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GENERAL PATHOLOGY

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INTRODUCTION

Pathology is the study of the causes of diseases, of how they develop and their effects on the body. It encompasses any deviation from a healthy or normal condition in any living creature.

AETIOLOGICAL AGENTS

Aetiological agents are factors capable of causing disease or tissue damage.

Internal factors

- Genetic – defects or mutations
- Immune system – defects or abnormal responses
- Aging – natural processes or premature aging

External factors

- Physical – trauma, pressure etc.
- Chemical – toxins, poisons, heavy metals etc.
- Infectious – parasites, bacteria, viruses, fungi etc.
- Environmental – nutrition (deficiencies or excesses)
  - – temperature
  - – hygiene
  - – radiation, e.g. ultraviolet light

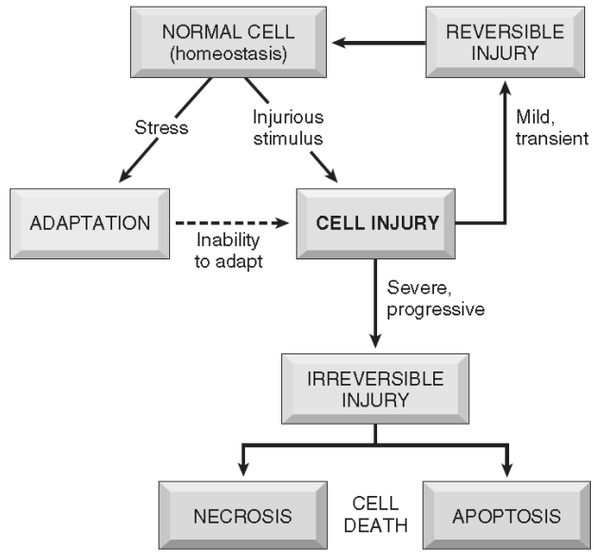
DISEASE CLASSIFICATIONS

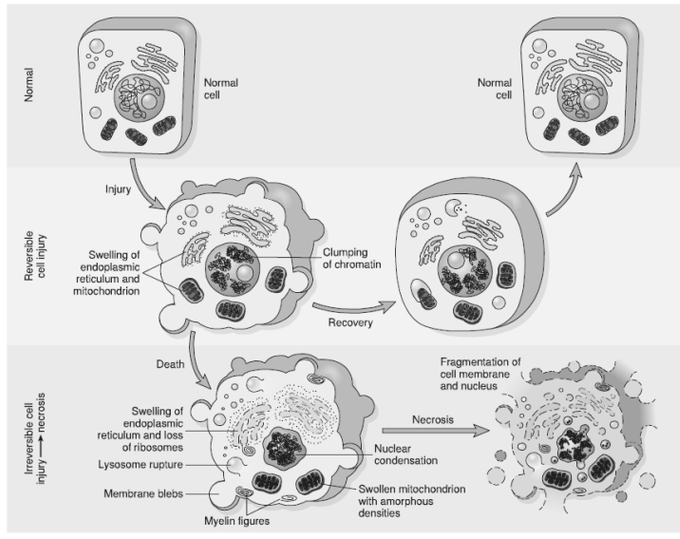
- **Acquired diseases-** diseases which develop at some stage during life, as a result of the effects of one or more aetiological agent acting during life.
- **Congenital diseases-** diseases present at birth or develop due to the effects of some aetiological factor on the developing embryo or foetus, on the mother before or during pregnancy, or on the uterus or placenta.
- **Hereditary diseases**- diseases or disorders that can be passed on from either or both parents to their offspring.
- **Idiopathic diseases**- diseases which we do not (yet) know the cause, though they may have recognisable development processes, lesions or clinical signs.

CELL INJURY

Reversible cell injury – cell injury causes alteration or loss of cell function and structural changes, but the cell can recover and regain structure.

Irreversible cell injury – cell injury causes alteration or loss of cell function and structural changes, but the cell cannot recover if the stimulus stops or is removed.





AGENTS

1. **Viruses** cause disease by disrupting cell function.
   - Some make repressor proteins that stop the synthesis of the host cell's proteins RNA and DNA.
   - They weaken cell membranes and lysosomal membranes leading to cell autolysis.

- Though some are harmless, many may mutate frequently evading the host's immune system.
- Some are associated with neoplasia.

2. **Bacteria**
   - **Invasiveness** – ability to invade tissues, which encompasses mechanisms for colonization (adherence and initial multiplication), ability to bypass or overcome host defense mechanisms and the production of extracellular substances which facilitate invasion.
   - **Toxigenesis** - ability to produce toxins.

3. **Fungi**
   - Damage to the host is by direct injury to tissues together with the host's associated inflammatory response.
   - Fungal toxin (mycotoxins) includes a diverse group of fungal peptides.
   - Aflatoxin is the best known example.

4. **Protozoa**
   - Damage to the host is by the metabolic waste products of the parasites.

5. **Black widow spider**
   - causes paralysis of the mammalian nervous system through its venom.
   - Releases neurotransmitters resulting in inflammation at the bitten area and ascending motor paralysis with destruction of peripheral nerve endings.

6. **Hymenopterous insect bites** from bees, wasps, hornets and yellow jackets.
   - **Bee venom** contains histamine, phospholipase A2, hyaluronidase and several toxic peptides which include mellitin (hemolyzing), apamin (neurotoxic) and mast cell-degranulating peptide.
   - Death is by systemic anaphylactic shock characterized by respiratory distress followed by vascular collapse.

7. **Snake venoms** are mixtures of up to 30 different peptides.
   - They contain phosphodiesterase, peptidases, hyaluronidase (spreading factor that cleaves internal glycoside bonds of acidic mucopolysaccharides to facilitate diffusion of toxin into tissues) and phospholipase A2 (direct lytic action on the membranes of the erythrocytes, platelets and other cells).

8. **All toads** contain skin glands that secrete repulsive chemicals.
   - More poisonous amphibians include the Colorado River toad (*Bufo alvarius*) the marine toad (*Bufo marinus*) and the poison dart frogs (*Dendrobates* spp.) of Central America secrete complex venoms all containing a toxin that mimics the action of cardiac glycosides, which poison the electrolyte pumps of heart muscle.
   - The *Bufo* species have parotid glands behind the eyes that secrete bufotoxin, a conjugation of bufagin (digitalis like toxin) and bufotenine (producing marked pressor action resembling that of oxytocin).

9. **Hyperthermia**
   - Leads directly to water loss causing an increase in blood pH, hemoglobin concentration and erythrocyte counts. In heatstroke, there may be degenerative changes in the myocardium, renal tubules and brain leading to permanent damage.

10. **Hypothermia**
    - Cellular injury due to intracellular water crystallization, temperature-induced protein changes and membrane damage.
    - Vascular impairment is through vasoconstriction which causes hypoperfusion and stasis while endothelial injury causes thrombosis and vascular integrity and thromboembolism.

11. **Radiation injury** (electromagnetic radiation – UV, x-rays and gamma rays and particle radiation)
    - Causes cell swelling characterized by endoplasmic reticulum vacuolation and mitochondrial swelling.
    - Chromosomal damage includes breakage, deletion and translocation.
    - Kills cells by free radical injury. Radiolysis of water in the cell leads to the formation of highly toxic hydroxyl radicals, superoxide anions and hydrogen peroxide, which will react with membrane phospholipids to cause lipid peroxidation.

12. **Protein energy malnutrition**
    - Delays healing by a variety of mechanisms by decreased production of antibodies, depressed complement system and depressed cell-mediated immunity.

13. **Free radicals** are volatile and tissue destructive molecules with atleast one unpaired electron.
    - They are toxic chemicals produced by the body during the process of metabolism, microbial killing and biochemical reaction.

- They are chemical terrorists inside the body that causes cell damage and leads to disease formation.
- They are similar to termites in woods, rust in metals and pest in plants.
- They are able to combine with unsaturated lipids in cell membrane, resulting in organic free radical (lipid radicals) formation. They rearrange and combine with oxygen to form lipid hydroxyperoxyl radical, which then undergoes further reaction to form another lipid radical and lipid peroxides.

14. **Lipid peroxidation** is a chain reaction causing the disruption of membranes and spatial integrity of enzyme systems. If reactive molecules can't be shuttled to next enzyme chain, more dangerous FR may be released.

DEGENERATION	NECROSIS
Sick cells; Deterioration; Progressive or retrogressive changes	Dead cells Final stage in irreversible degeneration; a point of no return
Patterns of degeneration **1. Intracellular and extracelullar accumulation** • Hydrophic degeneration • Fat overload (Fatty degeneration/ Fatty infiltration) • Carbohydrate overload (Glycogen degeneration) • Protein overload (Hyaline degeneration, Fibrinoid, Amyloidosis, Mucopolysaccharidosis) **2. Pigmentation** • Exogenous (carbon particles and dust particles) • Endogenous (melanin, hemoglobin breakdown products and fat breakdown products) **3. Mineralization** • Calcification (dystrophic and metastatic)	1. **Coagulative Necrosis** 2. **Liquefactive Necrosis** 3. **Caseous Necrosis** 4. **Fat Necrosis** 5. **Gangrene**

INTRACELLULAR AND EXTRACELLULAR ACCUMULATIONS

HYDROPHIC DEGENERATION (VACUOLAR OR BALLOONING DEGENERATION OR ACUTE CELLULAR SWELLING)

- Earliest indication of cell damage caused by failure of the ionic pump mechanism (energy dependent) and increase intracellular osmotic pressure.
- Characterized by cloudy swelling (ingress of water) and clear vacuoles (hydrophic or vacuolar degeneration) of variable size in the cytoplasm due to too much water and is associated with epithelial lesions in the skin, liver and kidney.
  - Occurs in many cell types, e.g. early stages of liver cell damage by toxins.

FATTY DEGENERATION/FATTY CHANGE / LIPIDOSIS/FAT PHANEROSIS/FATTY METAMORPHOSIS

- Accumulation of excessive intracellular lipid in vacuoles within non – adipocytes (kidney, heart and liver).
- Most commonly seen in the liver, renal tubular epithelium and cardiac myocytes, which metabolize lots of fat.
- Fat (lipid) accumulates in cells because of increased or long-term fat breakdown in the body and thus the cells encounter increased or long-term levels of fat in their immediate environment.

- This happens in malnutrition, when body fat is broken down and carried to the liver for metabolism, because there are inadequate dietary sources of energy. The liver cells therefore are presented with large amounts of fat in the blood entering the liver.
- Fatty change can also occur because the ability of cells to metabolise normal amounts of fat is decreased by cell damage (decreased cell metabolism because of toxic damage, or reduced oxygen supply due to heart dysfunction, respiratory disease or anaemia, or in diabetes mellitus).
- Fatty change can be idiopathic (i.e. of uncertain cause) in the livers of older cats.
- Exaggeration of triglyceride production.
- Diagnostic clue for liver injury (swollen, yellow greasy appearance)
  - Fatty liver occurs in diabetic dog and ketosis in cattle. The periacinar area (common area of fatty liver) becomes fatty in cases of mild anoxia or toxicity.

FATTY INFILTRATION/ FATTY IN GROWTH/ STROMAL INFILTRATION OF FAT/ LIPOMATOSIS/ STEATOSIS

- It is the deposition of lipid in the cytoplasm of adipose tissues found among the interstitial connective tissues through out the body.

GLYCOGEN DEGENERATION

- The presence of abnormally large amount of glycogen in the cell cytoplasm
- Glycogen, a branched polymer of glucose metabolism is the storage form of glucose and major deposition occurs in the liver, muscle and kidney.
  - Seen in the following conditions:
    - Hyperglycemia of any cause (diabetes mellitus)
    - Drug-induced (corticosteroids)
    - Enzymatic deficiencies associated with rare hereditary glycogen storage disease
    - Glycogen storing "clear cell" hepatocellular tumor

HYALINE OR PROTEIN DROPLETS

- Small, eosinophilic structures in the cytoplasm also called hyaline droplet degeneration.
- Present in renal tubular epithelium as a result of leakage of protein through the glomerulus into the urine and subsequent reabsorption by pinocytosis.

FIBRINOID

- Amorphous, bright, eosinophilic fibrils of various sizes found particularly in the damaged blood vessels derived from fibrin.
- Strongly associated with acute immunologically based-lesions like Arthus reaction and is involved in antigen-antibody complexes and complement or combination causing severe injury to the vessel wall and leakage of plasma protein into the lesion.

AMYLOID

- Amorphous eosinophilic material that accumulates particularly on basement membranes.
- Locally produced by reticuloendothelial cells, histiocytes and plasma cells.

Primary Amyloidosis

- Deposition of **amyloid protein AL** without identifiable predisposing cause. Results from the production of immunoglobulin-amyloid precursors by abnormal plasma cells (plasma cell dyscrasia).

Secondary Amyloidosis

- Deposition of amyloid protein AA
  - Occurs in chronic infectious diseases like tuberculosis and suppurative processes in which the immune system has been very active making immunoglobulins.
  - Associated with various neoplasms like lymphoma and multiple myeloma and in hyperimmunized animals used for antisera production. If associated with aging, it is a senile amyloidosis.

