

**Veterinarian Licensure
Examination Review
Supplemental Materials**

**VETERINARY
PATHOLOGY**



VETERINARY PATHOLOGY

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I. GENERAL PATHOLOGY

a. Definition of Terms

Pathology – the study of disease.

Veterinary Pathology – the study of disease of animals.

Disease – defined as:

The culmination of various defects, deficiencies or excesses at the cell or tissue level which may ultimately express in a clinically apparent dysfunction.

Lesion – this refers to abnormal microscopic and gross change in a cell, tissue, organ and system as a result of a disease. It also involves biochemical alterations.

Injury (or Injurious Agents) –any outside or inside influences in the animal or individual that would cause changes either in physiology and morphology of the cell.

Stress - any stimulus or succession of stimuli of such magnitude that tend to disrupt the homeostasis of the organism.

Pathogenesis – the sequential development of disease.

Homeostasis – the maintenance of the steady state in an organism by coordinated physiological processes or feedback mechanisms.

Pathogenicity – refers to the capacity to produce a disease.

Virulence – refers to the degree of pathogenicity or disease producing power of the organism.

Pathognomonic – set of lesions that would highly indicate the disease.

Prognosis – expected outcome of a disease.

Diagnosis – the act of deciding the nature, cause and course of a disease.

Types of Diagnosis:

Clinical Diagnosis – based on signs and symptoms

Morphological Diagnosis – based on gross and microscopic lesions.

Etiological Diagnosis – based on laboratory identification/isolation.

Definitive Diagnosis – or confirmatory diagnosis resulting to naming of the disease.

Iatrogenic – man-made or artificially- induced disease.

Idiopathic – the injurious agent or etiology is unknown.

Idiosyncrasy – or individual peculiarity.

Necropsy – (or **AUTOPSY**) post-mortem examination of animals.

Biopsy - is the removal of/and examination of tissue from a live individual or animal.

Histopathology – microscopic study of lesions in a tissue section.

Hematoxylin and Eosin (H & E) – the commonly used stain for histopathological examination.

Rudolf Virchow - the father of modern pathology.

Celsus – authored the four cardinal signs of inflammation.

Hippocrates – the father of medicine

Aristotle – father of veterinary medicine

Caduceus – this is the medical symbol with a serpent. In veterinary medicine, a V sign is superimposed.

b. Mechanisms and Causes of Cell Injury

Causes of Cellular Injury

1. Hypoxia

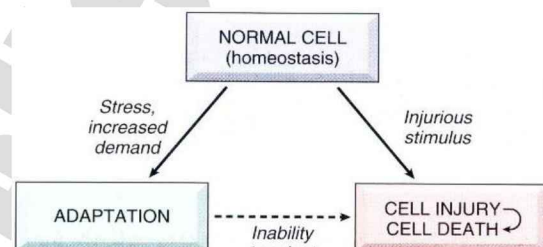
2. Physical agents including trauma, heat, cold, radiation and electric shock
3. Chemical agents and drugs
4. Infectious agents including bacteria, viruses, parasites, fungi etc.
5. Immunologic reactions
6. Genetic derangements
7. Nutritional imbalances

MECHANISM OF CELL INJURY

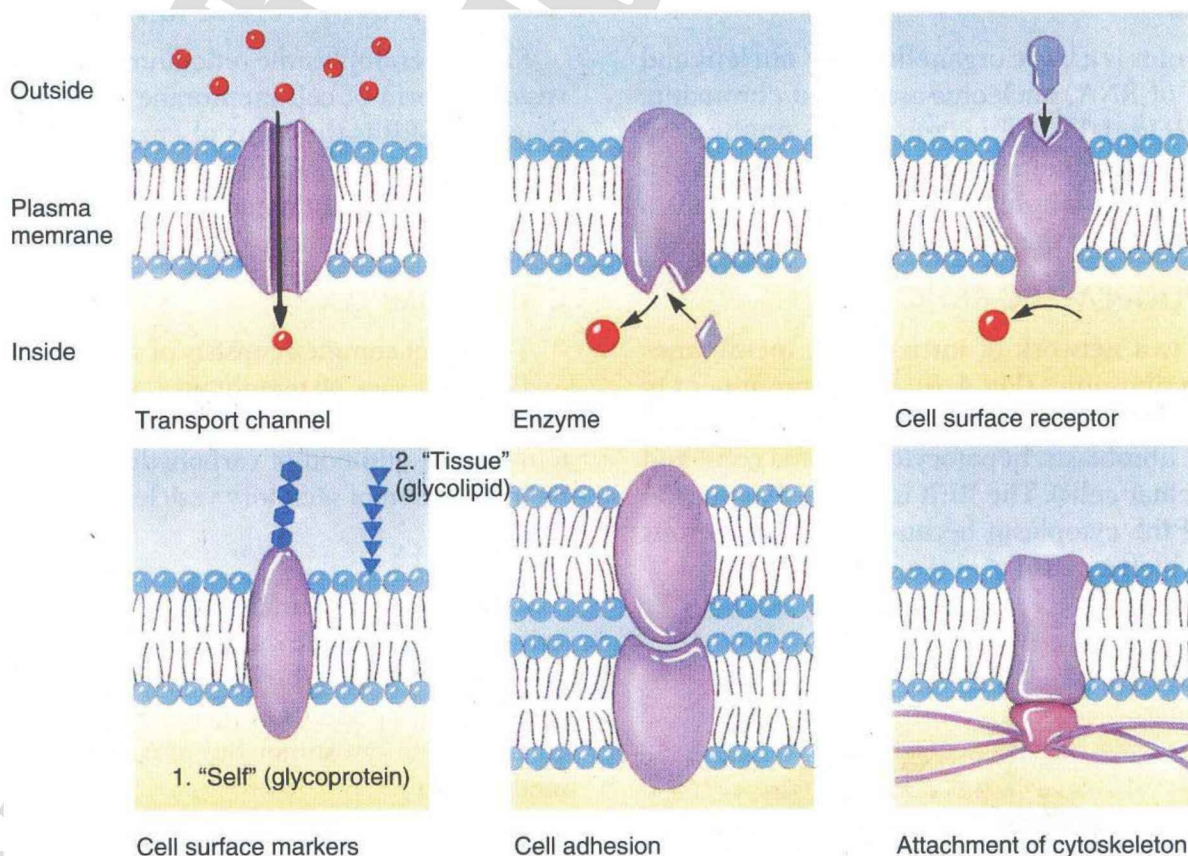
General principles:

Four intracellular systems are particularly vulnerable to cell injury.

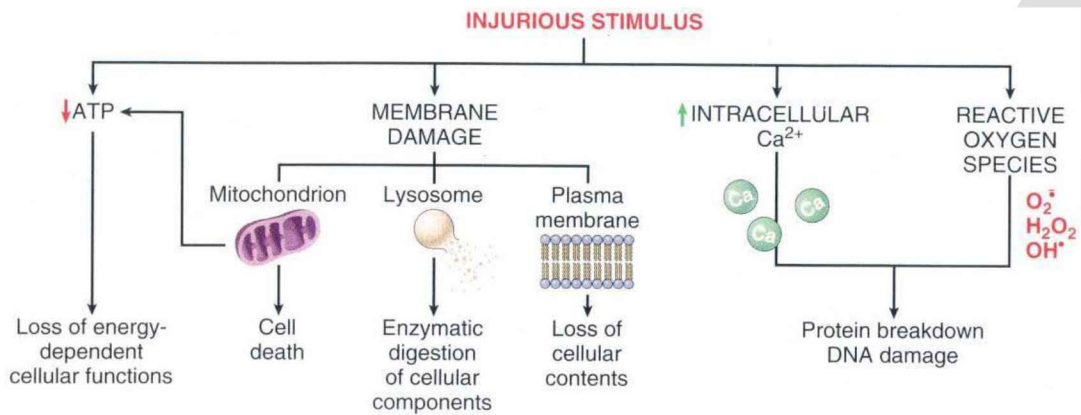
1. Maintenance of the integrity of the cell membrane.
2. Aerobic respiration and production of ATP.
3. Synthesis of enzymes and structural proteins.
4. Preservation of the integrity of the genetic apparatus.



Stages in the cellular response to stress and injurious stimuli.



Functions of transmembrane proteins. A variety of functions are performed by different types of cell membranes as shown.



Cellular and biochemical sites of damage in cell injury. ATP, Adenosine triphosphate.

c. Cellular and Tissue Responses to Injury

CELLULAR INJURY AND ADAPTATION

Degeneration – (implies a “sick cell”)

- a reversible form of injury
- an adaptive change that may progress to cell death (necrosis)

Cellular adaptation - this occurs when excessive physiologic stresses, pathologic stimuli result in a new but altered state that preserves the viability of the cell. e.g., hypertrophy – (increase in tissue mass); atrophy - (decrease in tissue mass)

Infiltrations - cells/tissues that accumulates substances in abnormal quantities.

- This occurs when cell injury is sublethal and sustained.

TYPES OF INTRACELLULAR ACCUMULATIONS:

WATER VACUOLES

Hydropic degeneration (acute cellular swelling, cloudy swelling) – occur because of marked mitochondrial damage, cessation of ATP production and failure of sodium pump leading to increased osmotic pressure within cells; selective permeability of cellular membranes affected leading to increased entry of water inside the cell.

- usually associated with epithelial lesions
- term not to be used for gross lesions

FAT VACUOLES

1. Fatty degeneration (Fatty change) -

presence or abnormal accumulation of fat droplets/globules within the cytoplasm of parenchymal cells. It peripherally displaces the nucleus giving a characteristic “ring appearance” in a cell.

- considered reversible injury if the cause is removed.

Mechanisms for the lesion:

- interference with protein production in the endoplasmic reticulum by either specific or nonspecific damage to the hepatocyte and

certain nutritional deficiencies; because lipoproteins cannot be formed, then lipid cannot be secreted from the cell.

- interference with the release of lipoproteins from the cell;
- impaired combination of lipid with protein;
- failure on oxidation of fatty acid presented to the liver by absorption from the intestine or from adipose tissue.

Special Notes:

- > The gross appearance of fatty liver is yellow.
- > Cats normally have large amounts of fat in their renal tubular epithelium.

2. Fatty Infiltration (or fatty replacement)

- presence or accumulation of fat or adipose cells in tissues in which they are not normally present. e.g., myocardial and skeletal muscle, as well as in the pancreas(not common)

Special stains for fats:

- Sudan stains
- Oil red-O

GLYCOGEN VACUOLES

- Glycogen degeneration – abnormal accumulation of glycogen in cytoplasm of parenchymal cells and appear as clear vacuoles..This occurs following a defect in glycogen metabolism as in diabetes mellitus.

Special stain for glycogen:

- Periodic Acid-Schiff or PAS stain

INTRACELLULAR INCLUSIONS

Hyaline Change (hyalinization, hyaline degeneration)

- refers to any alternation within cells or in the extracellular spaces or structure that gives a homogeneous, glassy-pink appearance in histologic sections stained with hematoxylin and eosin (H & E).

- Hyaline droplets are small eosinophilic structures in the cytoplasm of cells.

