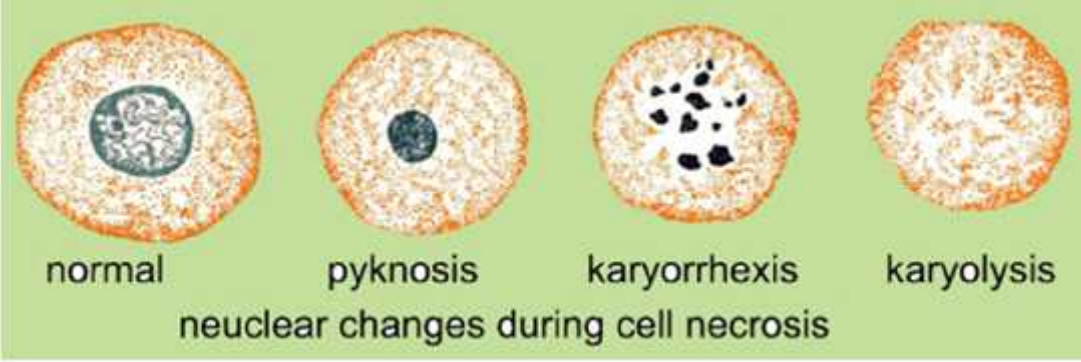
NECROSIS

Necrosis is defined as a localised area of death of tissue followed by degradation of tissue by hydrolytic enzymes liberated from dead cells; it is invariably accompanied by inflammatory reaction.Necrosis can be caused by various agents such as:

hypoxia, ischemia ,chemical and physical agents, microbial agents, immunological injury, etc.

Nuclear Changes in necrotic cell: These nuclear changes may include:

1) *pyknosis:* condensation of nuclear chromatin
2) *karyorrhexis* : fragmentation into many granular clumps
3) *karyolysis :* nucleus undergo dissolution



Types of Necrosis

Morphologically, there are five types of necrosis: coagulative,liquefaction (colliquative), caseous, fat, and fibrinoid necrosis.

1. Coagulative Necrosis. This is the most common type of necrosis caused by irreversible focal injury, mostly from sudden cessation of blood flow (ischaemia), and less often from bacterial and chemical agents. The organs commonly affected are the heart, kidney, and spleen.
Grossly, foci of coagulative necrosis in the early stage are pale, firm, and slightly swollen. With progression, they become more yellowish, softer, and shrunken.

Microscopically, the hallmark of coagulative necrosis is the conversion of normal cells into their 'tombstones' i.e. outlines of the cells are retained so that the cell type can still be recognised but their cytoplasmic and nuclear details are lost. The necrosed cells are swollen and appear more eosinophilic than the normal, along with nuclear changes described above. But cell

digestion and liquefaction fail to occur . Eventually,the necrosed focus is infiltrated by inflammatory cells and the dead cells are phagocytosed leaving granular debris and fragments of cell.

2. Liquefaction Necrosis. Liquefaction or colliquative necrosis occurs commonly due to ischaemic injury and bacterial or fungal infections. It occurs due to degradation of tissue by the action of powerfulhydrolytic enzymes. The common examples are infarct brain and abscess cavity.

Grossly, the affected area is soft with liquefied center containing necrotic debris. Later, a cyst wall is formed.

Microscopically, the cystic space contains necrotic cell debris and macrophages filled with phagocytosed material. The cyst wall is formed by proliferating capillaries, inflammatory cells, and gliosis (proliferating glial cells) in the case of brain and proliferating fibroblastsin the case of abscess cavity .

3. Caseous Necrosis. Caseous necrosis is found in the center of foci of tuberculous infections. It combines features of both coagulative and liquefactive necrosis.

Grossly, foci of caseous necrosis, as the name implies, resemble dry cheese and are soft, granular and yellowish.This appearance is partly attributed to the histotoxic effects of lipopolysaccharides present in the capsule of the tubercle bacilli, *Mycobacterium tuberculosis*.

Microscopically, the necrotic foci are structureless, eosinophilic, and contain granular debris The surrounding tissue shows characteristic granulomatous inflammatory reaction consisting of epithelioid cells with

interspersed giant cells of Langhans' or foreign body type and peripheral mantle of lymphocytes.