MUCOID DEGENERATION/ MYXOID OR MYXOMATOUS DEGENERATION, SEROUS ATROPHY OF FAT

- Accumulation of mucopolysaccharide (conjugate of protein and carbohydrate) in the extracellular spaces cause by blood borne toxins and lack of proper nutrition, cachexia and wasting disease.
  - Seen in endocardiosis (degenerative, senile condition of the heart valves) and in the adnexa of the skin in cases of hypothyroidism.

INCLUSION BODIES

- Indicator of viral infection, which may be intranuclear, intracytoplasmic, either basophilic or eosinophilic, single or multiple.

GOUT

- Disease brought by deposition of **uric acid and urate crystals** in tissues due to defects in purine metabolism (incomplete metabolism due to absence or inadequate amounts of uricase, a hepatic enzyme).
- Occurs in joint spaces, on other serous membranes such as the pleura or peritoneum or in renal tubules. It is most common in avian species with two forms namely: **articular and visceral** forms. Impaired renal excretion of uric acid causes gout in birds.
- Dalmation dogs lack a liver enzyme required to metabolise uric acid to a protein (allantoin) in the liver, and excrete uric acid in their urine. Hence, these dogs may develop urate or uric acid urinary calculi (uroliths).

PATHOLOGICAL PIGMENTATIONS

EXOGENOUS PIGMENTATION

PNEUMOCONIOSIS - occupational pathological pigmentation of the lungs of humans. The occupational hazards include silicosis, anthracosis, siderosis, berylliosis, calcicosis, and asbestosis.

ANTHRACOSIS - inhalation of carbon compounds producing black lungs in urban dogs.

SIDEROSIS- pigmentation and cellular reaction associated with the deposition of iron in the tissues

SILICOSIS- deposition of silica dust in the lungs

ENDOGENOUS PIGMENTATION

MELANOSIS

- The deposition of melanin, a brown/ black pigment in various tissues/ organs especially in lung, blood vessels and brain
- **Melanin** is the phenolic pigment and the principal pigment of the skin made by melanoblast and melanocytes from tyrosine.
- Albinism is the pathologic
- If found in the macrophages (melanophages), it is the result of the phagocytosis of pigments derived from injured melanocytes or epithelial cells. Melanophores are macrophages that pick up granules of melanin and are numerous in melanomas and melanosis.
- DOPA (dihydroxyphenylalanine) test is used to identify cells with the capability to make melanin.
- **Etiology**
  - Hyperadrenalism
  - Melanosarcoma
  - Melanoma

LIPID PIGMENTS result from oxidation and polymerisation of unsaturated lipids.

CEROID

- Brownish, granular product of partial breakdown of lipids picked up by macrophages.
- It is common in mammary tumors of dogs and seen in tissue damage or hemorrhage or both in which lipids become free in the tissues. Its development is related to choline deficiency and form from unsaturated lipids. It occurs principally within macrophages but also within hepatocytes.

LIPOFUSCIN (wear and tear pigment)

- Yellowish-brown granule in the cytoplasm of affected parenchymal cells like the hepatocytes, some glandular epithelial cells such as the sweat, mammary or ceruminous glands. Other cell types include the heart (brown atrophy of the heart in cattle during meat inspection), skeletal muscle, and adrenal gland, neurons in dogs, thyroid, parathyroid, kidney, ovary and testicle and smooth muscle in the intestine of Vitamin E deficient dogs known as “brown dog gout”.
- It is most commonly found in aged cells particularly the myocardial cells and neurons, hence the name aging pigment or cellular clinker.

HEMOGLOBIN PIGMENTS

HEMOSIDEROSIS

- Characterized by deposition of hemosiderin pigment in spleen and other organs.
- **Hematin** is an iron positive pigment chemically known as ferritin, the storage form of iron. It is a shiny golden yellow colour and occurs principally in the red pulp of the spleen and ovaria corpora hemorrhagica and chronically congested lungs. It indicates hemolytic anemia.
- In left-sided heart failure, RBC crosses the alveoli because of passive congestion and phagocytized by macrophages, commonly called “heart failure cells” and are often lying conspicuously free in the alveolar lumens.

HEMATIN

- The iron negative pigment following the action of acids to haemoglobin during tissue fixation.
- It is one of the most common tissue slide artifacts seen in sections.
- Known as the formalin pigment
- **Etiology/ Occurrence**
  - Extensive lysis of erythrocytes
  - Haemorrhage
  - Hemolytic anemia

BILE PIGMENTS

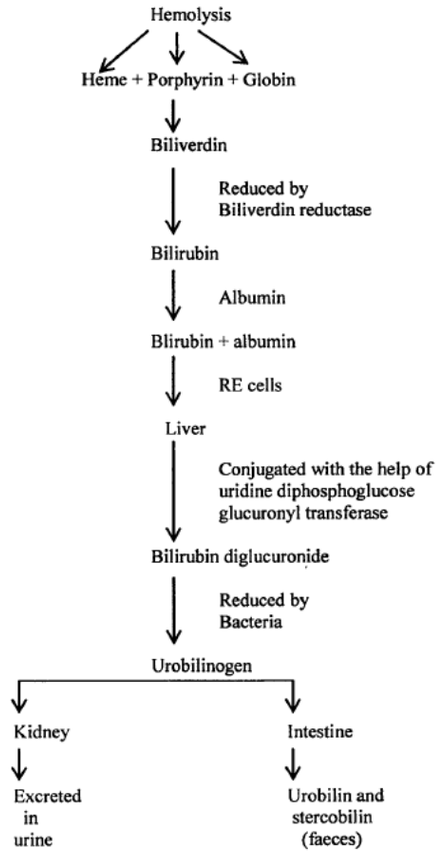
- Bile pigments are derived from the breakdown of erythrocytes such as bilirubin and biliverdin.
- The icterus is hyperbilirubinemia as a result of either excessive lysis of erythrocytes or due to damage in liver or obstruction in the bile duct.
- The haemolysis resulted into iron, globin and porphyin; the latter being converted into biliverdin.
- Biliverdin is reduced to produce bilirubin, an orange yellow pigment and bound to albumin and transported by RE cells to liver.
- In hepatic cells, it is separated from albumin and conjugated with glucuronic acid and excreted in bile as bilirubin diglucuronide.
- In intestine, it is further reduced by bacteria to urobilinogen, which is reabsorbed into circulation and carried to liver for reexcretion in bile while small amount enters in circulation and excreted through urine.
- The unabsorbed urobilinogen is oxidized in lower intestine to form urobilin and stercobilin, which gives normal pigment to faeces.

BILIRUBIN (HEMATOIDIN)

- The principal bile pigment and the normal breakdown product of the heme portion of haemoglobin

JAUNDICE

- Icterus is the generalized yellow discoloration of the tissues.
- It is firstly recognized in the sclera and is also seen in mucous membranes and skin due to rich elastin of these tissues.
- It is of three types: hemolytic, toxic and obstructive jaundice.



TYPES OF JAUNDICE:

1. HEMOLYTIC JAUNDICE

- Occurs as a result of excessive hemolysis in circulating blood.
- It is also known as prehepatic jaundice.
- Etiology
  - Piroplasmosis (*Babesia bigemina*)
  - Anaplasmosis (*Anaplasma marginale*)
  - Leptospirosis(*Leptospira ictehaemmorrhagae*)
  - Equine infectious anemia virus
  - Anthrax (*Bacillus anthracis*)
  - *Clostridium hemolyticum*
  - β- haemolytic streptococci

2. TOXIC JAUNDICE

- Occurs as a result of damage in liver leading to increased amount of unconjugated and conjugated bilirubin in blood.
- It is also known as hepatic jaundice.
- Etiology
  - Toxin/ Poisons
  - Copper poisoning
  - Leptospirosis

3. OBSTRUCTIVE JAUNDICE

- Occurs as a result of obstruction in bile duct causing hindrance in normal flow of bile.
- It is also known as post hepatic jundice.
- Etiology

- Blocking of bile canaliculi by swollen hepatocytes
- Obstruction in bile duct (Liver flukes, tapeworms and ascaris)
- Biliary cirrhosis, cholangitis and cholelithiasis
- Pressure on bile duct due to abscess, neoplasm.
- Inflammation and swelling at duct opening in duodenum.

VAN DEN BERGH REACTION- used by pathologists to determine the type of icterus present

Type of reaction	Type of jaundice	Type of pigment
1. Direct	Obstructive	Cholebilirubin
2. Indirect	Hemolytic	Hemobilirubin
3. Biphasic	Toxic/ Hepatocellular	Both pigments are present

PHOTOSENSITIZATION

Reaction brought about by the presence of photodynamic chemicals in the dermal tissues.

- **CONGENITAL**- metabolic defects in the steps of breakdown in porphyrins. Some accumulate and react with sunlight resulting in edema and inflammation on non-pigmented areas of the body exposed to sunlight. In cattle, it is recessively inherited while in cat and pigs, it is dominantly inherited.

- **HEPATOTOXIC**- arises from phylloerythrin, a metabolite of chlorophyll with photosensitising properties. Toxic damage to the liver impairs its normal degradation. Facial eczema of sheep is caused by ingestion of fungal toxin sporidesmin.

- **PRIMARY** - plants that contain compounds that are directly photosensitive by ingestion without hepatic injury, e.g. fagopyrism, which is a poisoning by buckwheat and hypericism by closely related species.

CALCIFICATION

The deposition of calcium phosphates and calcium carbonates in soft tissues other than bones and teeth. It may be classified as dystrophic and metastatic calcification.

DYSTROPHIC CALCIFICATION

- Characterized by the deposits of calcium salts in necrosed tissue of any organ.
- **Etiology**
  - White color muscle disease
  - Tuberculosis in cattle
  - Nodular worm infection in sheep
  - Degenerative nucleus pulposus in disc disease of dogs
  - Trichinosis
  - Histoplasmosis
  - Caseous lymphadenitis

METASTATIC CALCIFICATION

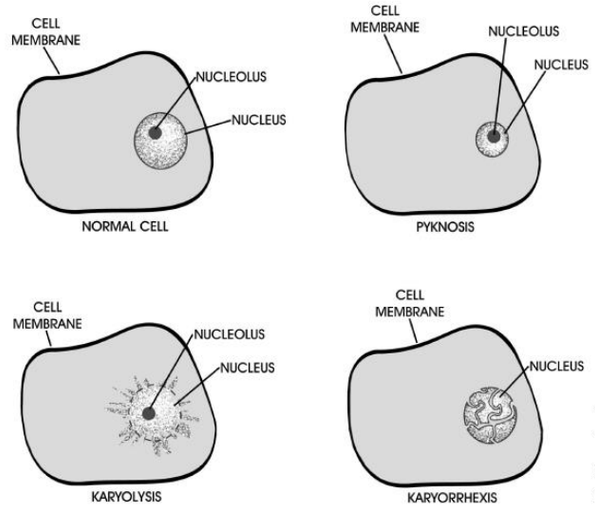
- Characterized by deposition of calcium salts in soft tissue as a result of hypercalcemia.
- **Etiology**
  - Hyperparathyroidism
  - Renal failure
  - Excess of vitamin-D
  - Increased calcium intake

NECROSIS

- Pathological local death of cells and tissues.
- Associated with loss of membrane integrity and leakage of cellular contents culminating in dissolution of cells, largely resulting from the degradative action of enzymes on lethally injured cells.

CELLULAR CHARACTERISTICS OF NECROSIS
Nuclear changes:

- **Pyknosis**- condensation or shrinking of nuclear chromatin.
- **Karyolysis**- dissolution of nuclear chromatin
- **Karyorrhexis**- shattering or breaking of the nucleus into numerous pieces and is the step in the development of caseous necrosis.



Cytoplasmic changes:

- **Increased eosinophilia** attributable in part to increased binding of eosin to denatured cytoplasmic proteins and in part to loss of the basophilia that is normally imparted by the ribonucleic acid (RNA) in the cytoplasm.
- **Cytoplasmolysis**- the cytoplasm becomes less and less dense until it disappears completely.

PATTERNS OF NECROSIS

1. COAGULATIVE (COAGULATION) NECROSIS

- The most common type of necrosis and it occurs in many of the 'solid' organs such as the kidney and heart.
- Affected organs retain their structure and are pale and firm as though they had been cooked.
- The dead cells often retain their outline when viewed under the microscope but are pale-staining and ghost-like.

Infarct is a special manifestation commonly caused by clots and emboli. It is initially red because of hyperemia but becomes progressively pale by 48 hours.

2. LIQUEFACTIVE NECROSIS

- Affected cells or tissues are liquefied dut to the actions of lysosomal enzymes derived from neutrophils and from autolytic digestion.
- The usual type of necrosis in the CNS, although the neuron cell bodies themselves initially show coagulation necrosis, followed by liquefaction.

Pus is a thick, opaque, creamy fluid matter composed of dead and dying neutrophils, tissue debris and microorganisms.

Malacia which is a special form, is a focus of softening in the brain and the spinal cord.