Example of intracellular hyaline include

1. Absorption of protein causing hyaline droplets in proximal epithelial cells of the kidney.
2. Russell bodies in plasma cells.
3. Viral inclusions in the cytoplasm or the nucleus.
4. Masses of altered intermediate filaments (such as alcoholic hyaline)

Inclusions

- occur in cells and may be very prominent, such as inclusion bodies induced by viral infection of cells.
- may be intranuclear (as in CD), intracytoplasmic (as in rabies) and either eosinophilic or basophilic.

SPECIFIC TYPES OF EXTRACELLULAR DEGENERATION CHANGES

1. Fibrinoid -

- an amorphous, bright, eosinophilic material found particularly in the walls of the blood vessels of various sizes.
- fibrin is the major component along with serum proteins, particularly immunoglobulins or antibodies.

2. Amyloidosis

- a disease where amyloid deposition leads to functional and morphological lesions
- Amyloid is an amorphous eosinophilic material that accumulates in tissues, particularly on basement membranes, and often causes clinically significant lesions.

2 types of amyloidosis

a. Primary amyloidosis

- results from the production of immunoglobulin
- amyloid precursors by abnormal plasma cells.
- e.g. myeloma – plasma cell tumor

b. Secondary amyloidosis

- occur in chronic infectious diseases in which the immune system actively produce immunoglobulins for prolonged periods..
- also occur in hyperimmunized animals.

3. Gout is the name of the disease that occurs when uric acid and urate crystals are deposited in tissue owing to defects in purine metabolism.

4. Cholesterol (Cholesterol defts)- crystal-like collection in tissue after severe tissue damage hemorrhage.

Xanthomatosis – similar condition in avian species that results from massive accumulation of lipids in macrophages.

5. Corpora amylacea – circular, laminated concretions found in glandular tissue or freely on secretions.

NECROSIS: Irreversible Injury

Necrosis

- rapid death of a limited portion of an organism.

- final stage in irreversible degeneration.

Necrobiosis - the term for the entire process of degeneration and death of cells

Gross indicators/characteristics of necrosis

The gross indications of necrosis are:

1. loss of color or paleness of the tissue
2. loss of strength of the tissue as it softens
3. a definite zone of demarcation between necrotic and viable tissue
4. the location or pattern of the lesion.

Cellular Characteristic of Necrosis

Microscopic indicators:

- a) acidophilia or eosinophilia of the cytoplasm
- b) lysis of the cytoplasm
- c) nuclear changes

Four types of nuclear changes may occur;

1. pyknosis, the condensation of nuclear chromatin into a dark, round, homogenous mass (condensed/smaller appearance of a nucleus)
2. karyorrhexis, the shattering of the nucleus into numerous fragments;
3. karyolysis, dissolution of nuclear chromatin, leaving a hollow, large, round, "ghost appearance" of the nucleus
4. complete absence of the nucleus.

TYPES OF NECROSIS

1) Coagulative or Coagulation Necrosis

- Coagulation necrosis refers to an area of necrosis in which the gross and microscopic architecture of the tissue and some of the cells are recognizable.

This condition may result from acute deprivation of blood supply.

2) Liquefactive or liquefaction necrosis)

- implies the rapid enzymic lysis of dead cells.
- This type of necrosis is seen particularly in the central nervous system, and in abscesses.

3) Caseous or Caseation Necrosis

- implies "curdled or cheesy" as in tuberculous lesions.
- characterized by the presence of friable, cheesy, amorphous material in necrotic area. This term is usual for tuberculous lesions.

4) Fat Necrosis -

- fat necrosis is distinctive type of necrosis and occurs in the abdominal cavity or under the skin.
- On cut surface, there are hard white gritty lumps.
- grossly, seen in cattle with severe hardening of the lower viscera with necrotic fats.
- microscopically, in dogs forming "calcium soaps"- seen in pancreatitis.

SPECIAL FORMS:**1. Gangrene or Gangrenous Necrosis**

- Gangrene occurs when saprophytic bacteria grow in necrotic tissue. The requirements are necrosis plus bacterial putrefaction.

There are two types of gangrene:

A. Dry gangrene

- commonly on skin or extremities in which there is little fluid in the necrotic tissue but there are saprophytes. Ischemia is the common cause as in tight bandages and casts.
- usual locations: extremities such as tail, ears or limbs.

B. Wet gangrene

- moist and usually black in color, contains gas bubbles, hemorrhage and edema in and around the lesion.

2. INFARCTION (Ischemic Necrosis)

Infarct – a form of coagulative necrosis resulting from a sudden deprivation of blood supply. Commonly occur in areas or organs with end-artery (i.e., kidney) blocked by thromboembolic lesions.

3. Zenker's Necrosis (Zenker's degeneration)

- a type of coagulative necrosis in striated muscles characterized by loss of striations in muscles following necrosis.

4. Fibrinoid Necrosis

- a special form of necrosis with fibrinoid accumulating along walls of blood vessel and connective tissues.

Other Terms Used In Association With Necrosis

Necrosis on a surface has several names.

1. Erosion – shallow area of necrosis confined to epidermis.
2. Ulcer – is an excavation of a surface produced by necrosis and sloughing.
 - implies involvement of the tissue below the surface layer.
3. Slough – a piece of necrotic tissue separating from viable tissue. Applied to necrosis of surface epithelia.

Other terms used in reference to necrosis:

1. Malacia – an area of liquefactive necrosis of the nervous tissues. Literally means "softening".
2. Sequestrum – an isolated necrotic mass.
 - process is called sequestration.

CALCIFICATION

- Calcification refers to the deposition of calcium salts in soft tissues.

Types of Calcification**1) DYSTROPHIC CALCIFICATION**

- When calcium salts are deposited in damaged cells and tissues.
(e.g. calcified nodules in intestinal serosa due to larval migration of *Oesophagostomum* spp.)

2) METASTATIC CALCIFICATION –

- deposition of calcium salts in vital tissues and is always associated with hypercalcemia.
- Term sometimes used for extensive metastatic calcification is **CALCINOSIS**.
- Calciphylaxis is a term that describes widespread deposition of calcium in tissues of individual due to iatrogenic calcium sensitizers such as vitamin D, parathyroid hormone or calcium ions.

ENZYMES RELEASED IN INJURED TISSUES:

Degenerating and necrotizing cells leak enzymes from cytoplasm into the blood and can be measured in serum.

1. Alanine transaminase, previously known as serum glutamic pyruvic transaminase (SGPT)
 - is released from the cytoplasm of injured liver cells in moderate injury,
2. Aspartate transaminase, formerly serum glutamic-oxaloacetic transaminase (SGOT), is located in mitochondria and is released in more extensive injury.

Other enzymes used to evaluate tissue damage are:

1. Lactic dehydrogenase (LHD)
2. Creatine phosphokinase (CPK)
3. Alkaline phosphatase (AP)

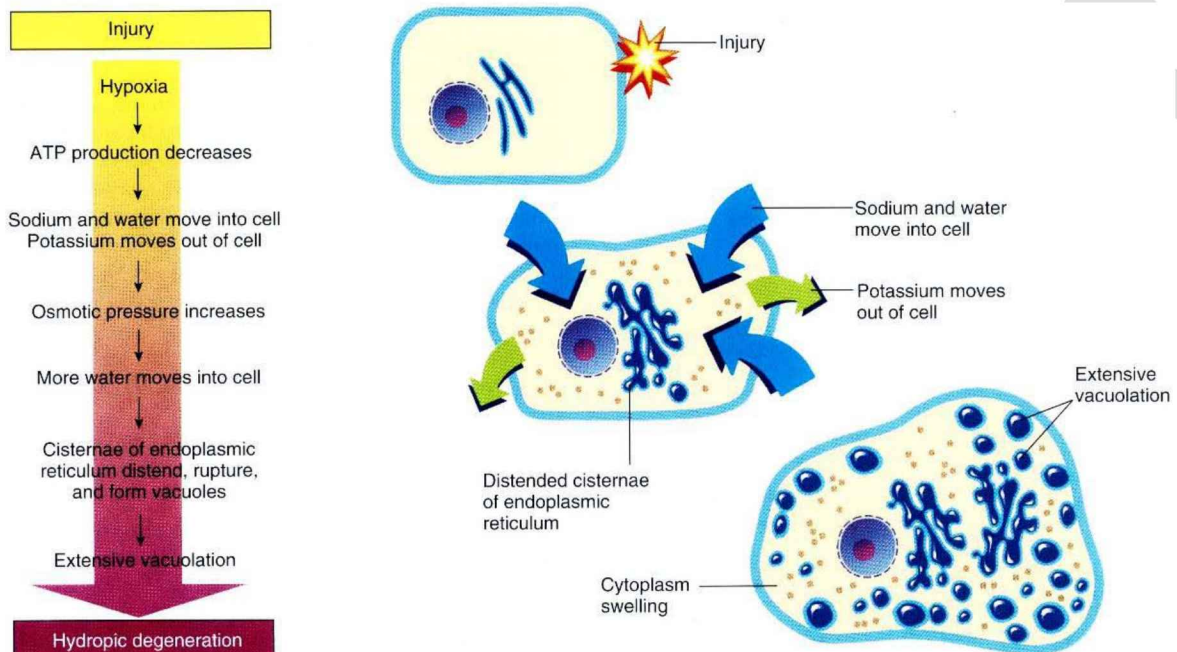
OUTCOME (or Sequela) OF NECROSIS

Necrosis will result to any of the following:

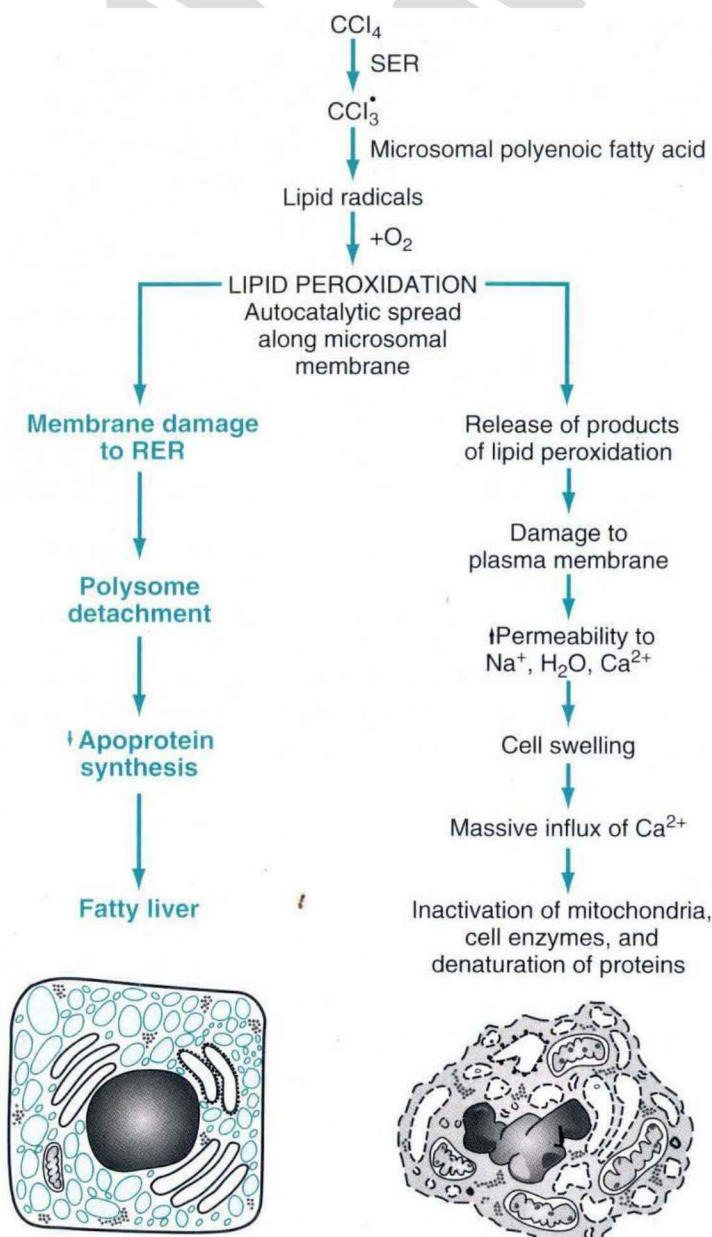
Localization	→ Calcification
	→ Sequestration
Lysis	→ Cyst
	→ Cavity
Secondary	
Infection	→ Abscess
	→ Gangrene
Resorption	→ Granulation tissue (Scar formation; fibrosis)

