventing normal movement of the muscle

Spinal Muscle Atrophy

Another type of atrophy is **spinal muscular atrophy**. This affects the muscles in the center of the body first and can hinder moving, walking, and breathing; however, it does not affect cognitive functioning. Spinal muscle atrophy can be broken down into different types.