3. CASEOUS (CASEATION) NECROSIS

- A variation of coagulative necrosis
- All of the structural details of the tissue are lost with the production of a dry, white, cheesy, granular material.
- Compared to coagulation necrosis, this is an older (chronic) lesion often associated with poorly degradable lipids of bacterial origin.

4. FAT NECROSIS

- Necrosis of adipose tissues.
- Types
  - **a. Enzymatic necrosis of fat**
    - Also called pancreatic necrosis of fat
    - The destruction of fats in the abdominal cavity and usuall adjacent to the pancreas by the activated pancreatic lipases in pancreatic fluid that has escaped from the duct system of the pancreas.
  - **b. Traumatic necrosis of fat**
    - Seen when adipose tissue is crushed.
    - It occurs in fat adjacent to the pelvic canal of heifers after dystocia and in the subcutaneous and intramuscular fat over the sternum of recumbent cattle.
  - **c. Fat necrosis of abdominal fat**
    - Characterized by masses of necrotic fat in the mesentery, omentum and retroperitoneally.

5. GANGRENOUS NECROSIS

- Another term applied to the gross appearance of ischemic necrotic tissue of the limbs, digits, tips of the ears, skin, lungs, intestines, and mammary gland and bacterial invasion of an infarct.
- **Types**
  - **a. Dry gangrene**
    - Occurs at extremities like tail, tip of ears, tip of scrotum, hoof etc. due to necrosis and invasion of saprophytes.
    - The evaporation of moisture takes place resulting into dry lesions.
    - **Etiology**
      - Mycotoxins from fungus *Fusarium equiseti* found on paddy straw in low lying areas with moisture
  - **b. Moist gangrene**
    - Mostly occurs in internal organs of body like lungs, intestine, stomach etc.
    - It occurs due to necrosis and invasion of saprophytes leading to dissolution of the tissues.
    - **Etiology**
      - Drenching of milk, medicines etc. e.g. aspiration pneumonia/ drenching pneumonia
      - Volvulus/ intussusception or torsion in intestine
  - **c. Gas gangrene**
    - Occurs in muscles particularly of thigh muscles of hind legs in

heifers in case of black leg (Black quarter).

- **Etiology**
  - *Clostridium chauvoei* and other Gram positive, rod, anaerobes and toxins

ZENKER NECROSIS

- Necrosis of striated muscle
- Disappearance of striations and nuclei

FIBRINOID NECROSIS

- A special form of necrosis, visible by light microscopy, usually in immune reactions in which complexes of antigens and antibodies are deposited in the walls of arteries.
- The deposited immune complexes, together with fibrin that has leaked out of vessels, produce a bright pink and amorphous appearance on H&E preparations called fibrinoid.

SEQUELAE OF NECROSIS

- **Tissue regeneration**: Healing of the area by replacement of dead cells by cells of the same type
- **Scar formation**: Healing of the area by replacement of dead cells by fibrous (scar) tissue
- **Erosion or Ulceration**: Loss of cells from a surface in or on the body, usually accompanied by inflammation. There is exposure of underlying tissues which is then vulnerable to bleeding or infection and continuation of inflammation.
- **Sequestration:** The area of dead and dying cells becomes walled off (isolated) from the rest of the body by a dense rim of fibrous tissue, which means that the necrotic process, usually accompanied by inflammation, can continue inside (as an abscess).

APOPTOSIS

A pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.

Apoptosis is generally synonymously used with **"programmed cell death"** but it differs from programmed cell death as apoptosis cannot be prevented by cycloheximide or actinomycin D, rather these chemicals accelerate the process of apoptosis while programmed cell death is prevented by these chemicals.

Apoptosis in Physiologic Situations

- Death by apoptosis is a normal phenomenon that serves to eliminate cells that are no longer needed and to maintain a constant number of cells of various types in tissues.
  - The programmed destruction of cells during embryogenesis
  - Involution of hormone-dependent tissues upon hormone deprivation
  - Cell loss in proliferating cell populations, such as intestinal crypt epithelia, in order to maintain a constant number
  - Elimination of cells that have served their useful purpose
  - Elimination of potentially harmful self-reactive lymphocytes, either before or after they have completed their maturation, in order to prevent reactions against the body's own tissues
  - Cell death induced by cytotoxic T lymphocytes, a defense mechanism against viruses and tumors that serves to kill virus-infected and neoplastic cells

Apoptosis in Pathologic Conditions

- Apoptosis eliminates cells that are genetically altered or injured beyond repair and does so without eliciting a severe host reaction, thereby keeping the extent of tissue damage to a minimum.
  - Radiation, cytotoxic anticancer drugs, extremes of temperature, and even hypoxia which damage DNA, either directly or through production of free radicals
  - Accumulation of misfolded proteins
  - Cell injury in certain infections, particularly viral infections
  - Pathologic atrophy in parenchymal organs after duct obstruction, such as occurs in the pancreas, parotid gland, and kidney

MECHANISMS OF APOPTOSIS

Apoptosis is initiated by two major pathways:

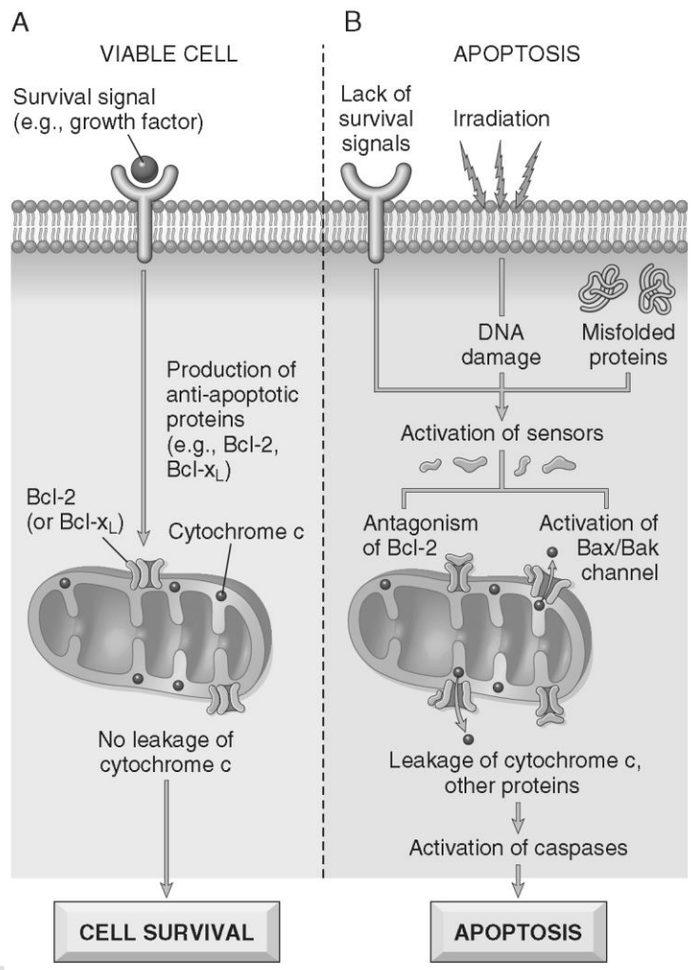
1. **Mitochondrial (intrinsic) pathway** is triggered by loss of survival signals, DNA damage and accumulation of misfolded proteins and is associated with leakage of pro-apoptotic proteins from mitochondrial membrane into the cytoplasm, where they trigger caspase activation. This is inhibited by anti-apoptotic members of the Bcl family,

which are induced by survival signals including growth factors.

2. **Death receptor (extrinsic) pathway** is responsible for elimination of self-reactive lymphocytes and damage by cytotoxic T lymphocytes and is is initiated by engagement of death receptors (members of the TNF receptor family) by ligands on adjacent cells.

CASPASES (cysteine-containing aspartate specific proteases) are family of protein-cleaving enzymes that bring much of the cellular changes in apoptosis.

- **Initiator caspases (caspases 8, 9 and 10)** respond to death signals and activate the second group, the executioner caspases.
- **Executioner caspases (caspases 3, 6 and 7)** make specific cuts in the key proteins that are required for cell survival.

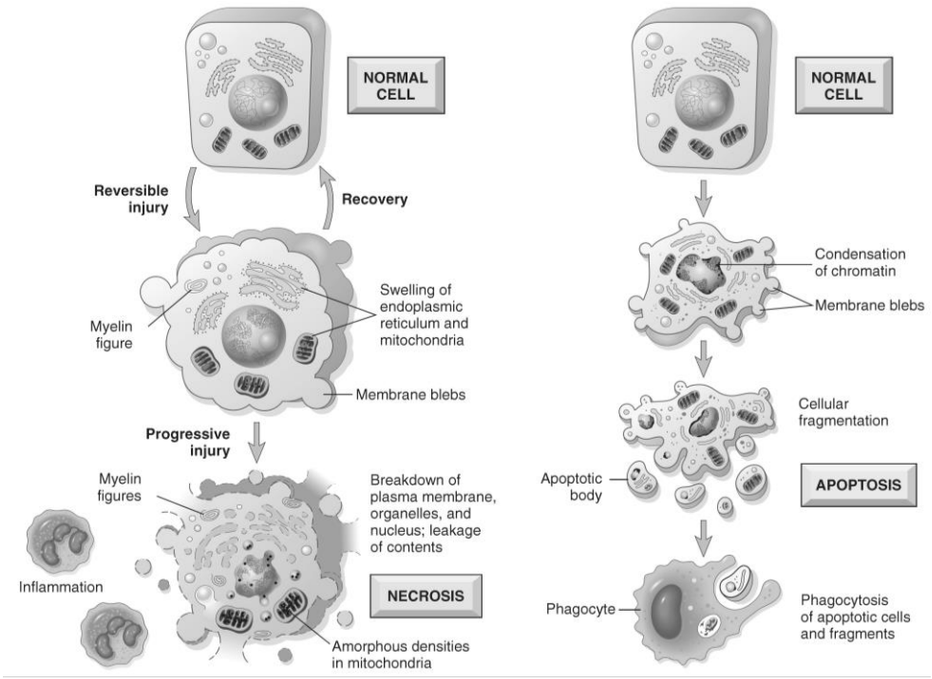


Alternative pathways in apoptosis and necrosis

Apoptosis	Necrosis
1. Shrinkage and pyknosis	1. Swelling
2. Budding and karyorrrhexis	2. Vacuolation, blebbing and increased permeability
3. Breakup into cluster of apoptotic bodies	3. Necrotic changes such as coagulation, shrinkage and karyolysis
4. No inflammation	4. Inflammation
5. Phagocytized by adjacent cells, both by macrophages, and tissue cells (epithelial or neoplastic cells)	5. Phagocytized by phagocytes

Comparative features of apoptosis and necrosis

FEATURE	APOPTOSIS	NECROSIS
Distribution	Usually single cells	Often contiguous cells
Cell size and shape	Shrinkage and convolution	Swelling
Nuclear morphology	Pyknosis Nuclear fragmentation	Lysis
Plasmalemma	Intact until phagocytized	Damaged and leaky
Cytoplasm	Retained in apoptotic bodies	Contents released
Inflammation	Absent	Typically present



Sequence of ultra-structural changes in injured cells

ORGANELLE AFFECTED	OBSERVABLE CHANGES	TIME FRAME
Mitochondria	Loss of mitochondrial matrix granules Contracted inner compartment Expanded outer compartment (swelling) Biochemical changes	**15 minutes**
Plasmalemma Mitochondria Endoplasmic reticulum	Loss of specialized structures (microvilli) Continuation of condensation Dilatation	**Between 15 & 30 minutes**
Polyribosomes Cytosol Mitochondria	Disaggregation and detachment from RER Pallid and swelling High amplitude swelling characterized by distension of inner mitochondrial compartment. Deposition of amorphous deposits	**Between 30 & 1 hour**
Mitochondria Endoplasmic reticulum Plasmalemma Nucleus	Continuation of swelling Increased number of flocculent densities in the matrix Breakage of outer mitochondrial membrane Continuation of swelling and fragmentation Breakage Pyknosis and early karyolysis	**2 to 4 hours**
Cytosol Nucleus	Organelle membrane fragment Appearance of myelin figures derived From membrane components Karyolysis	**4 hrs onward**
Lysosomes	Swelling and release of enzymes into the cytosol	**Later stages**

POST-MORTEM CHANGES

AUTOLYSIS

- Self-digestion process by tissue enzymes
- Characterized by the relative uniform destruction of the cell and its neighbors and the disintegration of cytoplasmic proteins into small granules, which are distributed throughout the cell.
- After death, a state of hypoxia occurs leading to decreased ATP. The cell organelles degenerate and the membrane of lysosomes dissolved which releases the lysosomal enzymes in the cell responsible for digestion of cells/ tissues. These enzymes cause disintegration of cell components into small granules in the cell.

PUTREFACTION

- Enzymatic decomposition of organic matter especially proteins by anaerobic glycolysis forming malodorous substances such as indole and skatole, nitrogenous bases such as cadaverine and putrescine and many other compounds.