AUTOLYSIS

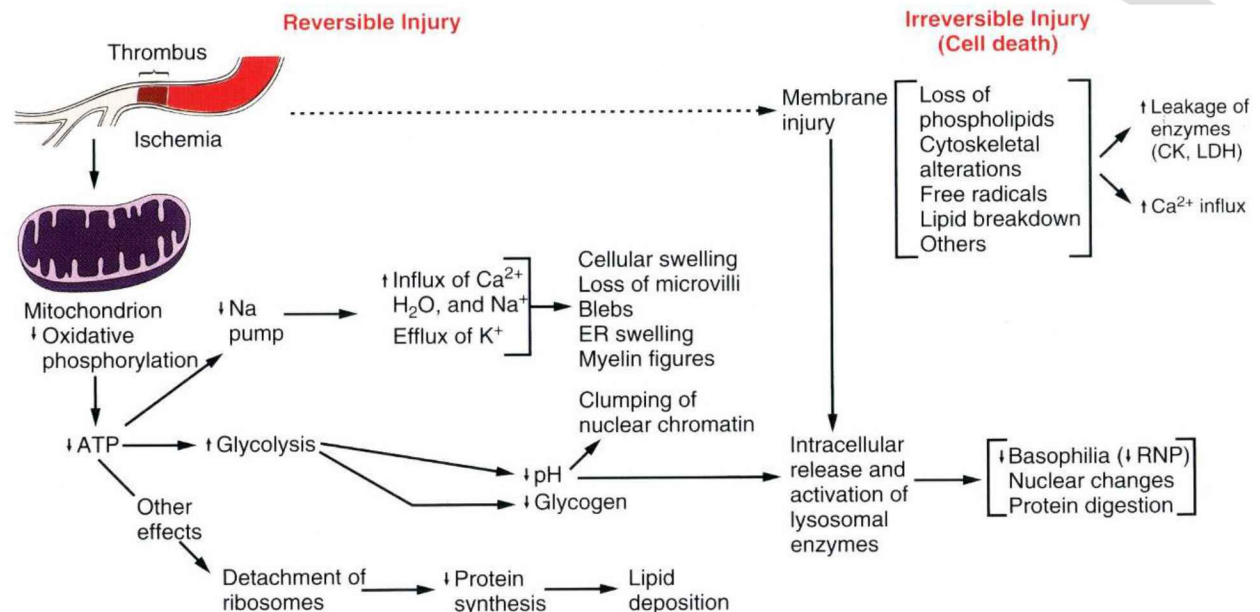
Autolysis means self-digestion by the tissues' enzymes that are present in, or released into, the cytoplasm of the cell after death.



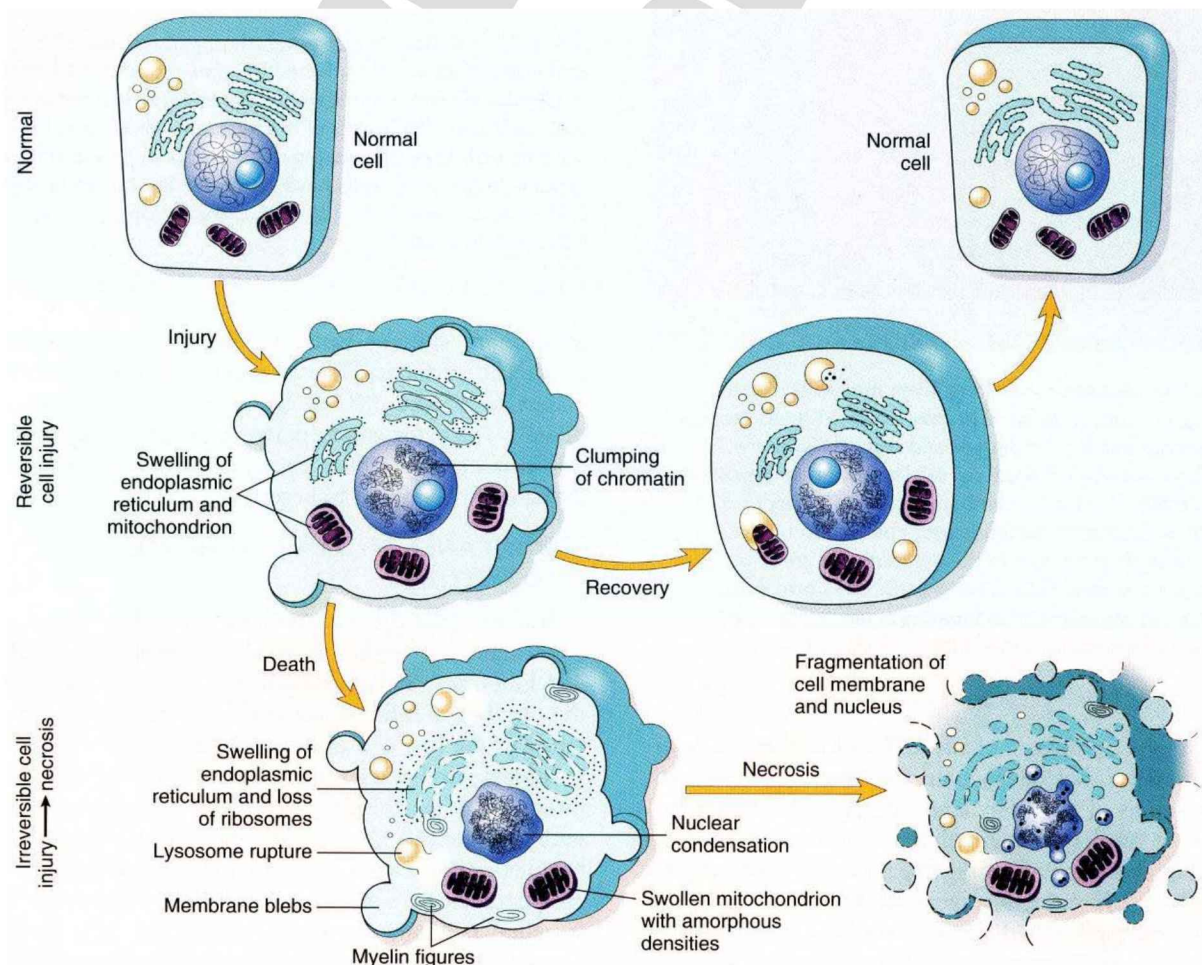
The process of acute swelling (hydropic degeneration). Swelling of the cell is the most common and most important response to cellular injuries of all types, including mechanical, anoxic, toxic, lipid peroxidation, viral, bacterial and immune mechanisms.



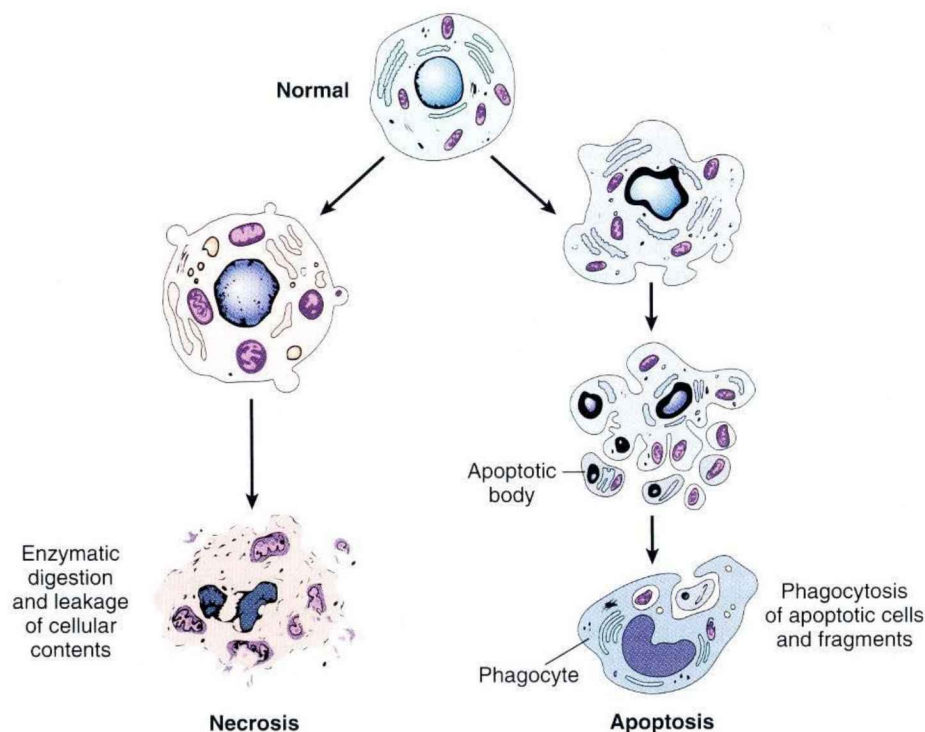
Sequence of events leading to fatty change and cell necrosis in carbon tetrachloride (CCl_4) toxicity. RER, Rough endoplasmic reticulum; SER, Smooth endoplasmic reticulum.



Postulated sequence of events in reversible and irreversible ischemic cell injury. Note that although reduced oxidative phosphorylation and ATP levels have a central role, ischemia can cause direct membrane damage. ER, endoplasmic reticulum; CK, creatine kinase; LDH, lactate dehydrogenase; RNP, ribonucleoprotein.