4. Fat Necrosis. Fat necrosis is a special form of cell death occurring at two anatomically different locations but morphologically similar lesions. These are: following *acute pancreatic necrosis,* and *traumatic fat necrosis* commonly in breasts. In the case of pancreas, there is liberation of pancreatic lipases from injured or inflamed tissue that results in necrosis of the pancreas as well as of the fat depots throughout the peritoneal cavity, and sometimes, even affecting the extra abdominal adipose tissue.Fat necrosis hydrolyses neutral fat present in adipose cells into glycerol and free fatty acids. The damaged adipose cells assume cloudy appearance. The leaked out free fatty acids complex with calcium to form calcium soaps (saponification) .

Grossly, fat necrosis appears as yellowish-white and firm deposits. Formation of calcium soaps imparts the necrosed foci firmer and chalky white appearance.

Microscopically, the necrosed fat cells have cloudy appearance and are surrounded by an inflammatory reaction. Formation of calcium soaps is identified in the tissue sections as amorphous, granular and basophilic Material

5. Fibrinoid Necrosis. Fibrinoid necrosis is characterised by deposition of fibrin-like material which has the staining properties of fibrin. It is encountered in various examples of immunologic tissue injury (e.g. in immune complex vasculitis, autoimmune diseases, Arthus reaction etc), arterioles in hypertension, peptic ulcer etc.

Microscopically, fibrinoid necrosis is identified by brightly eosinophilic, hyaline-like deposition in the vessel wall. Necrotic focus is surrounded by nuclear debris of neutrophils Local haemorrhage may occur due to rupture of the blood vessel.

APOPTOSIS

Apoptosis is a form of 'coordinated and internally programmed cell death' having significance in a variety of physiologic and pathologic conditions (*apoptosis* is a Greek

Pathologic Processes:

1. Cell death in tumours exposed to *chemotherapeutic agents*.

2. *Cell death by cytotoxic T cells* in immune mechanisms such as in graft-versus-host disease and rejection reactions.

3. Progressive *depletion of T cells* in the pathogenesis of AIDS.

4. *Cell death in viral infections*.

5. *Pathologic atrophy* of organs and tissues on withdrawal of stimuli e.g. prostatic atrophy after orchiectomy, atrophy of kidney or salivary gland on obstruction of ureter or ducts,respectively.

6.Cell death in response to *injurious agents* involved in causation of necrosis e.g. radiation, hypoxia and mild thermal injury.

7. In *degenerative diseases of CNS* e.g. in Alzheimer's disease.

Contrasting Features of Apoptosis and Necrosis.

Feature	Apoptosis	Necrosis
1. Definition	Programmed and coordinated cell death	Cell death along with degradation of tissue by hydrolytic enzymes
2. Causative agents	Physiologic and pathologic processes	Hypoxia, toxins
3. Morphology	1) No Inflammatory reaction 2) Death of single cells 3) Cell shrinkage 4) Cytoplasmic blebs on membrane 5) Apoptotic bodies 6) Chromatin condensation 7)Phagocytosis of apoptotic bodies by macrophages Lysosomes and other organelles intact	1 Inflammatory reaction always present 2) Death of many adjacent cells 3) Cell swelling initially 4) Membrane disruption 5) Damaged organelles 6) Nuclear disruption 7) Phagocytosis of cell debris by macrophages
4. Molecular changes	1)Lysosomes and other organelles intact 2) Genetic activation 3) Initiation of apoptosis by intra- and extracellular stimuli	1) Lysosomal breakdown with liberation of 2)hydrolytic enzymes 3) Cell death by ATP depletion, membrane damage, free radical injury

GANGRENE

Gangrene is a form of necrosis of tissue with superadded putrefaction. The type of necrosis is usually coagulative due to ischaemia (e.g. in gangrene of the bowel, gangrene of limb).On the other hand, gangrenous or necrotising inflammation is characterised by primarily inflammation provoked by Virulent bacteria resulting in massive tissue necrosis. Thus,the end-result of necrotising inflammation and gangrene is the same but the way the two are produced, is different. The examples of necrotising inflammation are:

Types of Gangrene:

1)Dry Gangrene:This form of gangrene begins in the distal part of a limb due to ischaemia. The typical example is the dry gangrene in the toes and feet of an old patient due to arteriosclerosis. trauma,ergot poisoning. It is usually initiated in one of the toes which is farthest from the blood supply, containing so little blood that even the invading bacteria find it hard to grow in the

necrosed tissue. The gangrene spreads slowly upwards until it reaches a point where the blood supply is adequate to keep the tissue viable. A line of separation is formed at this point

between the gangrenous part and the viable part.

Morphologic Features. Grossly, the affected part is dry, shrunken and dark black, resembling the foot of a mummy. It is black due to liberation of haemoglobin from haemolysed red blood cells which is acted upon by hydrogen disulfide (HS) produced by bacteria resulting in formation of black iron sulfide. The line of separation usually brings about complete separation with eventual falling off of the gangrenous tissue if it is not removed surgically

Histologically, there is necrosis with smudging of the tissue. The line of separation consists of inflammatory granulation tissue .

2)Wet Gangrene

Wet gangrene occurs in naturally moist tissues and organs such as the mouth, bowel, lung, cervix, vulva etc. Diabetic foot is another example of wet gangrene due to high sugar content in the necrosed tissue which favours growth of bacteria. Bed sores occurring in a bed-ridden patient due to pressure on sites like the sacrum, buttocks and heels are the other important clinical conditions included in wet gangrene.

Morphologic Features. Grossly, the affected part is soft, swollen, putrid, rotten and dark. The classic example is gangrene of bowel, commonly due to strangulated hernia, volvulus or intussusception. The part is stained dark due to the same mechanism as in dry gangrene

Histologically, there is coagulative necrosis with stuffing of affected part with blood. There is ulceration of the mucosa and intense inflammatory infiltration. Lumen of the bowel contains mucus and blood. The line of demarcation between gangrenous segment and viable

bowel is generally not clear-cut

3) Gas Gangrene. It is a special form of wet gangrene caused by gas-forming clostridia (gram-positive anaerobic bacteria) which gain entry into the tissues through open contaminated wounds, especially in the muscles, or as acomplication of operation on colon which normally contains clostridia. Clostridia produce various toxins which produce necrosis and oedema locally and are also absorbed producing profound systemic manifestations.

Morphologic Features. Grossly, the affected area is swollen, oedematous, painful and crepitant due to accumulation of gas bubbles within the tissues. Subsequently, the affected tissue becomes dark black and foul smelling.

Microscopically, the muscle fibres undergo coagulative necrosis with liquefaction. Large number of gram-positive bacilli can be identified. At the periphery, a zone of leucocytic infiltration, oedema and congestion are found. Capillary and venous thrombi are common.

PATHOLOGIC CALCIFICATION

Deposition of calcium salts in tissues other than osteoid or enamel is called pathologic or heterotopic calcification. Two distinct types of pathologic calcification are recognised:

Dystrophic calcification, which is characterised by deposition of calcium salts in dead or degenerated tissues with normal calcium metabolism and normal serum calcium levels.

Metastatic calcification, on the other hand, occurs in apparently normal tissues and is associated with deranged calcium metabolism and hypercalcaemia.

Etiology and pathogenesis of the two are different but

morphologically the deposits in both resemble normal

minerals of the bone.

Histologically, in routine H and E stained sections,calcium salts appear as deeply basophilic, irregular and granular clumps. The deposits may be intracellular,extracellular, or at both locations. Occasionally, heterotopic
bone formation (ossification) may occur. Calcium deposits can be confirmed by special stains like silver impregnation,method of *von-Kossa* producing black colour,and *alizarin red S* that produces red staining. Pathologic calcification is often accompanied by diffuse or granular deposits of iron giving positive Prussian blue reaction in Perl's stain.

Feature	Dry Gangrene	Wet Gangrene
1. Site	Commonly limbs	More common in bowel
2. Mechanisms		