PSEUDOMELANOSIS

- Greenish or bluish discolouration of tissues/ organs after death.
- Saprophytes causing putrefaction also produce hydrogen sulfide which chemically reacts with iron portion of hemoglobin to produce iron sulfide.
- Iron sulfide is a black pigment and produces green, gray or black shades on combination with other tissue pigments.

RIGOR MORTIS

- The contraction and shortening of muscles after death of animal leading to stiffening and immobilization of body.
- It occurs 2-4 hrs after death and remains until putrefaction sets in.
- Rigor mortis begins in cardiac muscles first and then in skeletal muscles of head and neck with a progression towards extremities.
- It is enhanced by high temperature and increased metabolic activity before death; while it is delayed by starvation, cold and cachexia.
- Rigor appears quickly in case animal is died due to strychnine poisoning as a result of depletion of energy source ATP.
- Muscle fibers shorten due to contraction and remain in contraction in the absence of oxygen, ATP and creatine phosphate.
- Rigor mortis remains until 20-30 hrs of death, the duration depends on autolysis and putrefaction.
- It disappears in same order as it appeared from head, neck to extremities.
- It can be used to determine the length of time after the death of animal.

ALGOR MORTIS

- Cooling of body.
- As there is no circulation of blood after death, which maintains the body temperature, body becomes cool after death.
- Depends on temperature of the body at death (e.g. fever, environmental temperature, insulation of the carcass [fat, wool, coverings], body mass, air movement and other factors and is difficult to interpret precisely for establishing time of death.

LIVOR MORTIS

- Gravitational settling of the blood to the down side of the animal and is most evident in the lungs and skin and in the cortex of the kidney.
- It is often not appreciated in animals because of pigmented skin or a thick hair coat and thus is most likely to be evident in white-skinned animals with little hair (e.g., white pigs).

POST-MORTEM CLOTTING

- Clotting of blood after death of animal mainly due to excessive release of thrombokinase from dying leucocytes and endothelial cells
- Must be distinguished from antermortem mural arterial thrombi and thromoemboli.
- Post-mortem clots are unattached to vessel walls and tend to be shiny ad wet and form a perfect cast of vessel lumens. Antermortem mural arterial thrombi are attached to arterial walls, tend to be dry and duller in color and are laminated with a tail extending downstream from the point of attachment.
- In anthrax, postmortem clot does not appear.
- Two types:
    1. **Red or current jelly clot** forms when the components of blood are evenly distributed throughout the clot. It occurs due to rapid clotting of blood.
    2. **Yellow or chicken fat clot** occurs when the components of blood are not distributed evenly. The ventral position is red and upper position in yellow due to WBC fibrin and serum. It occurs due to prolonged coagulation time of blood leading to sediment of red blood cells.

BLOATING

- A result of postmortem bacterial gas formation in the lumen of the GI tract.
- Herbivores tend to bloat more rapidly and severly than carnivores.

DISPLACEMENT OF ORGANS

- Due to rolling of dead animal
- Mainly intestine/ stomach and uterus are affected with displacement which can be differentiated from antemortem by absence of passive hyperemia.

BILE IMBIBITION

- Bile in the gall bladder starts to penetrate its wall and stain adjacent tissues yellowish, and later this may become greenish brown.
- Tissues involved include the adjacent liver and any intestine in contact with the gallbladder.

HEMOGLOBIN IMBIBITION

- Red staining of tissue, especially evident in the endocardium and tunica intima of arteries and veins.
- Once the integrity of the intima is lost, hemoglobin released by lysed erythrocytes penetrates the vessel wall and extends into the adjacent tissue.

ANOXIA

Oxygen deficiency may be partial (hypoxia) or total (anoxia).

Type	Definition/Mechanism	Example
1. Anoxic	Inadequate oxygen in the presence of adequate blood supply -Circulatory failure -Erythrocyte deficiency -Respiratory failure	Shock Anemia
2. Ischemic	Decreased arterial flow and pressure with stagnation and decrease in oxygen delivery -Arterial blockade	Pneumonia
3. Cytotoxic	Interference with utilization of oxygen by the cell -Mitochondrial lesion	Infarction Cyanide poisoning
4. Stagnant	Ischemia due to reduced flow of oxygenated blood	Hypovolemic shock

DISTURBANCES IN CIRCULATION

Hyperemia and congestion both refer to an increase in blood volume within a tissue but they have different underlying mechanisms.

HYPEREMIA	CONGESTION
Deals with arterial blood	Deals with venous blood
Active process	Passive process
Local	Local (strangulated piece of intestine)
Generalized leads to shock	Generalized and affects heart and the lungs

Classification of pathological hyperemia

Duration	Extent	Mechanism	Example
1. Acute (Abrupt onset)	Local (Limited)	Active (Increased arteriolar flow)	Chemically mediated inflammation
2. Acute	Local	Passive (Venous impedance)	Volvulus (twisting) or torsion of abdominal organ Obstructed veins
3. Chronic (Long time)	Local	Passive	Extravascular tumor Abscesses Hepatic cirrhosis
4. Chronic	General (Systemic)	Passive	Heart problems Primary pulmonary diseases

HEMORRHAGE

Escape of all the constituents of blood from blood vessels. It may occur through two processes:

- **HEMORRHAGE BY RHEXIS** – blood escape from a break or large defect in a blood vessel.
- **HEMORRHAGE BY DIAPEDESIS –** blood leaves through intact wall of blood vessel
  -red blood cells escape from capillaries during inflammation rendering the capillaries leaky

HEMORRHAGIC DIATHESIS is a disease that results in marked bleeding tendencies.

As per size, the haemorrhage is classified as under:

- **PETECHIAE**- minute (**1 to 2 mm in diameter**) hemorrhages into skin, mucous membranes, or serosal surfaces

- **PURPURA**- slightly larger (**3 to 5 mm**) hemorrhages.

- **ECCHYMOSES**- larger **(1 to 2 cm**) subcutaneous hematomas
  -Colloquially called **bruises**.
  -Extravasated red cells are phagocytosed and degraded by macrophages; the characteristic color changes of a bruise are due to the enzymatic conversion of hemoglobin (red-blue color) to bilirubin (blue-green color) and eventually hemosiderin (golden-brown).

- **PAINTBRUSH HEMORRHAGE-** lined or streaked appearance of hemorrhage. Ecchymotic and paintbrush hemorrhages are often found at necropsy on epicardial and endocardial surfaces of the heart and in the tracheal mucosa in cattle and horse in agonal event owing to labored breathing and terminal muscular activity in the process of dying which is often misinterpreted as septicemia.

- **HEMATOMA** is the accumulation of blood in spherical shaped mass.

According to location, the haemorrhage is classified as:

- **Hemothorax**: Blood in thoracic cavity.
- **Hemopericardium**: Blood in pericardial sac. When there is increased amount of blood in pericardial sac, it causes heart failure and is known as **cardiac temponade.**
- **Hemoperitoneum**: Blood in peritoneal cavity.
- **Hemoptysis**: Blood in sputum.
- **Hematuria**: Blood in urine.
- **Epistaxis**: Blood from nose.
- **Metrorrhagia**: Blood from uterus.
- **Melena**: Bleeding in faeces.
- **Hematemesis**: Blood in vomitus.

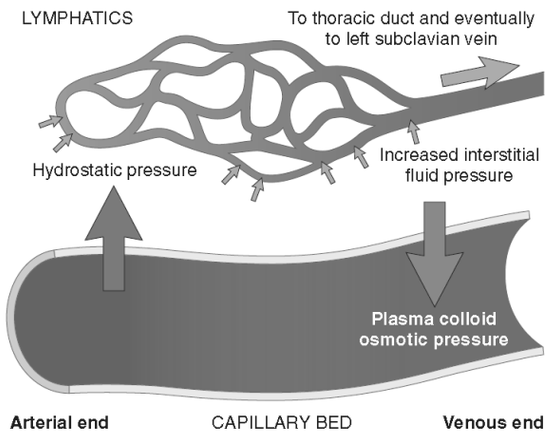
OEDEMA

Accumulation of excessive fluid in intercellular spaces and/ or in body cavity.

- Fluid movement between the vascular and interstitial spaces is governed mainly by two opposing forces—**the vascular hydrostatic pressure and the colloid osmotic pressure** produced by plasma proteins.

- Normally, the outflow of fluid produced by hydrostatic pressure at the arteriolar end of the microcirculation is neatly balanced by inflow due to the slightly elevated osmotic pressure at the venular end; hence there is only a small net outflow of fluid into the interstitial space, which is drained by lymphatic vessels.

- Capillary hydrostatic and osmotic forces are normally balanced so there is little net movement of fluid into the interstitium. However, **increased hydrostatic pressure or diminished plasma osmotic pressure** leads to extravascular fluid accumulation (edema). Tissue lymphatics drain much of the excess fluid back to the circulation by way of the thoracic duct; however, if the **capacity for lymphatic drainage is exceeded**, tissue edema results.



- The edema fluid that accumulates owing to increased hydrostatic pressure or reduced intravascular colloid typically is a protein-poor **transudate**; it has a specific gravity less than 1.012.

Type of oedema	Fluid characteristic	How does it develop?	Why does it develop?
Inflammatory	High protein Contains cells	Leaky capillaries	Damage to endothelial wall
Non-inflammatory	Low protein	↑plasma hydrostatic pressure	↑venous pressure due to heart disease ↓ venous outflow (blockage-neoplasia, fibrosis/scars and trauma)
		↓plasma osmotic pressure	loss of plasma protein (malnutrition, chronic diarrhea); renal disease ↓synthesis of plasma proteins (chronic liver disease); anemia
		↑tissue osmotic pressure	↑salt and water retention (kidney disease)
		↓lymph drainage	lymphatic obstruction (blockage-neoplasia, fibrosis/scars and trauma)

usually greater than 1.020.protein-rich **exudate** with a specific gravity usually greater than 1.020.

DISEASES:

- Gut edema is caused by *Escherichia coli*
- Malignant edema is caused by *Clostridium septicum*
- Bottle jaw in sheep or subcutaneous edema is caused by *Hemonchus* spp
- Stalking up seen in the limbs of horse

DISTRIBUTION OF EDEMA

Extravascular fluid collection in the body

- pleural cavity- **hydrothorax**
- pericardial cavity- **hydropericardium**
- peritoneal cavity- **hydroperitoneum or ascites**
- tunica vaginalis of the testicles- **hydrocele**

ANASARCA is severe, generalized edema marked by profound swelling of subcutaneous tissues and accumulation of fluid in body cavities

DEPENDENT EDEMA- fluid accumulation in the lowermost portion of the body (ventral abdomen and limbs)

PITTING EDEMA- Finger pressure over edematous subcutaneous tissue displaces the interstitial fluid, leaving a finger-shaped depression.

BRAIN EDEMA

Mechanisms:

- **Vasogenic** (increased vascular permeability)- most common type. The blood brain barrier is breached where blood moves into the intracellular space of the white matter and is due to vascular injury, hematomas, infarcts, inflammation and neoplasm.

- **Cytotoxic** (increased cell fluid and normal vascular integrity)- accumulation of fluid in the cells affecting both the gray and white matter in case of altered metabolism like in ischemia
- **Hydrostatic** (increased intracranial pressure)- accumulation of protein free fluid in extracellular space due to increased hydrostatic pressure accompanying hydrocephalus.

- **Osmotic** (abnormal osmotic pressure)- primary cause is hypotonicity of plasma (water intoxication) by excessive drinking and altered ADH secretion.

SHOCK

Characterized by systemic hypoperfusion of tissues; it can be caused by diminished cardiac output or by reduced effective circulating blood volume. The consequences are impaired tissue perfusion and cellular hypoxia.

- Although shock initially is reversible, prolonged shock eventually leads to irreversible tissue injury that often proves fatal.
- Shock is the final common pathway for several potentially lethal events, including exsanguination, extensive trauma or burns, myocardial infarction, pulmonary embolism, and sepsis.

HYPOVOLAEMIC SHOCK

- Shock due to decreased blood volume. Hypovolaemia means decreased blood volume.

- Causes include severe haemorrhage or dehydration.

Forms of shock which involve vasodilation are:

1. **CARDIOGENIC SHOCK**
   - Results from low cardiac output due to myocardial pump failure
   - May be caused by myocardial damage (infarction), ventricular arrhythmias, extrinsic compression (cardiac tamponade), or outflow obstruction (e.g., pulmonary embolism).
2. **SEPTIC OR TOXIC SHOCK**
   - Results from arterial vasodilation and venous blood pooling that stems from the systemic immune response to microbial infection.
   - Toxins involved in toxic shock include bacterial toxins, toxins released by damaged tissue (e.g. in cases of gangrene) and some venoms.
3. **NEUROGENIC SHOCK**
   - Occurs in animals severely frightened or traumatised, or in extreme pain.
   - Nerves stimulate peripheral vasodilation leading to loss of effective circulating blood volume
4. **ANAPHYLACTIC SHOCK**
   - An example of extreme hypersensitivity
   - A circulatory collapse accompanied by the binding of antigens to cell bound antibodies mediated by the massive intravascular release of histamine inducing increased arteriolar and venous dilatation.