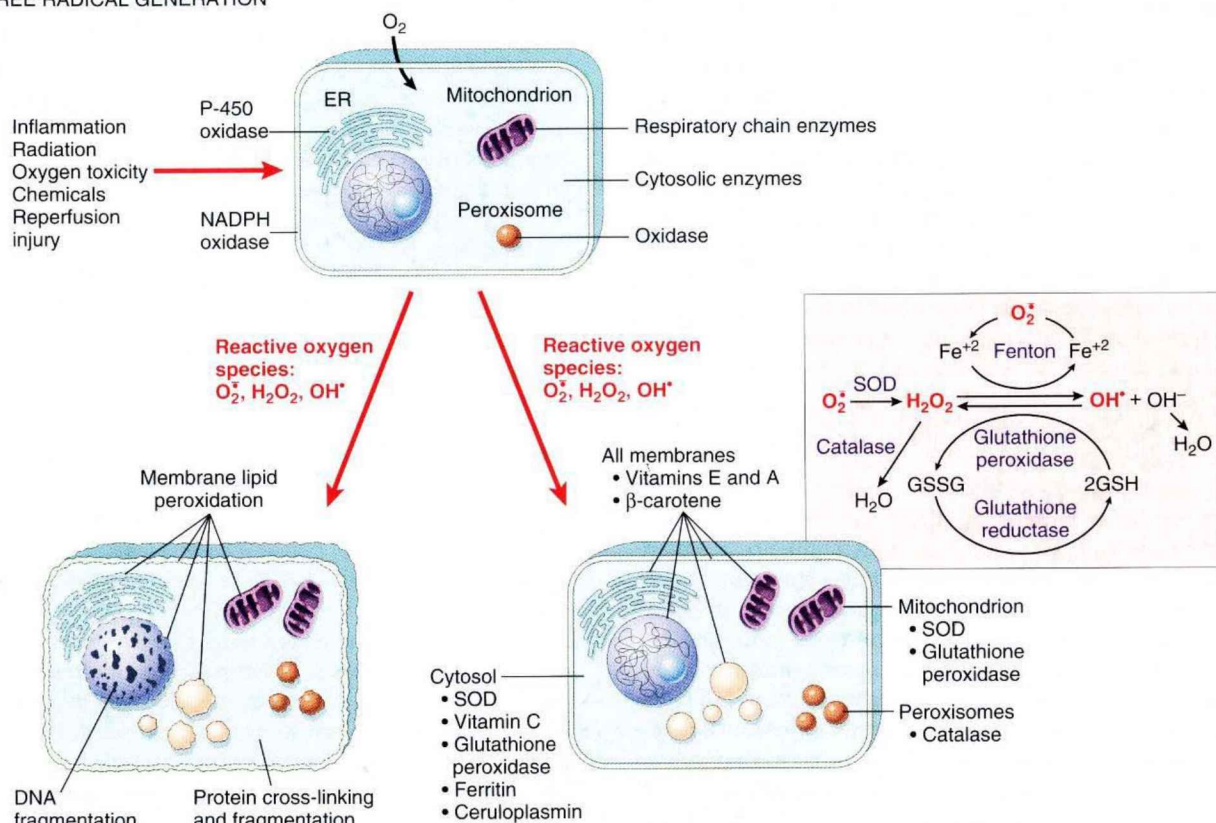


Normal cell and the changes in reversible and irreversible cell injury. Reversible injury is characterized by generalized swelling of the cell and its organelles, blebbing of the plasma membrane, detachment of ribosomes from the endoplasmic reticulum, and clumping of nuclear chromatin. Transition of irreversible injury is characterized by increasing swelling of the cell, swelling and disruption of lysosomes, presence of large amorphous densities in swollen mitochondria, disruption of cellular membranes, and profound nuclear changes. The latter include nuclear condensation (pyknosis), followed by fragmentation (karyorrhexis) and dissolution of the nucleus (karyolysis). Laminated structures (myelin figures) derived from damaged membranes of organelles and the plasma membrane first appear during the reversible stage and become more pronounced in irreversible damaged cells.



The sequential ultrastructural changes seen in necrosis (left) and apoptosis (right). In apoptosis, the initial changes consist of nuclear chromatin condensation and fragmentation, followed by cytoplasmic budding and phagocytosis of the extruded apoptotic bodies. Signs of cytoplasmic blebs, and digestion and leakage of cellular components characterize necrosis.

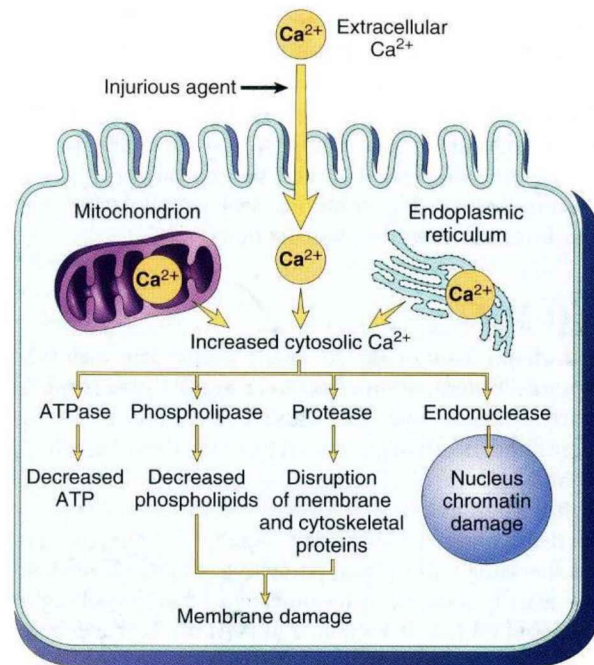
FREE RADICAL GENERATION



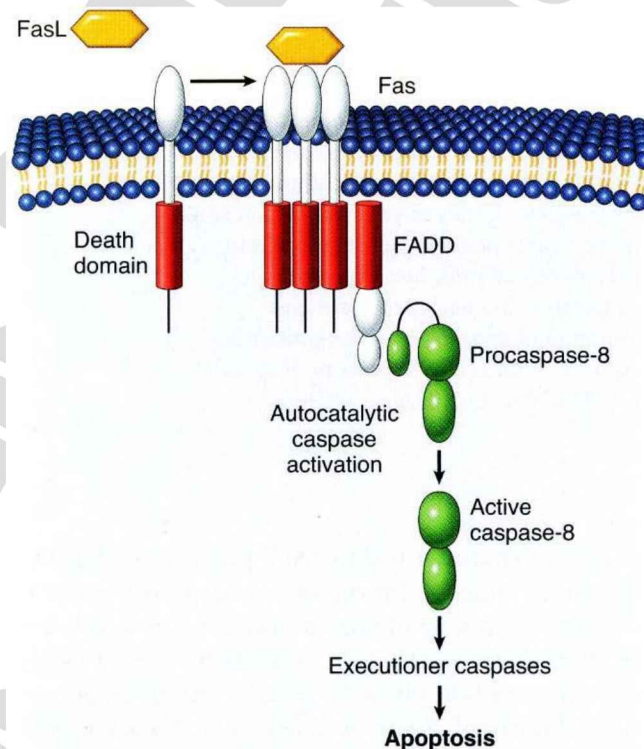
CELL INJURY BY FREE RADICALS

NEUTRALIZATION OF FREE RADICALS — NO CELL INJURY

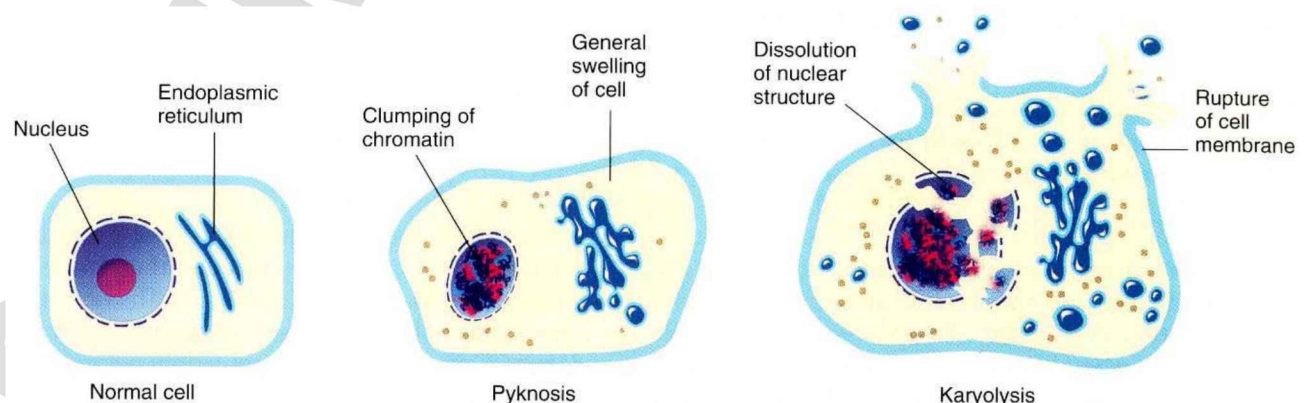
The role of reactive oxygen species in cell injury. O_2 is converted to superoxide (O_2^*) by oxidative enzymes in the endoplasmic reticulum (ER), mitochondria, plasma membrane, peroxisomes, and cytosol. O_2^* is converted to H_2O_2 by dismutation and thence to OH by the Cu^{2+}/Fe^{2+} catalyzed Fenton reaction. H_2O_2 is also derived directly from oxidases in peroxisomes. Not shown is another potentially injurious radical, singlet oxygen. Resultant free radical damage to lipid (peroxidation), proteins, and DNA leads to various forms of cell injury. Note that superoxide catalyzes the reduction of Fe^{3+} to Fe^{2+} , thus enhancing OH generation by the Fenton reaction. The major antioxidant enzymes are superoxide dismutase (SOD), catalase, and glutathione peroxidase. GSH, Reduced glutathione; GSG, oxidized glutathione; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate.



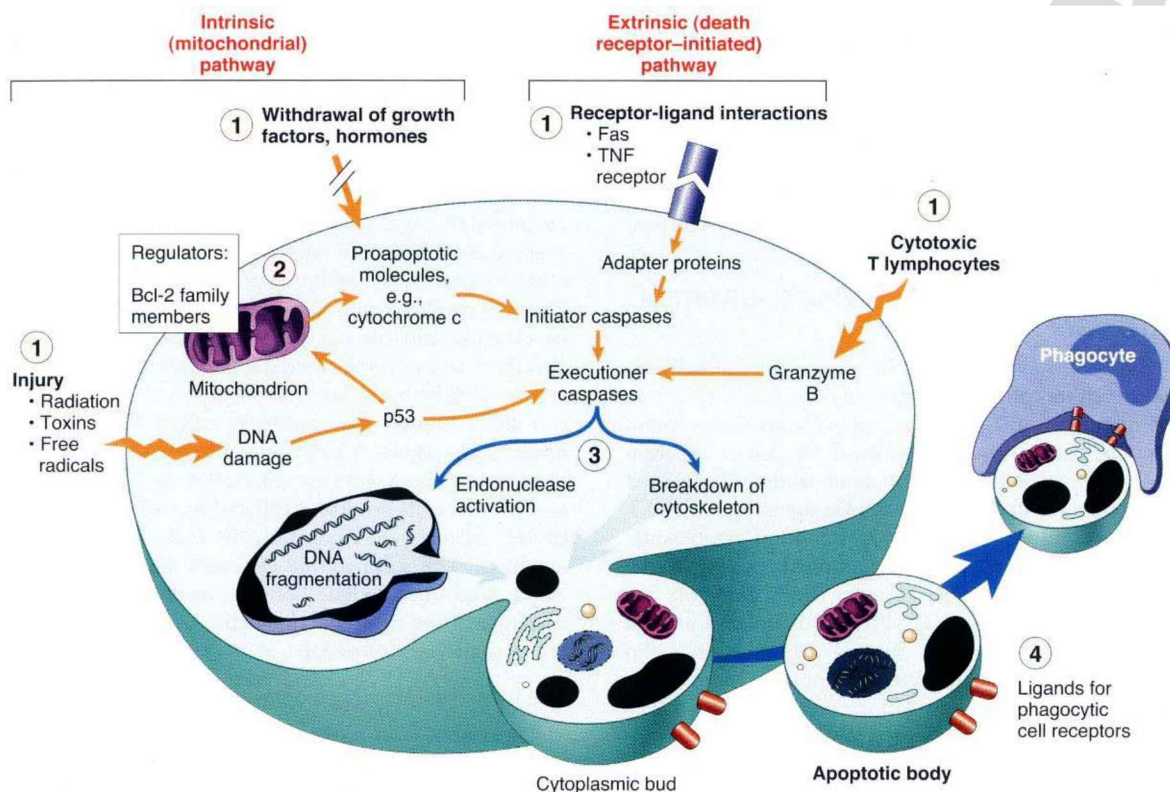
Sources and consequences of increased cytosolic calcium in cell injury.



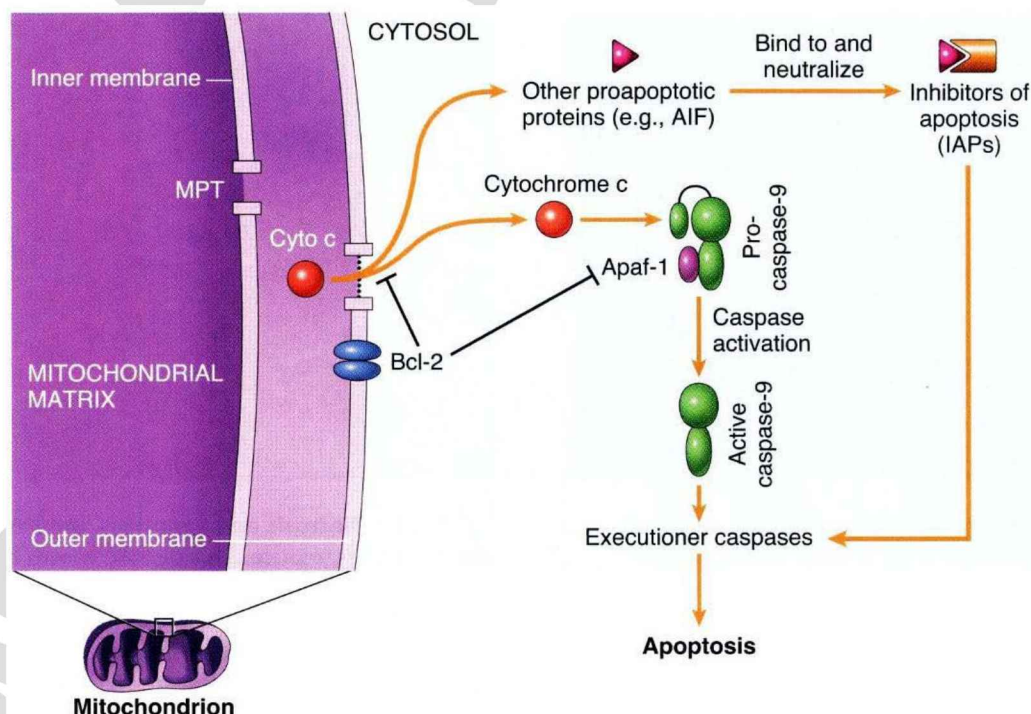
The extrinsic (death receptor-initiated) pathway of apoptosis, illustrated by the events following Fas engagement. FADD, Fas-associated death domain; FasL, Fas ligand.



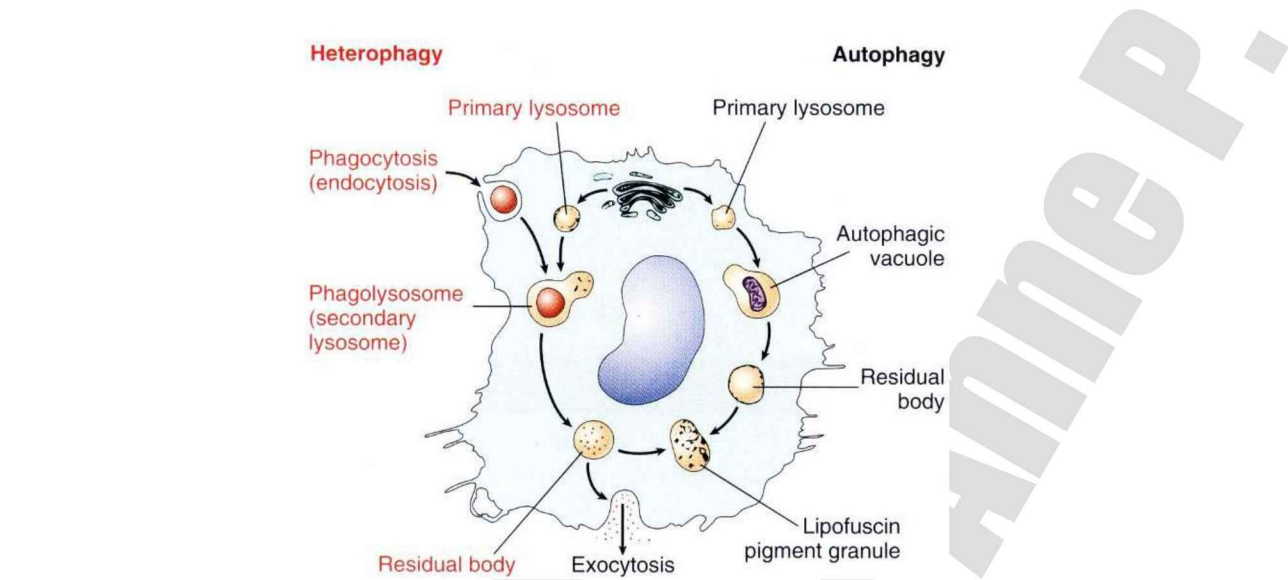
Cytoarchitecture of cellular necrosis. Schematic representation of nuclear and cytoplasmic changes in the stages of necrosis.



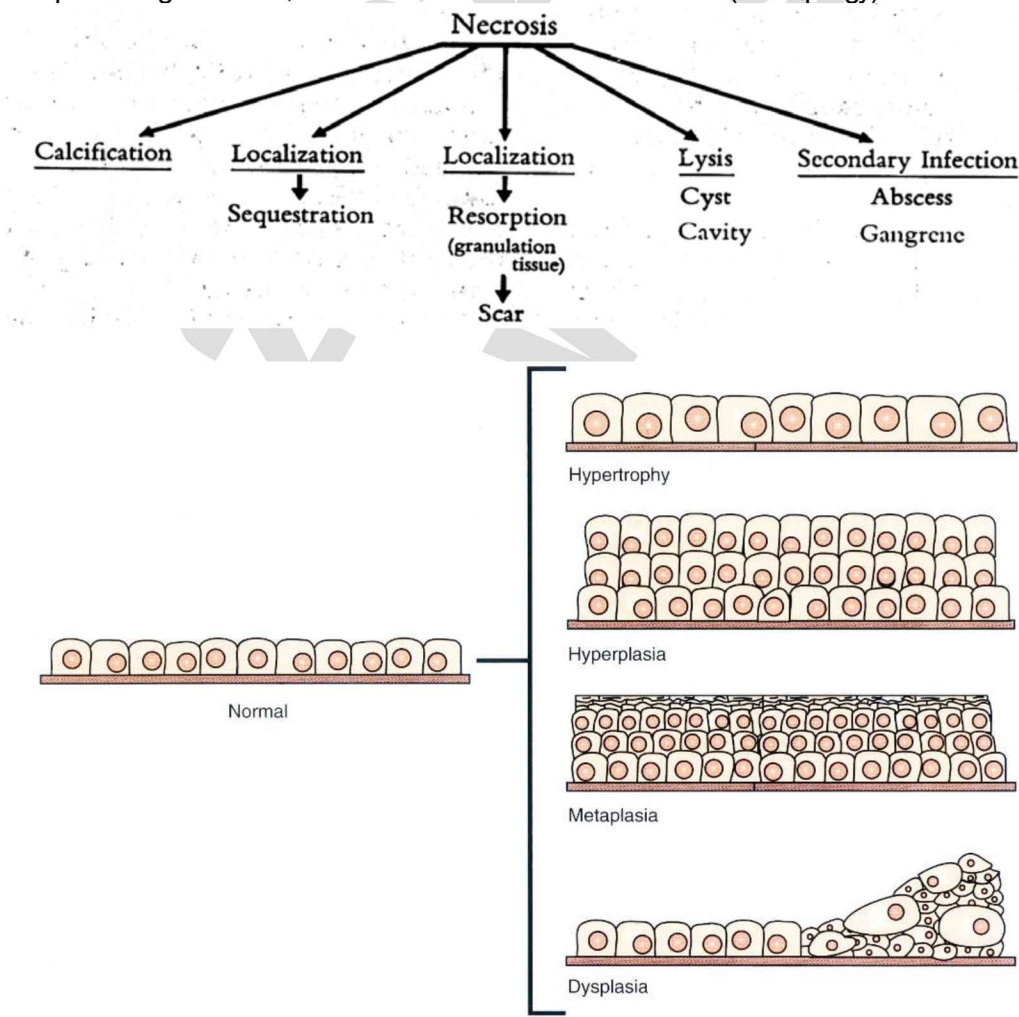
Mechanisms of apoptosis. Labeled (1) are some of the major inducers of apoptosis. These include specific death ligands (tumor necrosis factor [TNF] and Fas ligand), withdrawal of growth factors or hormones, and injurious agents (e.g., radiation). Some stimuli (such as cytotoxic cells) directly activate execution caspases (right). Others act by way of adapter proteins and initiator caspases, or by mitochondrial events involving cytochrome c. (2) Control and regulation are influenced by members of the Bcl-2 family of proteins, which can either inhibit or promote the cell's death. (3) Executioner caspases activate latent cytoplasmic endonucleases and proteases that degrade nuclear and cytoskeletal proteins. This results in a cascade of intracellular degradation, including fragmentation of nuclear chromatin and breakdown of the cytoskeleton. (4) The end result is formation of apoptotic bodies containing intracellular organelles and other cytosolic components; these bodies also express new ligands for binding and uptake by phagocytic cells.



The intrinsic (mitochondrial) pathway of apoptosis. Death agonist cause changes in the inner mitochondrial membrane, resulting in the mitochondrial permeability transition (MPT) and release of cytochrome c and other proapoptotic proteins into the cytosol, which activate caspases. AIF, Apoptosis-inducing factor.