ISCHAEMIA

Deficiency of arterial blood in any part of an organ.

- It is also known as local anemia.
- Its phases include:
  - **Anoxic phase**- shut down of blood flow
  - **Post-ischemic phase**- blood flow begins again. Much of the tissue injury in a survivor animal of ischemia is during the post-ischemic phase.
- **Etiology**
  - External pressure on artery
  - Narrowing/ obliteration of lumen of artery
  - Thrombi/emboli

INFARCTION

An area of ischemic necrosis caused by occlusion of the vascular supply to the affected tissue.

- Infarcts are classified on the basis of their color (reflecting the amount of hemorrhage).
  - ✓ **RED INFARCTS** occur (1) with venous occlusions (such as in ovarian torsion); (2) in loose tissues (e.g., lung) where blood can collect in infarcted zones; (3) in tissues with dual circulations such as lung and small intestine, where partial, inadequate perfusion by collateral arterial supplies is typical; (4) in previously congested tissues (as a consequence of sluggish venous outflow); and (5) when flow is reestablished after infarction has occurred (e.g., after angioplasty of an arterial obstruction).
  - ✓ **WHITE INFARCTS** occur (1) with arterial occlusions in solid organs with end-arterial circulations (e.g., heart, spleen, and kidney), and (2) where tissue density limits the seepage of blood from adjoining patent vascular beds.

SLUDGED BLOOD

Agglutination of erythrocytes in the vascular system of an animal.

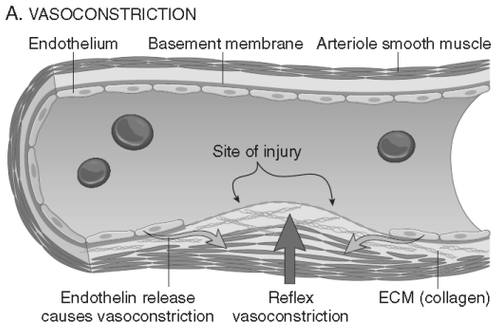
- **Etiology**
  - Fluctuation in blood flow
  - Slow rate of blood flow

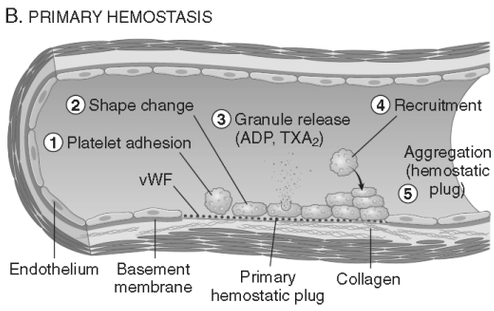
HEMOSTASIS

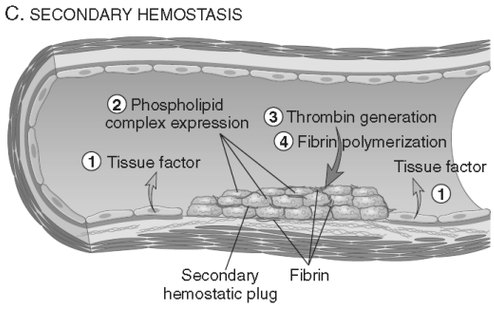
Comprises a series of regulated processes that maintain blood in a fluid, clot-free state in normal vessels while rapidly forming a localized hemostatic plug at the site of vascular injury.

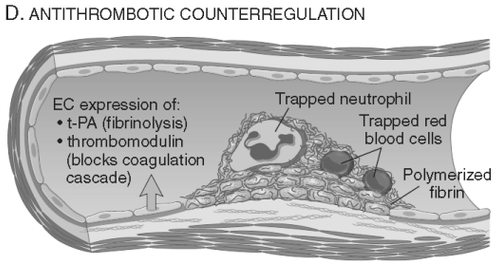
- Vascular injury causes transient arteriolar vasoconstriction through reflex neurogenic mechanisms, augmented by local secretion of **endothelin** (a potent endotheliumderived vasoconstrictor). This effect is fleeting, however, and bleeding would quickly resume if not for the activation of platelets and coagulation factors.
- Endothelial injury exposes highly thrombogenic subendothelial **extracellular matrix (ECM)**. Platelets bind via glycoprotein

1b (GpIb) receptors to von Willebrand factor (vWF) on ECM and are activated, undergoing a shape change and granule release. Released adenosine diphosphate (ADP) and thromboxane A2 (TxA2) induce additional platelet aggregation. This platelet aggregate fills the vascular defect. The formation of the initial platelet plug is called **primary hemostasis.**







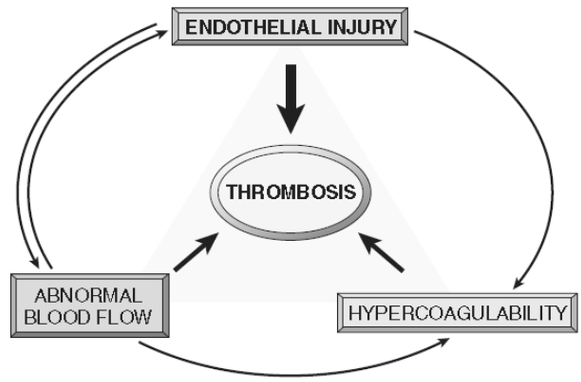


- Endothelial injury also exposes tissue factor (also known as factor III or **thromboplastin**), a membrane-bound procoagulant glycoprotein synthesized by endothelial cells. Exposed tissue factor, acting in conjunction with factor VII, is the major in vivo trigger of the coagulation cascade and its activation eventually culminates in the activation of **thrombin**, which has several roles in regulating coagulation.
- Activated thrombin promotes the formation of an insoluble fibrin clot by cleaving fibrinogen; thrombin also is a potent activator of additional platelets, which serve to reinforce the hemostatic plug. This sequence, termed **secondary hemostasis**, results in the formation of a stable clot capable of preventing further hemorrhage.
- As bleeding is controlled, Counterregulatory mechanisms, such as release of t-PA (tissue plasminogen activator, a fibrinolytic product) and thrombomodulin (interfering with the coagulation cascade), are set into motion to ensure that clot formation is limited to the site of injury.

THROMBOSIS

Formation of clot of blood in vascular system in the wall of blood vessel.

- The pathologic counterpart of hemostasis.
- The three primary abnormalities that lead to thrombus formation (called Virchow's triad):
  (1) endothelial injury,
  (2) stasis or turbulent blood flow, and
  (3) hypercoagulability of the blood.



THROMBI CLASSIFICATION

BASED ON LOCATION

- **Vascular thrombi**- within the cardiovascular system
- **Cardiac thrombi**- heart itself
- **Arterial thrombi**- are white due to fibrin, platelets and WBC in the arteries
- **Vein thrombi**- occur more quickly, more loosely arranged and often contain red blood cells. They are larger and result from predisposing factors such as shock and heart failure. Venous thrombosis causes necrosis in hind legs of downer cows
- **Lymphatic thrombi**

- **Capillary thrombi**

BASED ON LOCATION WITHIN THE HEART OR BLOOD VESSEL

- **Mural thrombi**- endocardial wall
- **Valvular thrombi**- valves of the heat
- **Occlusive thrombi**- totally occlude blood vessels.
- **Saddlle thrombi-** at the bifurcation of blood vessel

BASED ON CONTENT OF PATHOGENIC AGENT

- **Septic thrombi-** contain bacteria
- **Aseptic thrombi-** no pathogenic agent present
- **Parasitic thrombi-** contains parasites

BASED ON PREDOMINATING COLOR

- **Red thrombi-** composed of all blood cell components
- **Pale or white thrombi-** composed entirely of platelets
- **Laminated or mixed thrombi-** layered red and white thrombi

FATES OF THROMBUS

- **Propagation-** The thrombus enlarges through the accretion of additional platelets and fibrin, increasing the odds of vascular occlusion or embolization.
- **Embolization-** Part or all of the thrombus is dislodged and transported elsewhere in the vasculature.
- **Dissolution.** If a thrombus is newly formed, activation of fibrinolytic factors may lead to its rapid shrinkage and complete dissolution. With older thrombi, extensive fibrin polymerization renders the thrombus substantially more resistant to plasmin-induced proteolysis, and lysis is ineffectual.
- **Organization and recanalization.** Older thrombi become organized by the ingrowth of endothelial cells, smooth muscle cells, and fibroblasts into the fibrin-rich thrombus. In time, capillary channels are formed that—to a limited extent—create conduits along the length of the thrombus, thereby reestablishing the continuity of the original lumen.

DIC

DISSEMINATED INTRAVASCULAR COAGULATION

- The sudden or insidious onset of widespread thrombosis within the microcirculation.
- There is massive activation of the coagulation system resulting in the consumption of platelets and numerous coagulation factors (hence the synonym consumption coagulopathy).
- Causes include extensive tissue injury, neoplasia, systemic immunological reactions including anaphylaxis and acute septicemic infections (viral diseases).

EMBOLISM

The sudden blocking of an artery or vein by an obstruction that arrived in the bloodstream.

- An **embolus** is an intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin.
- The vast majority of emboli derive from a dislodged thrombus—hence the term **thromboembolism**.
- Left-sided valvular thrombosis produces systemic circulation emboli whereas righ-sided valvular thrombosis produces pulmonary embolism.
- **Etiology**
  - Thrombus, Fibrin
  - Bacteria
  - Neoplasm
  - Clumps of normal cells
  - Fat
  - Gas
  - Parasites

INFLAMMATION

A protective response involving host cells, blood vessels, and proteins and other mediators that is intended to eliminate the initial cause of cell injury, as well as the necrotic cells and tissues resulting from the original insult, and to initiate the process of repair.

- Characterized by 5 cardinal signs:
  - **Redness** – rubor
  - **Heat** – calor
  - **Pain** – dolor
  - **Swelling** – tumor
  - **Loss of function** – functio laesa

NOMENCLATURE OF INFLAMMATION

System	Structure	Term
Integumentary system	Skin	Dermatitis
	Epidermis	Epidermitis
	Subcutaneous Adipose Tissue	Panniculitis
	Sweat gland	Hidradenitis
	Sebaceous gland	Sebaceous adenitis
	Fascia	Fascitis
	Hair Follicle	Folliculitis
	Skin Around the Nail	Paronychia
Skeletal and Joint System	Bone	Osteitis
	Bone marrow	Osteomyelitis
	Endosteum	Endostitis
	Periosteum	Periostitis
	Cartilage	Chondritis
	Cartilage and Bone	Osteochondritis
	Joints	Arthritis
	Synovial bursa	Bursitis
	Tendon	Tenosynovitis
	Fibrous connective tissue	Fibrositis
Muscular system	Muscle	Myositis
Nervous system	Brain	Encephalitis
	Gray matter	Polioencephalitis
	White matter	Leukoencephalitis
	Meninges	Meningitis
	Dura mater	
	Subarachnoid	Arachnoiditis
	Subarachnoid plus Pia mater	Leptomeningitis
	Spinal cord	Myelitis
	Nerves	Neuritis
	Many nerves	Polyneuritis
	Spinal nerve root	Radiculitis
Special senses	Eye	Opthalmitis
	Inner Eye	Panopthalmitis
	Ocular Cavities	Endopthalmitis
	Cornea	Keratitis
	Cornea and Conjunctiva	Keratoconjunctivitis
	Conjunctiva	Conjunctivitis
	Uveal Tract	Uveitis
	(Iris, Ciliary Body, and Choroid)	
	Retina	Retinitis
	Eyelids	Blepharitis
	Ear Cartilage	Auricular Chondritis
	External Ear Canal	Otitis Externa
	Middle Ear Structure	Otitis Media
	Inner Ear Structure	Otitis Interna or Labyrinthitis
	Ear drum	tympanitis
Circulatory system	Endocardium	Endocarditis
	Myocardium	Myocarditis

	Pericardium	Pericarditis
	Artery	Arteritis
	Vein	Phlebitis
	Aorta	Aortitis
	Blood vessel	Vasculitis
Respiratory system	Nasal Cavity	Rhinitis
	Sinuses	Sinusitis
	Larynx	Laryngitis
	Trachea	Tracheatis
	Larynx and Trachea	Laryngotracheitis
	Bronchi	Bronchitis
	Lungs	Pneumonitis/ Pneumonia
	Alveoli(walls)	Alveolitis
	Pleura	Pleuritis or Pleurisy
	Diaphragm	Diaphragmitis
Digestive system	Mouth	Stomatitis
	Gums	Gingivitis
	Periodontal tooth	Periodontitis
	Vascular tissue of tooth	Pulpitis
	Tonsil	Tonsilitis
	Tongue	Glossitis
	Salivary gland	Sialoadenitis
	Pharynx	Pharyngitis
	Esophagus	Oesophagitis
	Rumen	Rumenitis
	Reticulum	Reticulitis
	Omasum	Omasitis
	Abomasum	Abomasitis
	Stomach	Gastritis
	Intestine	Enteritis
	Ileum	Ileitis
	Cecum	Typhilitis
	Colon	Colitis
	Liver	Hepatitis
	Bile Duct	Cholangitis
	Gall Bladder	Cholecystitis
	Biliary System	Cholangiohepatitis
	Pancreas	Pancreatitis
	Peritoneum	Peritonitis
Urinary System	Kidney	Nephritis
	Glomerulus and Tubular Involvement	Glomerulonephritis
	Glomeruli	Glomerulitis
	Renal pelvis	Pyelitis
	Renal pelvis and Kidney	Pyelonephritis
	Ureter	Ureteritis
	Urinary Bladder	Cystitis
	Urethra	Urethritis
Reproductive system	Ovary	Oophoritis or Ovaritis
	Fallopian Tube	Salphingitis
	Endometrium	Endometritis
	All layers of Uterine Wall	Metritis
	Cervix	Cervicitis
	Vulva	Vulvitis
	Vagina	Vaginitis or Colpitis