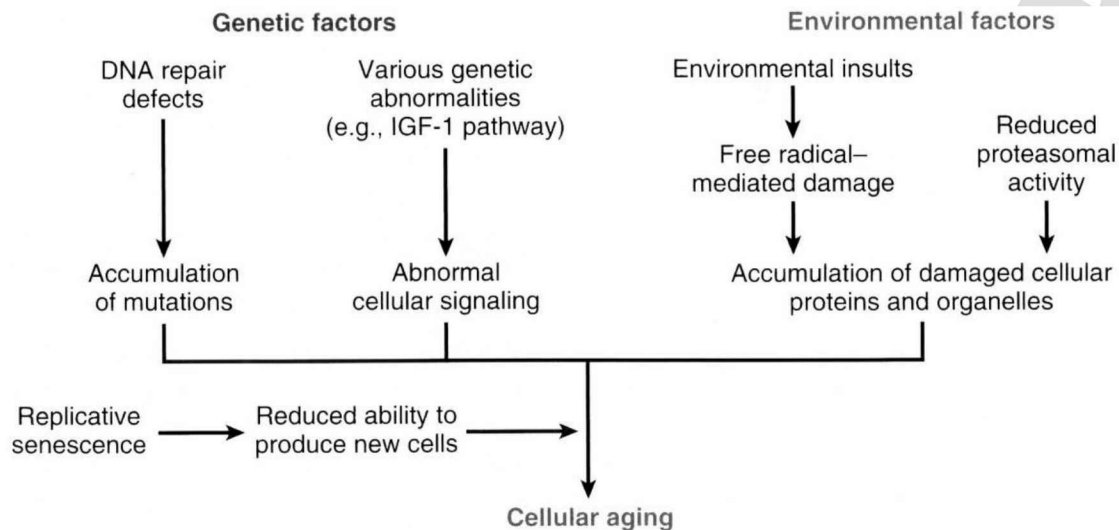
Autophagy and heterophagy. Schematic representation of heterophagy (left) and autophagy (right). The mechanisms are similar for processing cell debris, both from intrinsic and extrinsic sources (heterophagy).



Adaptive changes in epithelium

Differences between Lipofuscin and Most Ceroid Pigments in Vivo

	Lipofuscin	Ceroid
Universality (invariably present in humans and all domestic animals)	Yes	No
Intrinsically (intracellularly in lysosomes of postmitotic and stable cells)	Yes	No
Time dependence	Yes	No
Initial occurrence	Infancy	Anytime
Deleteriousness	Never demonstrated	Frequent
Accumulation rate	Very slow	Usually rapid
Tissue distribution	Only intracellular	Intracellular and extracellular
Mode of formation	Mainly autophagy	Mainly heterophagy
Origin of precursors	Mainly intracellular	Mainly extracellular



Mechanisms of cellular aging. Genetic factors and environmental insults combine to produce the cellular abnormalities characteristic of aging. IGF-1, Insulin-like growth factor-1.

Endothelial cells produce prostacyclin

1 Prostacyclin is formed by endothelial cells from arachidonic acid by a process catalyzed by prostacyclin synthase. Prostacyclin prevents the adhesion of platelets to the endothelium, and prevents intravascular clot formation.

Endothelial cells control vascular cell growth

Angiogenesis occurs during normal wound healing and vascularization of tumors. Endothelial cells secrete factors that stimulate angiogenesis.

Some of these factors induce endothelial cell proliferation and migration; others activate endothelial cell differentiation or induce a secondary cell type to produce angiogenic factors.

Endothelial cells modulate smooth muscle activity

Endothelial cells secrete smooth muscle cell relaxing factors (such as **nitric oxide**), and smooth muscle cell contraction factors (such as **endothelin-1**).

Vasoactive role

Endothelin-1 (vasoconstrictor)
Nitric oxide (vasodilator)

Smooth muscle cell

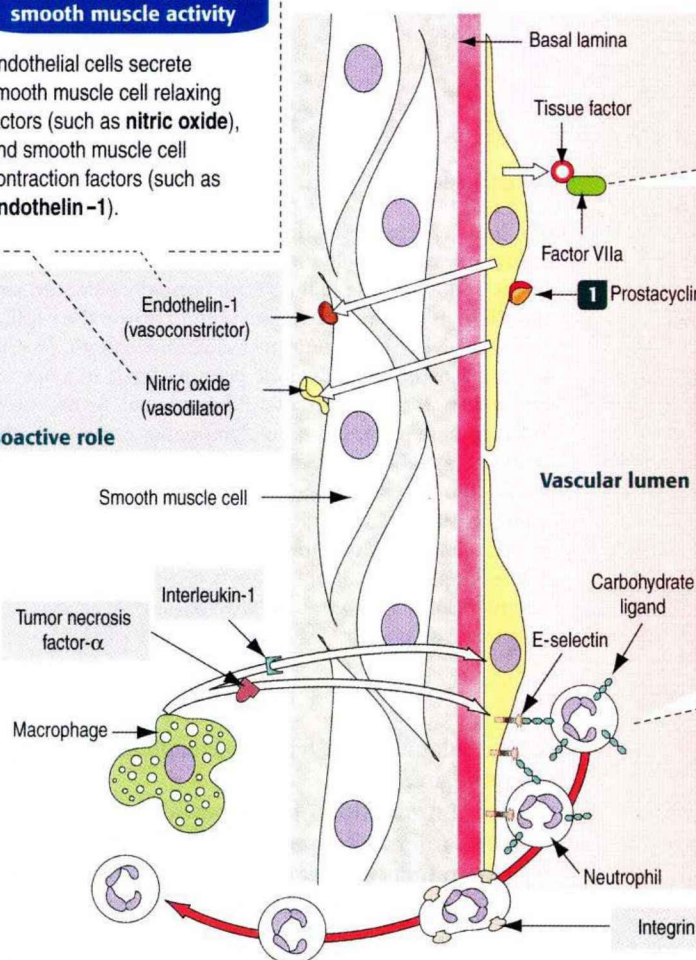
Endothelial cells trigger blood coagulation

Endothelial cells release **tissue factor** which binds to factor VIIa to convert factor X into factor Xa and initiate the common pathway of blood clotting.

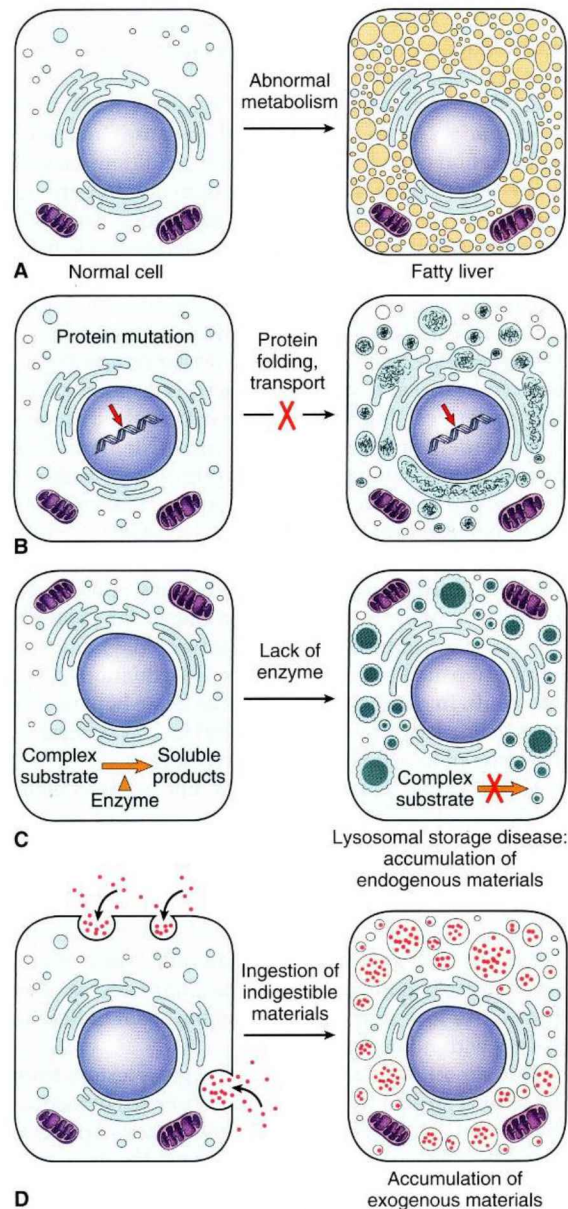
Thrombin (bound to its receptor on platelet surfaces) acts on fibrinogen to form fibrin monomers. **Fibrin monomers** self-aggregate to form a soft fibrin clot cross-linked by factor XIII. **Both platelets and fibrin form a hemostatic plug when there is an injury to the wall of a blood vessel.**

Endothelial cells regulate the traffic of inflammatory cells

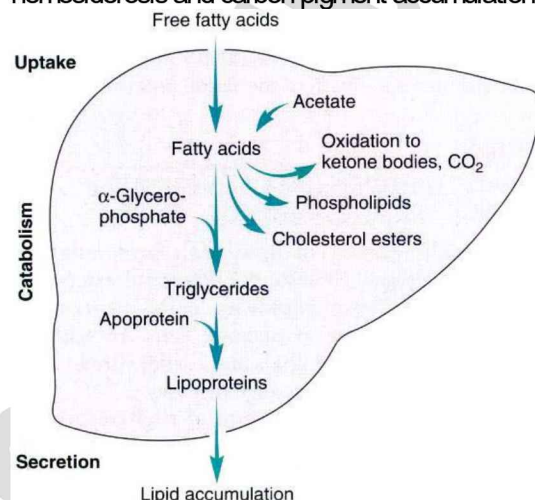
Endothelial cells facilitate transendothelial migration of cells involved in an inflammatory reaction (for example, **neutrophils**) in the surrounding extravascular connective tissue. **Activated macrophages** secrete **tumor necrosis factor- α** and **interleukin-1**, which induce the expression of **E-selectin** by endothelial cells.



Bioactive mediators from endothelial cells.



Mechanisms of intracellular accumulations. A, Abnormal metabolism, as in fatty change in the liver; B, mutations causing alterations in protein folding and transport, as in α 1-antitrypsin deficiency; C, deficiency of critical enzymes that prevent breakdown of substrates that accumulate in lysosomes, as in lysosomal storage diseases; And D, inability to degrade phagocytosed particles, as in hemosiderosis and carbon pigment accumulation.



Fatty liver. Schematic diagram of the possible mechanisms leading to the accumulation of

triglycerides in a fatty liver. Defects in any of the steps of uptake, catabolism, or secretion can result in lipid accumulation in the cell.

d. Types of Post-Mortem Changes

POSTMORTEM CHANGES

Terms used in reference to post-mortem conditions:

1. Rigor mortis - is the stiffening of muscles after death and relates to contraction of muscles fibers owing to depletion of ATP.
2. Algor mortis - the gradual cooling of the body after death.
3. Livor mortis is the gravitational settling of blood to the downside of the animal.

Other post-mortem changes:

1. imbibition with hemoglobin- discoloration results from breakdown of hemoglobin and the action of bacterial hydrogen sulfide on hemoglobin.
2. imbibition with bile
3. post-mortem clots (currant-jelly and chicken fat clots)

e. Pathological Pigmentation

Pigmentations may be exogenous, that is, derived from outside the body, or endogenous, produced within the body.

2 FORMS OF PIGMENTATION

1) EXOGENOUS PIGMENTATION -

- Exogenous pigmentations are usually caused by inhalation of compounds in mineral or organic dust and become visible in the respiratory tract and draining lymph nodes.

PNEUMOCONIOSIS

- occupational pathological pigmentations e.g., silicosis, anthracosis and asbestosis, are caused by chemical or dust inhalation.

ANTHRACOSIS

- occurs as a result of inhalations of carbon compounds. Important lesion for animals.

EXOGENOUS PIGMENTS

Examples: silver, lead, iron, carbon, dusts, tetracyclines, plant-derived (carotene), Aspergillus molds etc..

2) ENDOGENOUS PIGMENTATION - ENDOGENOUS PIGMENTS

1. MELANIN PIGMENTS

- Melanin is a normal pigment made by melanoblasts and melanocytes and present in cells, which receive it from melanocytes.
- Melanin pigmentation - granular protein containing pigment produced by melanocytes.