	Mammary Gland	Mastitis
	Testes	Orchitis
	Prostate Gland	Prostatitis
	Epididymis	Epididymitis
	Glans Penis	Balanitis
	Prepuce	Posthitis
	Penis and Prepuce	Balano-posthitis
	Spermatic cord	Funiculitis
Endocrine system	Pituitary gland	Hypophysitis
	Thyroid gland	Thyroiditis
	Parathyroid gland	Parathroiditis
	Adrenal gland	Adrenalitis
Hemolymph system	Thymus	Thymitis
	Spleen	Splenitis
	Lymph node	Lymphadenitis

ACUTE AND CHRONIC INFLAMMATION

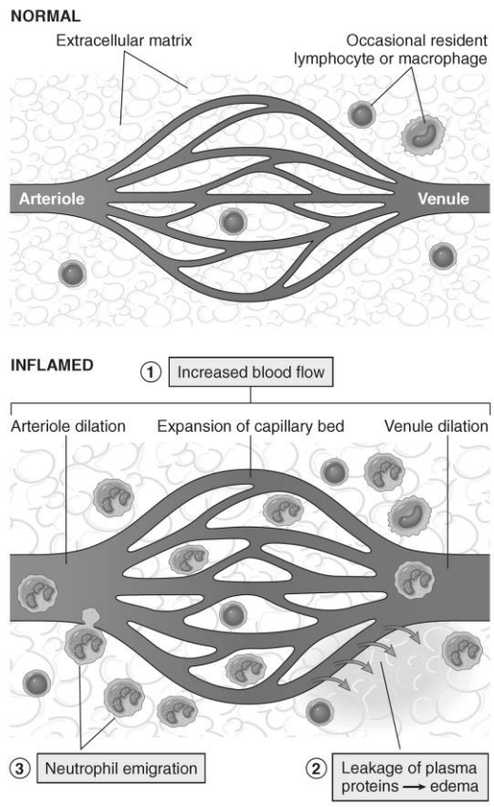
Acute inflammation	Chronic inflammation
Exudative inflammation	Proliferative or granulomatous inflammation
Begins with 4-6 hours	Slower onset and more protracted course. It follows acute inflammation but can occur without acute inflammation
There is exudation of fluid and plasma proteins	There is less vascular dilation and exudation
Neutrophils predominate	Macrophages, lymphocytes, plasma cells, eosinophils, fibroblast and neutrophils (chronic active)

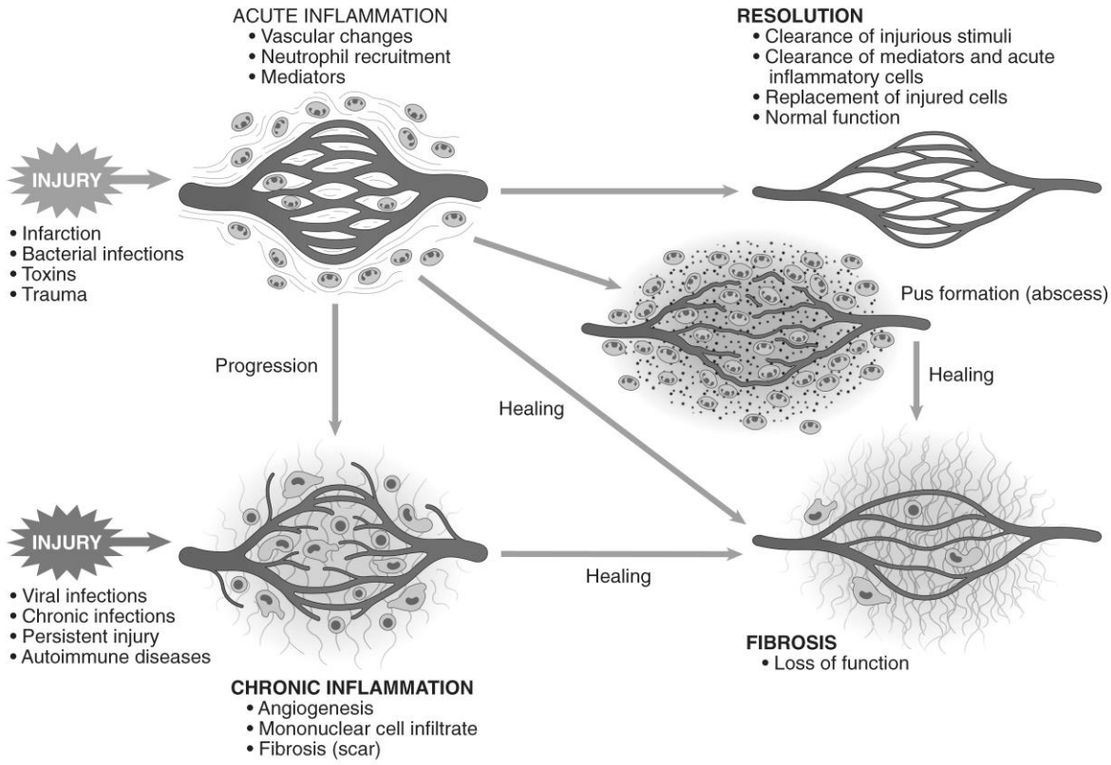
ACUTE INFLAMMATION

- Has two major components
  - **Vascular changes:** alterations in vessel caliber resulting in increased blood flow (vasodilation) and changes in the vessel wall that permit plasma proteins to leave the circulation (increased vascular permeability). In addition, endothelial cells are activated, resulting in increased adhesion of leukocytes and migration of the leukocytes through the vessel wall.
  - **Cellular events:** emigration of the leukocytes from the circulation and accumulation in the focus of injury (cellular recruitment), followed by activation of the leukocytes, enabling them to eliminate the offending agent.

CHRONIC INFLAMMATION

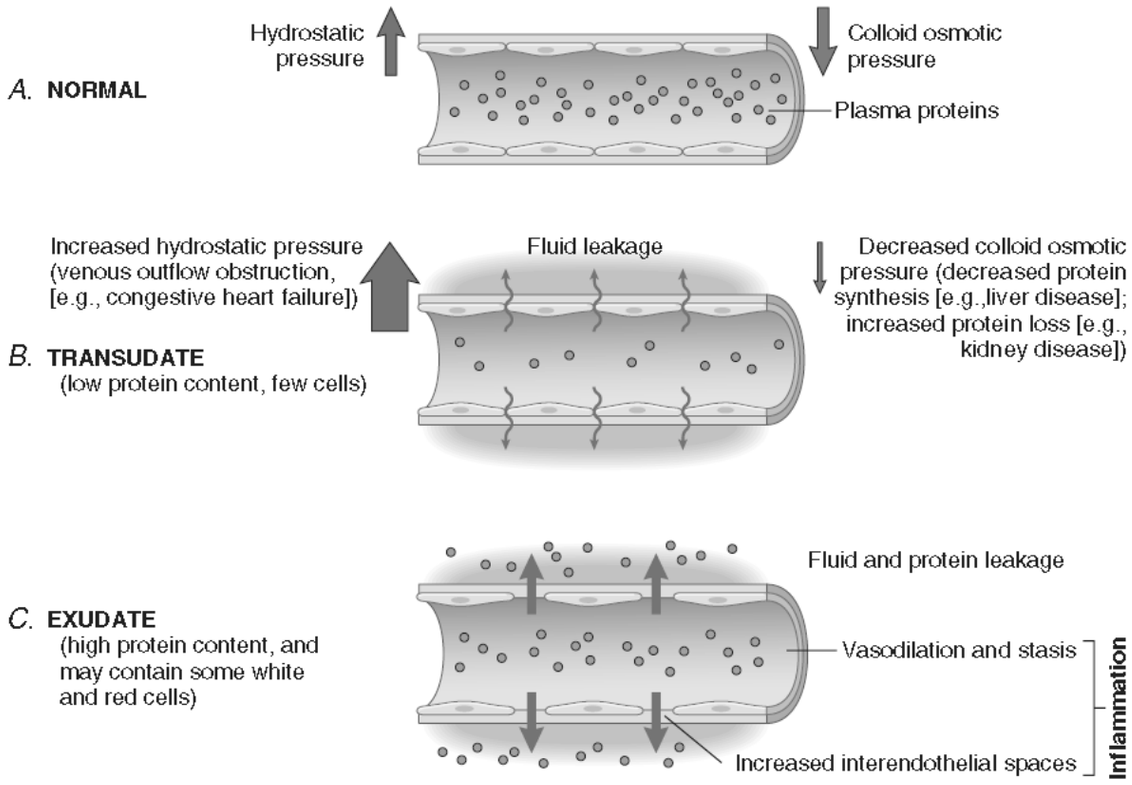
- Characterized by:
  - Infiltration with mononuclear cells, including macrophages, lymphocytes, and plasma cells
  - Tissue destruction, largely induced by the products of the inflammatory cells
  - Repair, involving new vessel proliferation (angiogenesis) and fibrosis





INFLAMMATORY EXUDATE

Exudate	Transudate	Modified transudate
High protein	Low protein	Mild increase
(between 3 and 7 g/l)	(less than 3 g/l)	(3-5 g /l)
High cell count	Low cell count	Mild increase in cell count
(as high as 100,000/ul)	(less than 500 nucleated cells/ul)	(less than 5,000 /ul)
Seen in inflammation	Non inflammation	Seen in mild inflammation



CELLS IN THE INFLAMMATORY EXUDATE

INFLAMMATORY CELL	COMPOSITION	DESCRIPTION/FUNCTION
Neutrophils	60-70% in carnivores (**most numerous** cells in circulating blood in these species); 50% in horse and 20-30% in ruminants	• Heterochromatic and multilobulated • Aggresively phagocytic • First to migrate abundantly to the tissues • Synonymous with **polymorphonuclear cells**, **heterophils** (avians) and **microphage** (tissue and pus cells)
Eosinophils	1-5%	• Bilobed nuclei • Phagocytic but are less so than neutrophils • Present in allergic reactions and parasitic infections • Known as the **mystery cells**
Basophils	1% (least numerous leukocytes)	• Bilobed or horse –shaped nuclei • Have the **least lobulation** among the granulated nuclei • Present in hypersensitivity reactions
Lymphocytes	**Most abundant** agranulocyte; chronic phase	• Spherical or ovoid heterochromatic nucleus • For humoral and cell-mediated immunity
Plasma cells	Subacute or chronic phase	• Eccentric nucleus resembling a wagon wheel or clock face • Derived from B-lymphocytes in the presence of antigen and produce antibodies
Monocytes/macrophages	Chronic phase	• Kidney shaped to trilobed nucleus • **Largest** cell
Platelets	Present in inflammation	• Non-nucleated but nucleated in avians

MACROPHAGE SYSTEM/RETICULOENDOTHELIAL SYSTEM (RES)

- **Monocytes** – blood
- **Histiocytes and macrophages** – connective tissues
- **Reticular cells** – lymphatic and myeloid tissues
- **Endothelium like littoral cells** – linings of lymphatic sinuses and sinusoids of bone marrow
- **Alveolar macrophages (dust cells)** – air spaces of the lungs
- **Pulmonary intravascular macrophages (PIMs)** – capillaries of the lungs of ruminants, cats and pigs
- **Kupffer cells** – sinusoids of the liver
- **Microglia** – CNS
- **Gitter cells** – large active cells with phagocytized debris and many of these are newly emigrated from the blood and microglia
- **Osteoclasts** – bone

Epithelioid cells

- Activated macrophages mostly present in granuloma
- Hallmark of granulomatous inflammation
- They are elongated with marginal nucleus looking like a columnar epithelial cells, hence the name

Giant cells

- Multinucleated macrophages fused together to kill the microorganisms.
- They are formed by the fusion of many macrophages to phagocytose larger particles such as yeast fungi and mycobacteria.
- **Types:**
  - **Foreign body giant cells**- They are having many nuclei up to 100 which are uniform in size and shape. Seen in chronic infectious granulomas of tuberculosis.
  - **Langhans giant cells**-They are horse shoe shaped giant cells having many nuclei and are of characteristically

present in tubercle. The nuclei are mostly arranged at periphery giving horse shoe shape.

- **Touton giant cells**- Multinucleated cells having vacuolation in the cytoplasm due to increased lipid content. They mostly occurs in xanthoma.
- **Tumor giant cells**- These are larger, pleomorphic and hyperchromatic cells having numerous nuclei with different size and shape. They are not true giant cells and not formed from macrophages but are found in cancers as a result of fast division of nuclei in comparison to cytoplasm.

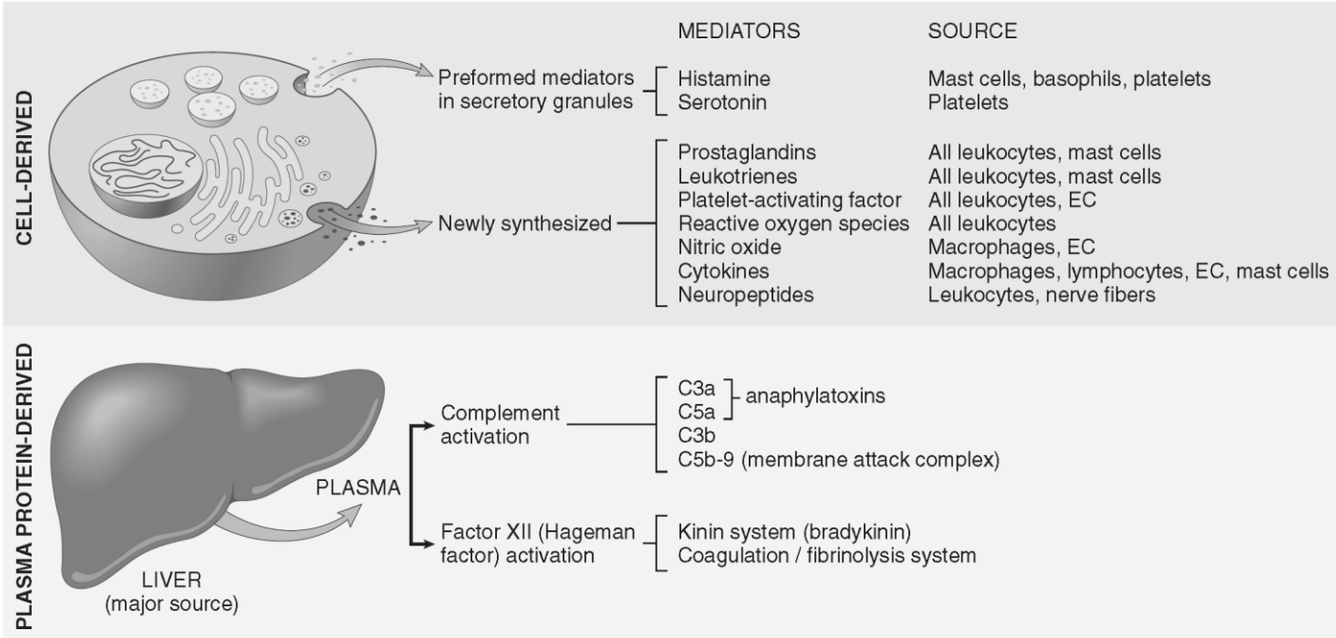
TYPES OF INFLAMMATORY EXUDATES

Type of exudate	Principal component	Location
Serous	Main component is fluid (serum/plasma) rather than cells	Present on serous surfaces and also within body organs
Fibrinous	Rich in fibrinogen which will clot to form yellowish gel	Observed on mucosal and serosal surfaces of the intestine, pleura, peritoneum and synovial membrane
Hemorrhage or sanguineous	Erythrocytes	
Catarrhal or mucupurulent	Mucus/Mucin accompanied by neutrophils, tissue debris, fibrin and rbcs	Mucous membranes of the alimentary, respiratory and reproductive tracts
Purulent or suppurative	Neutrophils (pus)	Body cavity (empyema)

CHEMICAL MEDIATORS AND REGULATORS OF INFLAMMATION

AUTACOIDS – chemical messengers acting on the vascular endothelia and leukocytes contributing to an inflammatory reaction.

- Mediators may be produced locally by cells at the site of inflammation, or may be derived from circulating inactive precursors (typically synthesized by the liver) that are activated at the site of inflammation
- Cell-derived mediators are normally sequestered in intracellular granules and are rapidly secreted upon cellular activation (e.g., histamine in mast cells) or are synthesized de novo in response to a stimulus (e.g., prostaglandins and cytokines produced by leukocytes and other cells).
- Plasma protein–derived mediators (complement proteins, kinins) circulate in an inactive form and typically undergo proteolytic cleavage to acquire their biologic activities.



MEDIATORS OF CELL ATTRACTION AND FUNCTION

- Cytokines
- Anaphylatoxins
- Leukotrienes
- Complement factor (C3b)
- Miscellaneous (lysosomal enzymes)

SUMMARY OF THE ACTIONS OF MEDIATORS IN ACUTE INFLAMMATION

1. Vascular dilatation
    a. Histamine
    b. Prostaglandin
    c. Kinins
2. Increased permeability
    a. Histamine
    b. Anaphylatoxins (C3a and C5a)
    c. Kinins
    d. Platelet activating factors
3. Neutrophil adhesion
    a. Tumor necrosis factor
    b. Interleukin 1
    c. C5a
    d. Leukotrienes
4. Neutrophil chemotaxis
    a. C5a
    b. Leukotrienes
    c. Fibrin degradation products
    d. Interleukins 1 and 8
    e. Bacterial products
5. Fever
    a. Interleukin 1
    b. Tumor necrosis factor
    c. Prostaglandin
6. Pain
    a. Kinins
    b. Prostaglandin
7. Tissue necrosis
    a. Neutrophil lysosomal content
    b. Free radicals
    c. Causative agent

TYPES OF CELLS BASED ON THEIR REGENERATIVE CAPACITY

Labile cells	Stable cells	Permanent cells
Continuously multiplying through out life with the capacity to regenerate	Don't actually multiply but have retained proliferative capacity	No regeneration occurring
Examples include bone marrow cells, lymphoid tissues, epithelium of the skin and mucous membranes	Examples include most of the glandular like pancreas, kidney, liver and salivary glands. Examples of mesenchymal tissues like the fibroblast, osteoblasts, chondroblasts, vascular endothelium, skeletal and smooth muscles	Examples like the neurons, skeletal and cardiac muscles

HEALING

Refers to the restoration of tissue architecture andfunction after an injury. It occurs by two types of reactions:

- **Regeneration**
    - Occurs by proliferation of residual (uninjured) cells that retain the capacity to divide, and by replacement from tissue stem cells.
    - Leads to complete restoration of the original tissue.
    - It is the typical response to injury in the rapidly dividing epithelia of the skin and intestines, and some parenchymal organs, notably the liver.
- **Repair**
    - If the injured tissues are incapable of regeneration, or if the supporting structures of the tissue are severely damaged, repair occurs by the laying down of connective (fibrous) tissue, a process that results in scar formation.
    - Although the fibrous scar cannot perform the function of lost parenchymal cells, it provides enough structural stability that the injured tissue is usually able to function.
    - The term **fibrosis** is most often used to describe the extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction).

- If fibrosis develops in a tissue space occupied by an inflammatory exudate, it is called **organization** (as in organizing pneumonia affecting the lung).

HEALING BY FIRST INTENTION

- Primary union
- The healing of a clean, uninfected surgical incision approximated by surgical sutures
- The incision causes only focal disruption of epithelial basement membrane continuity and death of relatively few epithelial and connective tissue cells. As a result, epithelial regeneration is the principal mechanism of repair.

HEALING BY SECOND INTENTION

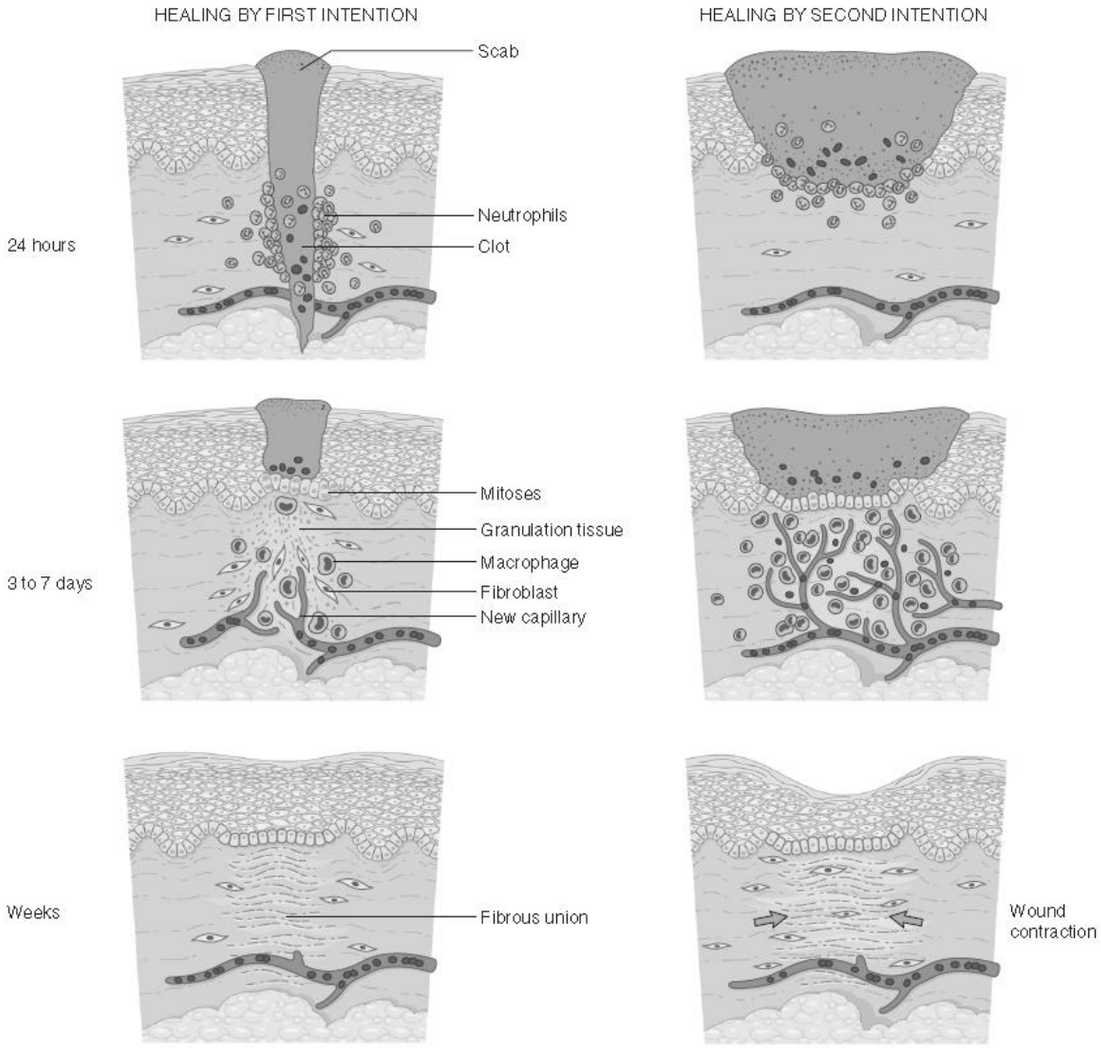
- Secondary union
- When cell or tissue loss is more extensive, such as in large wounds, at sites of abscess formation, ulceration, and ischemic necrosis (infarction) in parenchymal organs, the repair process is more complex and involves a combination of regeneration and scarring.
- Secondary healing differs from primary healing in several respects:

✓ A larger clot or scab rich in fibrin and fibronectin forms at the surface of the wound.

✓ Inflammation is more intense because large tissue defects have a greater volume of necrotic debris, exudate, and fibrin that must be removed. Consequently, large defects have a greater potential for secondary, inflammation-mediated, injury.

✓ Larger defects require a greater volume of granulation tissue to fill in the gaps and provide the underlying framework for the regrowth of tissue epithelium. A greater volume of granulation tissue generally results in a greater mass of scar tissue.

✓ Secondary healing involves wound contraction. Within 6 weeks, for example, large skin defects may be reduced to 5% to 10% of their original size, largely by contraction. This process has been ascribed to the presence of myofibroblasts, which are modified fibroblasts exhibiting many of the ultrastructural and functional features of contractile smooth muscle cells.



GROWTH DISORDERS

1. ATROPHY – reduce size or number of an organ or tissue because of a decrease in the size or number of constituent cells. It is a presumption that the organ was normal in size and function before the occurrence of atrophy.

2. ABIOTROPHY - premature degeneration after a normal development. Cause is genetic where initially developed tissues undergo degeneration causing loss of cells and functions. Usually an irreversible disorder that occurs in the nervous system
– cerebellar abiotrophy.

3. HYPERTROPHY – increase size of an organ or tissue because of an increase size of the specialized cells.

4. HYPERPLASIA – increase in size of an organ or tissue because of an increase in the number of specialized cells.

5. METAPLASIA – conversion of specialized, differentiated cell type to another mature cell type.

6. DYSPLASIA – abnormal growth. Imperfect arrangement of normal-looking cells.

CONGENITAL – disorders present at birth. Effects on longevity vary from being lethal to shortened life span to being inconsequential.