Increased production occurs in association with:

- excessive UV or sunlight exposures
- melanoma (tumors of melanocytes)
- excessive irradiation

Albinism - complete absence of melanin; a congenital defect.

Albino – individual affected.

Melanosis is the presence of melanin in abnormal location such as on the pleura, meninges or heart.

2. LIPID PIGMENTS

a. Lipofuscin

- yellowish-brown granules in the cytoplasm of affected parenchymal cells.
- also known as “wear and tear pigment”.

Vitamin E deficiency may hasten formation of lipofuscin formation.

b. Ceroid

- found in macrophages following tissue damage or hemorrhage or both.

3. HEMOGLOBIN AND PORPHYRIN DERIVATIVES

Hemoglobin derivatives

Hemoglobin.

- visible if released from red blood cells in large quantities.
- will appear microscopically as a distinctive reddish-orange color in renal tubules if it crosses the glomerulus.
- kidney is usually almost black in color when this occurs, and it is indicative of an acute hemolytic crisis e.g. is chronic copper poisoning in sheep and cattle.

1) Hematins

- results from the action of acid or alkali on hemoglobin.
- very common as “formalin pigment” when unbuffered formalin is used for fixation.

2) Hemosiderin

- iron-stored form pigment chemically known as ferritin seen in cases of trauma, excessive hemorrhage or hemolysis.
- Hemosiderin pigment is brown, contains iron and is usually present in macrophages of the reticuloendothelial system.
- Common in hemorrhagic and hemolytic lesions
- a common finding, and if quite prominent as a lesion, the term hemosiderosis is used.
- often called “heart-failure cells” – alveolar macrophages that did phagocytosis or picking-up of hemosiderin.

Hemochromatosis

- excess accumulation of non-iron staining brown pigment in hepatocytes and renal tubular epithelium.

Bilirubin– usually seen in association with jaundice.

- amount increases following excessive hemorrhage or hemolysis, and failure of the liver to conjugate bilirubin into bile.

Jaundice (or icterus), occurs when bilirubin is presented in the plasma in excess and all tissues are stained yellowish-brown.

Jaundice is of three types:

- a. Prehepatic or hemolytic jaundice
- b. Hepatic jaundice
- c. Posthepatic or obstructive jaundice

a. Prehepatic type- following acute hemolytic conditions excess bilirubin are brought to the liver in larger quantities to be conjugated with glucuronic acid. Because of its excessive quantity in the plasma, many cannot be processed, so it builds up in the blood as unconjugated bilirubin and with overload thence will accumulate in tissues.

- Excess conjugated bilirubin will also appear in the blood, feces and urine from the overload.

b. Hepatic jaundice occurs from direct damage to liver cells and there is release of conjugated and unconjugated bilirubin into the blood.

c. Posthepatic jaundice- in here, the bilirubin has passed through the liver but blocked from entry into the intestine (*i.e.*, tumor growth, parasites *etc.*)

Porphyria –

- abnormal synthesis of hemoglobin lead to porphyrin accumulation.
- accumulates in the blood may cause pigmentation of tissues along with jaundice and also photosensitization.

Porphyria- name of the condition and may be:

- a. congenital porphyria
- b. hepatotoxic porphyria
- c. primary porphyria

a. congenital type

- there is a metabolic defect in the steps of breakdown of porphyrins

b. hepatotoxic type

- accumulates when toxic damage to the liver impairs its normal degradation. The liver lesion is usually chronic and involves the bile duct system.
- arises from phylloerythrin, a metabolite of chlorophyll that has photosensitizing properties.

c. primary type

- caused by plants that contain compounds directly photosensitive by ingestion without hepatic injury.

f. Disturbance in Circulation

Impairment of the function, composition or structure of the blood or blood vessels may have serious consequences to the tissues.

Hemorrhage – when red blood cells escapes the blood vessels.

Escape of blood may occur by:

- a. rhexis – injured or destructed vessel
- b. diapedesis- intact vessel

Hyperemia – refers to a lesion in which excess blood may be drawn into an area. Usually on the arterial side of circulation.

Congestion – lesion where blood passively accumulates in an area. Usually on the venous side.

Infarct – refers to a lesion where blood may be kept from reaching an area of tissue and the tissue becomes necrotic.

a necrotized, vascular area blocked by embolic lesion.

Infarction – process of necrotizing an area blocked by thrombus or other embolic lesion.

Thrombus – an intravascular solid clot formed.

Thrombosis – refers to a process by which a blood may clot within blood vessels.

Embolus - a vascular space-occupying lesion.

- may be a dislodged blood clot, a parasite, or an air bubble.

Embolism – process whereby a floating mass may occlude vascular channels.

Shock – is the generalized failure of peripheral circulation.

HEMORRHAGE

Hemorrhages occur when red blood cells are present outside the blood vessels. The vessel may be physically damaged (hemorrhage by rhexis) so that the cells simply flow out through, or the cells may pass through an intact vascular wall by a process called diapedesis.

Petechial hemorrhage - tiny pinpoint hemorrhage measuring 1 to 2 mm sized foci

Ecchymotic hemorrhage - larger areas of hemorrhage measuring 2 to 3 cm in size

Paint-brush type - refers to extensive streaking with hemorrhage.

- (lesion as if someone literally splashed red paint on the tissue)

The above three types usually occur on serosal or mucosal surfaces and are visible but cannot be palpated.

Hematoma (or more appropriately HEMATOCYST) – occurs when sufficient red cells come out in one area to form a lump

Massive hemorrhage into a body cavity is called: hemopericardium, hemothorax or hemoperitoneum, depending on the area affected.

Purpura is a clinical term applied to an animal that has extensive petechial and ecchymotic hemorrhages on serous and mucous surfaces.

- more of a descriptive term.

Bruise – (skin lesion) is a result of hemorrhage.

Hemosiderin-laden macrophages and erythrophagocytosis are indications of former hemorrhage.

Diseases that result in marked bleeding tendencies are named hemorrhagic diatheses.

COMMON TERMINOLOGIES APPLIED TO HEMORRHAGES:

Ecchymosis (*pl. ecchymoses*) – hemorrhage measuring 2 to 3 cm in size; usually irregular and mottled in appearance.

Enterorrhagia – hemorrhage within the intestinal tract.

Epistaxis – nasal bleeding.

Extravasation – extensive hemorrhage within the tissue.

Hemarthrosis – hemorrhage in joint cavity.

Hematocysts (commonly termed as *hematoma*) – the accumulation of blood producing a lump. A “black-eye” is a classic example..

Hemopericardium – hemorrhage into the pericardial cavity.

Hemoptysis – spitting or expectoration with blood.

Hemothorax – hemorrhage into the thoracic cavity.

Metrorrhagia – passage of blood through the uterus.

Hematemesis – vomition of blood.

Hematochezia – defecation of blood.

Paint-brush hemorrhage – linear or streaked appearance of hemorrhage.

Petechia(e)– pinpoint hemorrhage one to two millimeter-sized foci

Purpura – ecchymotic and petechial lesions in the skin, mucous membrane or serosae which may be caused by various factors, including blood disorders, vascular abnormalities and trauma.

EDEMA – refers to the abnormal accumulation of fluid in tissue spaces.

- defined as excessive visible accumulation of extracellular fluid in interstitial tissues and in various body cavities.

- it may be a transudate or an exudate.

Edema is a lesion and not a disease.

In general, the etiology relates to changes in:

- a. hydrostatic pressure of blood
- b. osmotic pressure of blood and tissue fluid
- c. permeability changes of capillaries
- d. lymphatic obstruction

Recognition of Edema

Subcutaneous tissues may show swelling.

- excess clear fluid, most easily visualized beneath the skin or between the layers of mucous membranes or in lobules of the lung.

- in histopathology, it appears as homogenous “PINK-STAINING” material by usual H & E.

Anasarca - generalized edema.

- extreme edema in the entire body, as occurs in some aborted fetuses.

Pulmonary edema - a common lesion affecting lungs and is often the immediate cause of death in many different disease conditions. (*i.e.* resultant of left congestive heart failure or LCHF)

Edema is a characteristic lesion in some specific diseases.

- “gut edema” caused by *Escherichia coli* in pigs

- “malignant edema” caused by *Clostridium septicum* in several species.

Hydrothorax – excess fluids in the thoracic or pleural cavity.

- this lesion arises from leakage of surface pleural lymphatic vessels in very edematous lungs.

Hydropericardium - excess fluids in pericardial sac.
- arises from excess flow of lymph within the myocardium, usually as a result of vascular damage or degeneration in the myocardium.

Ascites or hydroperitoneum – excess fluids in peritoneal cavity.

Ascites occur when there is:

- 1) heart failure though increased venous hydrostatic pressure in abdominal organs, particularly in the liver.
- 2) fibrotic or chronic liver diseases and chronic congestion may also cause of ascites.
- 3) reduced flow of blood in the kidney in chronic renal failure activates the renin system and eventually raises blood volumes and the intravascular hydrostatic pressure.
- 4) hypoproteinemia.

Note: Bouin's fluid or solution – fixative of choice to retain edema lesion.

TYPES OF EDEMA

1. Localized edema
2. Generalized edema (as in anasarca).

In Active Process, edema is an:

EXUDATE – (an inflammatory effusion or edema)

Characterized by:

1. high protein content
2. increased specific gravity
3. increased number of inflammatory cells

In Passive Process, edema is a:

TRANSUDATE – (a non-inflammatory effusion or edema)

Characterized by:

1. low protein content
2. low specific gravity
3. low or absence of inflammatory cells

ISCHEMIA, THROMBOSIS AND INFARCTION

ISCHEMIA

Ischemia - is a localized anemia

- a reduction of blood flow to an area (usually arterial blood).

Ischemia may be caused by:

- a) Compression of blood vessels
- b) Obstruction of blood vessels (thrombosis, embolism)

Ischemia results to infarction (if it lodges in organs with so called "end arteries" such as the kidneys, spleen and brain).

- if partial or gradual, atrophy may result.

Infarction

- refers to acute ischemic coagulation necrosis of an area of tissue.

- the area of necrotized tissue is called an infarct.

ALTERATIONS IN BLOOD COAGULATION

A review of blood clotting is a must in understanding pathologies involving coagulation process.

Simply, coagulation refers only to the formation of fibrin (a clot).

Changes in Blood Coagulation

1) Disseminated Intravascular Coagulation (DIC) - refers to a pathological formation of blood clots in the living animal body, and denotes a defect in hemostasis.

Mechanism involved in DIC include the following:

- a) Activation of the intrinsic clotting mechanism independent of tissue damage – this occurs following activation of Hageman factor (Factor XII) following shock, loss of fibrinolysis in kidney disease, and increased fibrinogen in moribund animals.
- b) activation of the extrinsic clotting mechanism – occur in widespread tissue injury releasing tissue thromboplastin.
- c) direct activation of prothrombin by proteolytic enzymes – occur in pancreatitis (i.e., trypsin) and in snakebites.

Effects of DIC include hemorrhagic diatheses or uncontrolled bleeding tendencies (consumptive coagulopathy and shock).

Thrombus – refers to ante-mortem intravascular blood clot.

- is a solid structure formed in the blood stream from the normal constituents of the blood.