POST-NATAL CONGENITAL DISORDERS
DEFECTS UNDER CONGENITAL GROWTH DISORDERS

7. APLASIA – failure of an organ or tissue to develop. Also applicable when a tissue failed to renew itself (aplastic anemia).

8. HYPOPLASIA – failure of an organ to reach normal size. May be inherited or due to damage to proliferating stem cells by infections, toxins or physical agents. Intermediate phase between aplasia and normality.

NEOPLASM

An abnormal mass of tissue with exceeded growth, uncoordinated and persistent in the same excessive manner after cessation of the stimulus, which evoked the change.

Nomenclature of neoplasm and characteristics

	BENIGN	MALIGNANT
Mesenchymal	Fibroma (connective tissue)	Fibrosarconma
Epithelial		
a. Glandular	Adenoma	Adenocarcinoma
b. Non-glandular	Epithelioma and Papilloma	Carcinoma
	Slow growing	Rapidly growing
	Non-invasive	Invasive
	Non-spreading	Spreading
	Well-differentiated	Poorly differentiated
	Harmless	Harmful

METASTASIS

is the spread of neoplasm to sites elsewhere in the body not directly associated with the primary mass.

MECHANISMS OF METASTASIS

1. Lymphatic invasion and transportation.
   - Draining lymph node can become affected early in the process.
   - Malignant epithelial-based tumors can spread via the lymphatics.

2. Hematogenous invasion and transportation.
   - Via veins, venules and capillaries as arterial walls are too thick for penetration.
   - As for lymphatic invasion, the pattern of spread of metastasizing neoplasm reflects the distribution of the invaded blood vessels.
   - Intestinal tumor may initially metastasize to the liver via the portal circulation.

- Lungs are common sites of metastasis because it is the first capillary bed encountered.
- Malignant mesenchymal tumors can spread via the blood vessels.

3. Exfoliation and implantation.
    - Malignant tumors with access to a serosal surface such as the peritoneum may exfoliate into the cavity, spread and implant and proliferate throughout the cavity.
    - Malignant ovarian and intestinal neoplasm can spread in this way.

EFFECTS OF NEOPLASIA ON HOST

1. Space occupying especiallly in the brain and spinal cord
2. Physical obstruction especially in the alimentary tract, urinary tract and airways.
3. Inappropriate release of hormones from endocrine gland and tumors.
4. Inappropriate production of hormone like substances from non-endocrine tumors.
    - The release of parathyroid like substances by non-endocrine tumors mostly from anal sac carcinomas and lymphosarcomas leading to hypercalcemia.
5. Cachexia, which is the loss of weight, emaciation and weakness.
    - Anorexia
    - Disturbance in energy metabolism – effect of enzymes
    - Disturbance in fat metabolism – tumor necrosis factor

CELL GROWTH FACTORS

The genetic-based factors for the development of neoplasia include the two basic groups of genes at the center of growth factors.

a. Oncogenes
    - Proto-oncogenes encourage and promote the normal growth and division of cells.
    - Oncogenes are mutated forms of proto-oncogenes resulting in excessive cell multiplication.
    - They are dominant. The presence of one normal gene at a locus (proto-oncogene) and one mutated gene, the abnormal gene takes control.

b. Tumor suppressor genes
    - Tumor suppressor genes control cell transformation and proliferation.
    - Behave as recessive.
    - Examples include p53 and Rb gene.

TYPES OF HYPERSENSITIVITIES

Hypersensitivity	Immunologic mediator	Mechansim	Examples
Type I	Ig E	Mediator release	Insect bite reaction
			Hay fever
			Asthma late phase reaction
			Drug reaction
			Food allergies
Type II	IgG, Ig M	Cytotoxic or complement mediated	Transfusion reaction
			Neonatal isoerythrolysis
			Autoimmune hemolytic anemia and thrombocytopenia
			Hemolytic reaction to drugs
Type III	IgG, IgM	Immune complex	Immune complex glomerulonephritis
			Purpura hemorrhagica
			Staphylococcal dermamtitis
			Systemic lupus erythematosus
Type IV	Sensitized T cells	Delayed hypersensitivity	Allergic contact dermatitis
			Tuberculin reaction
			Chronic granulomatous inflammation

ONCOLOGY

Mesenchymal Tumors			
Origin	**Tissue/cell origin**	**Benign**	**Malignant**
Connective tissue and related tissue	Fibrous CT -fibroblast Fat – adipocyte Cartilage – chondrocyte Bone – osteoblast	Fibroma Lipoma Chrondroma Osteoma	Fibrosarcoma Liposarcoma Chrondrosarcoma Osteosarcoma
Endothelium and related tissue	Blood vessel -vascular endothelium Lymph vessel -lymphatic endothelium Synovium -synovial lining cell Mesothelium –mesothelial cell Meninges - meningeal CT cell Ovary - modified mesothelium	Hemangioma Lymphangioma Synovioma Meningioma Adenoma	Hemangiosarcoma Lymphangiosarcoma Synovial sarcoma Mesothelioma Malignant meningioma Adenocarcinoma
Hematopoietic and lymphoid tissue	Lymphoid tissue – lymphocytes Bone marrow – leukocytes and erythrocytes Connective Tissue - Mast cell - Histiocyte	n/a n/a Mast cell tumor Histiocytoma	Lymphoma Leukemia Malignant mast cell Malignant histiocytoma
Muscle	Smooth muscle Skeletal muscle	Leiomyoma Rhabdomyoma	Leiomyosarcoma Rhabdomyosarcoma
Epithelial tumors			
Lining or covering epithelium	Skin -Squam. epithelial cells -Adnexal cells -Melanocyte	Papilloma Adenoma Melanocytoma	Squamous Cell Carcinoma Adenocarcinoma/Carcinoma Malignant melanoma
	Upper alimentary tract -Squam. epithelial cells	Papilloma	Carcinoma

	Lower alimentary tract -Columnar epithelium	Adenoma	Adenocarcinoma /Carcinoma
	Upper respiratory tract - Columnar epithelium	Adenoma	Adenocarcinoma /Carcinoma
	Lung -Columnar epithelium of bronchi and bronchioles -Alveolar epithelium	Adenoma Adenoma	Adenocarcinoma /Carcinoma Adenocarcinoma /Carcinoma
	Urinary Tract -Transitional epithelium	Papilloma	Transitional cell carcinoma
	Uterus -Columnar epithelium	Uterine polyp	Endometrial carcinoma / adenocarcinoma
	Lining of glands/ducts -Prostate, thyroid, bile ducts of liver, etc.	Adenoma	Adenocarcinoma Carcinoma
Solid epithelial organs	Glands -Pancreas, salivary duct,	Adenoma	Adenocarcinoma
	Liver -Hepatocyte	Hepatoma	Hepatocellular carcinoma
	Kidney -Renal tubule cell	Renal tubular adenoma	Renal cell carcinoma
	Testicle -Sertoli cell -Interstitial cell -Germ cell	 Sertoli cell tumor Interstitial cell tumor Seminoma/Teratoma	 Sertoli cell tumor Seminoma/Teratocarcinoma
	Ovary -Stromal cell -Germ cell	 Granulosa cell tumor Luteoma Thecoma Dysgerminoma Teratoma	 n/a n/a n/a Dysgerminoma Teratocarcinoma
Neural tumors			
Glial Cells	CNS -Astrocyte -Oligodendrocyte -Microglial cell PNS -Schwann cell	 n/a n/a n/a Schwannoma (Benign peripheral nerve sheath tumor)	 Astrocytoma/Glioblastoma Oligodendroglioma Microgliomatosis Malignant schwannoma (Malignant PNST)
Neural Cells	CNS -Neuron PNS -Neuron	 n/a Ganglioneuroma	Primitive neuroectodermal tumor n/a

Mixed tumors			
Various	Mammary gland -Epithelium & myoepithelium	Ben mixed mammary tumor (dog) Complex adenoma	Mal mixed mammary tumor (dog) Complex adenocarcinoma
	Testicle -Germ cell	Teratoma	Teratocarcinoma
	Ovary -Germ cell	Teratoma	Teratocarcinoma

NUTRITIONAL PATHOLOGY

Vitamin/Mineral	Deficiency effect	Toxicity
1. Vitamin A for vision, normal growth of epithelial cells and bone remodelling	Epithelial disorders (metaplasia) Faulty bone remodelling	Deforming cervical spondylosis (cat); GI signs and lameness
2. Vitamin D (D2 –ergocalciferol (more potent) and D3-cholecalciferol). For GIi absorption of calcium and growth development of bone	Rickets	Hypercalcemia, dystrophic calcification
3. Vitamin E for anti oxidant and stabilizing lipid membranes	Muscle dystrophy, testicular degeneration, Steatitis, immune suppression	No documentation in dog and cat, antagonizes Vit. K metabolism leading to coagulopathy
4. Vitamin K Forms: K1 (plants) K2 (intestinal flora) K3 (synthetic)	Coagulopathy (deficiency of factors II, VII, IX and X)	Hypersensitivity reaction; K1 and K3 supplementation has been associated with Heinz body anemia in dog and cat
WATER SOLUBLE VITAMINS		
5. Thiamine (B1) Participate as coenzyme in CHO metabolism (thiamine pyrophosphate)	Anorexia, neurological signs (ventroflexion in cats), cardiac signs preceding death	
6. Riboflavin (B2) Constituents of 2 enzymes: riboflavin 5-phosphate and FAD). Important in oxidative enzyme systems (TCA cycle and oxidative phosphorylation)	Anorexia, weight loss, poor coat, cataract (cat) or corneal opacity (dog)	
7. Niacin (Nicotinic acid) Converted to nicotinamide which is a component of NAD and NADH	Inflammation and ulceration of oral mucosa (black tongue in dog), nonspecific signs of	Vasodilatation and cutaneous flushing in dog

(coenzyme to the oxidation-reduction rxn for the utilization of all nutrients	anorexia and weight loss	
8. Panthotenic acid Constituent of coenzyme A	Non-specific signs: anorexia, poor growth and fatty liver	
9. Pyridoxine (B6) Constituent of the coenzyme pyridoxal 5-phosphate (involved in nitrogen and amino acid metabolism	Microcytic hypochromic anemia, increased urinary excretion of oxalates and poor growth	
10. Folic acid (Folacin) Constituent of the coenzyme tetrahydrofolate (enzymatic transfer of single carbon units – synthesis of thymidine	Weight loss, anemia and leukopenia	
11. Biotin Coenzyme involved in carboxylation reaction (transfer of CO2 groups). Important in carbohydrate and lipid metabolism	Scaly dermatitis	
12. Vitamin B12 (Cobalamin) Involved in the transfer of single carbon units (methyl group). Function is linked with folic acid and important in carbohydrate, fat metabolism and myelin synthesis	Poor growth, weight loss and anemia	
13. Choline Function as methyl donor and also a component of phospholipid and precursor of acetylcholine	Anorexia, poor growth and fatty liver	
Vitamin C (ascorbic acid) Important in the hydroxylation of lysine and proline. Affects collagen formation and the conversion of dopamine into norepinephrine and tryptophan into serotonin		
MACROMINERALS	**DEFICIENCY**	**EXCESS**
15. Calcium	Secondary nutritional hyperparathyroidism and tetany	Interference with the absorption of zinc, copper, iron and phosphorus, altered skeletal remodelling
16. Phosphorus	Abnormal bone development	Calcium deficiency, rickets, osteomalacia and possible renal toxicity
17. Magnesium	Poor growth, skeletal abnormalities and neurological signs	Predispose to struvite urolith formation in cats resulting to alkaline urine formation

18. Potassium	Weakness and polymyopathy	
19. Sodium	Fatigue and poor growth (not readily seen)	Neurological signs occur when inadequate water is available
20. Chloride	Hypokalemia, metabolic acidosis, weakness, ataxia	
TRACE ELEMENTS	**DEFICIENCY**	**EXCESS**
21. Iron	Hypochromic, microcytic anemia, weakness and fatigue	Anorexia, weight loss and hepatoxicity
22. Copper	Anemia, rusty coat color	Anemia, progressive liver disease (dog) with copper storage disease (Wilson disease)
23. Zinc	Poor growth, anorexia, testicular atrophy, parakeratosis, achromotrichia (generic dog food disease)	Relatively non toxic; can interfere with the absorption of dietary calcium, iron and copper; chronic excess can cause haemolytic anemia
24. Selenium	Degeneration of skeletal and cardiac muscle in dog	Pulmonary edema and sudden death in dog
25. Cobalt	Poor growth and anemia	
26. Iodine	Goiter	
ULTRA TRACE ELEMENTS	**ROLE**	
27. Molybdenum	Constituents of several enzymes	
28. Fluorine	Teeth and bone development	
29. Chromium	Carbohydrate metabolism and insulin function	
30. Nickel	Membrane function and RNA metabolism	
31. Silicon	Skeletal and connective tissue growth and development	
32. Vanadium	Insulin mimetic and fat metabolism	
33. Arsenic	Possibly haemoglobin production	