Thrombosis - the process by which a thrombus is formed, formation of intravascular blood clots adherent within blood vessels. Its formation is influenced by three factors which is classically known as the Virchow's triad of thrombosis.

Virchow's triad of thrombosis:

1. changes in the rate of flow or hemodynamics
2. changes in the vessel wall
3. changes in the blood itself

Results of Thrombosis

The result of thrombosis may be as follows.

1. Lysis and complete removal occur in a minor vascular injury through resorption of the fibrin by fibrinolysis and neutrophils.
2. Plasmin is formed from a beta globulin called plasminogen, a normal component of serum, and is activated during stress, infection or shock, as well as being released from injured tissue.
1. Contraction of a thrombus will occur if it remains on a surface.

Hyaline thrombi - thrombi in capillaries.

Thrombi may be red, white or laminated.

May be septic or nonseptic.

May be valvular if on the valves of the heart; or mural if on the wall of a vessel.

Thrombi may also be arterial, venous, capillary or lymphatic.

Thrombi are usually attached to blood vessel wall.

May break, detach and become an EMBOLUS.

Embolism - refers to a process where a solid mass is transported from one part of the body to another through the circulatory system.

The mass is called embolus (*p.l. emboli*)

Embolism is a common cause of infarction.

Emboli can be:

1. fragments of thrombi
2. parasites
3. mass of bacteria, fungi
4. foreign bodies
5. gas bubbles
6. groups of tumor cells
7. venipuncture of skin or hair
8. fats or oils

SHOCK

- a generalized failure of peripheral circulation.

Shock is a clinical term that means peripheral circulatory failure with pooling of the blood in the terminal circulatory bed in small vessels.

The causes of shock may be classified as:

1. septic
2. hypovolemic
3. cardiogenic
4. neurogenic

LESIONS THAT MAY INDICATE SHOCK

1. Congestive Atelectasis

Severe congestive lesion on lungs found at postmortem indicates shock due to pooling of blood in respiratory bed.

2. Visceral Pooling.

This happens in animal that die with a failing circulation whereby considerable fluid may be present in the intestine, and the fluid contains so many red cells that the fluids look like blood. This blood may have seeped through by diapedesis.

3. Acute Renal Tubular Necrosis.

Increased blood volume may be detrimental, as in heart failure. The renal lesions associated with shock arise from excessive vasoconstriction in the initial stages of the sequence, to the point that acute ischemic degeneration and necrosis occur randomly throughout the kidney.

4. Sludging.

This refers to slowing down of the circulation, settling out of red cells from plasma and increased stickiness of blood. Sludging is common in shock.

5. Disseminated Intravascular Coagulation (DIC).

This refers to widespread, or at times localized, formation of microthrombi in capillaries, arterioles and venules. DIC in intravascular coagulation and can arise by way of the extrinsic or intrinsic systems or by stasis of flow. The lesions of DIC are common in acute gram-negative septicemia in animals (such as hemorrhagic septicemia in cattle due to *Pasteurella multocida*). DIC may also be caused by antigen-antibody complexes, tissue damage, intravascular hemolysis, systemic hypersensitivity or by extensive diffuse endothelial damage.

ACIDOSIS AND ALKALOSIS

Normal blood pH (7.35 and 7.45)

Bicarbonate-carbonic acid – main buffer system

Excess bicarbonates – alkalosis

- happens with prolonged vomiting

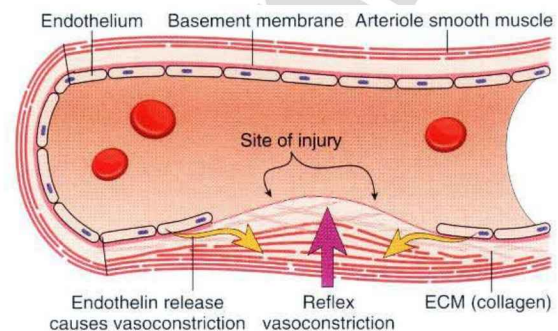
Excess carbonic acid – acidosis

- happens with prolonged diarrhea

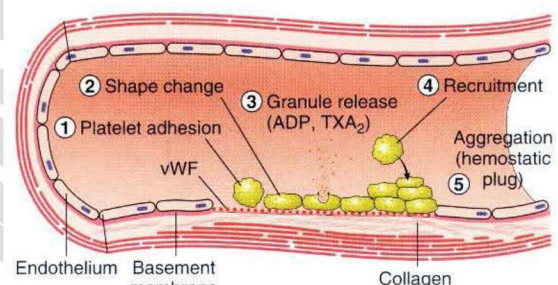
Dehydration – refers to loss of body fluids (also plasma fluids).

Clinically:

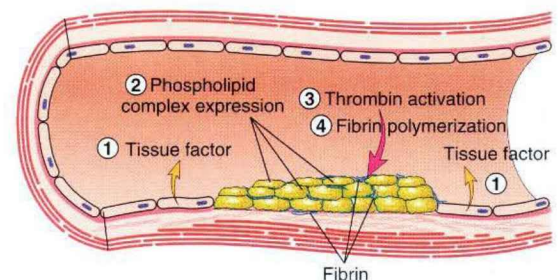
1. sunken eyes
2. loss of elasticity in the skin.



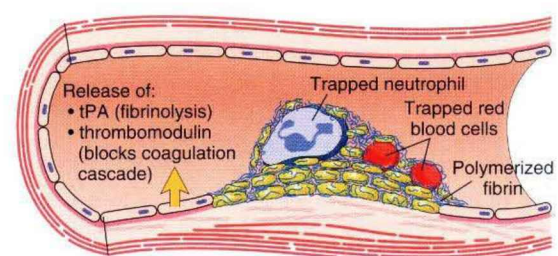
A VASOCONSTRICTION



B PRIMARY HEMOSTASIS



C SECONDARY HEMOSTASIS

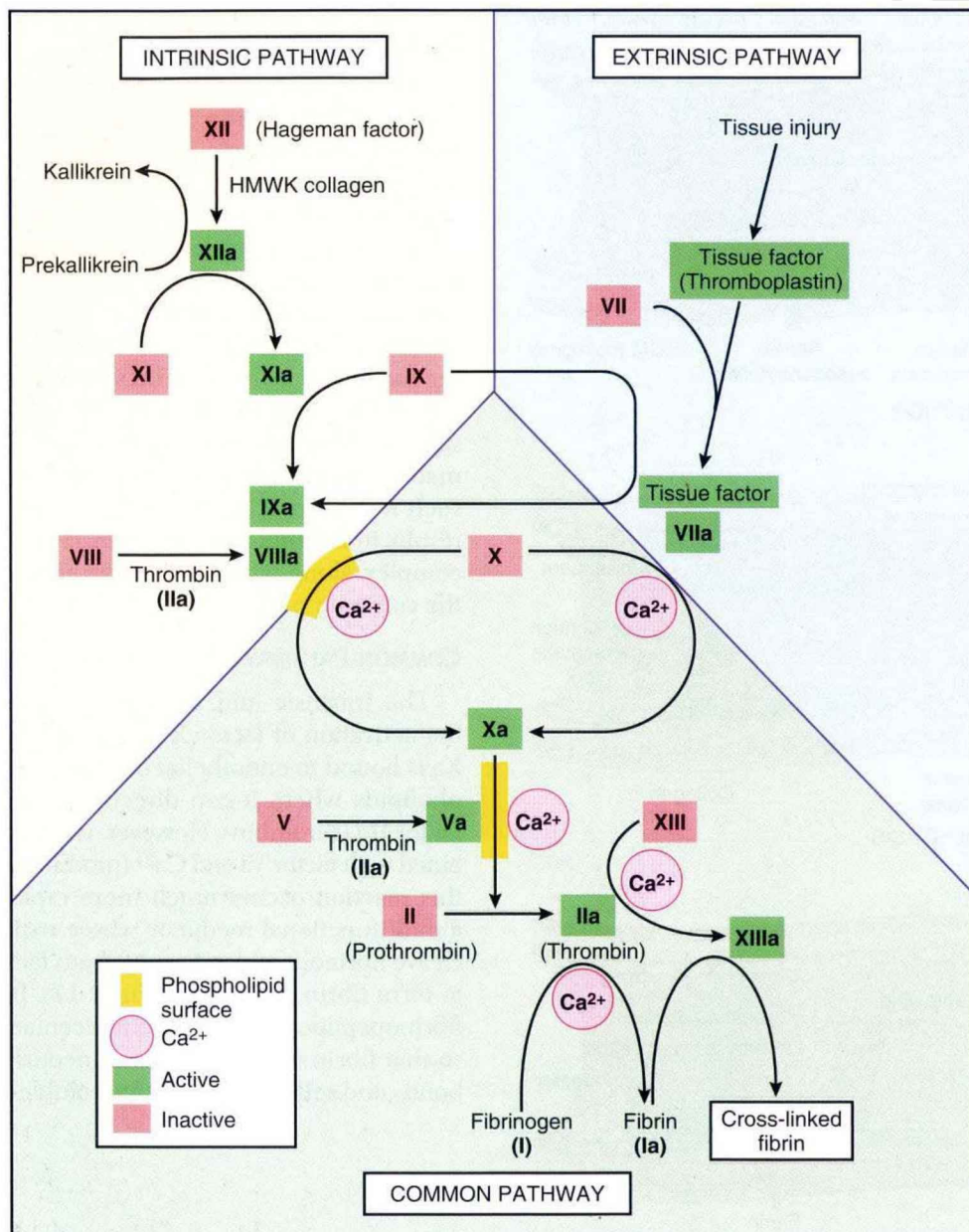


D THROMBUS AND ANTITHROMBOTIC EVENTS

Diagrammatic representation of the normal hemostatic process. A, After vascular injury, local neurohumoral factors induce a transient vasoconstriction. B, After endothelial injury and disruption that exposes the subendothelial extracellular matrix (ECM), platelets adhere to the ECM via von Willebrand's factor (vWF) and are activated, undergoing a shape change and granule release; released ADP and thromboxane A₂ (TXA₂) lead to further platelet aggregation to form the

primary hemostatic plug. C. Local activation of the coagulation cascade (involving tissue factor and platelet phospholipids) results in fibrin polymerization, “cementing” the platelets into a definitive secondary hemostatic plug. D. Counter-regulatory mechanisms,

such as release of tissue plasminogen activator (tPA) (fibrinolytic) and thrombomodulin (interfering with the coagulation cascade), limit the hemostatic process to the site of injury.



The coagulation cascade. Note the common link between the intrinsic and extrinsic pathways at the level of factor IX activation. Factors in red boxes represent inactive molecules; activated factors are indicated with a lower case “a” and dark background. PL, Phospholipid surface; HMWK, high molecular weight kininogen. Not shown are the anticoagulant inhibitory pathways.

Highlights on Thrombosis, Embolism, and Aneurysm

1. Thrombus

- is an aggregation of blood factors that may form when the blood flow in the arteries or veins is impeded.
- It frequently causes vascular obstruction at its site of origin.
- The thrombus can be classified based on its location and the syndrome it produces (eg, venous thrombosis in large animals associated with prolonged venous catheterization, pulmonary arterial thrombosis associated with heartworm disease in dogs).

- All or part of a thrombus may break off and be carried through the bloodstream as an embolus that lodges distally at a point of narrowing
- Embolization can also occur when foreign material (eg, bacteria, air, fat, catheter piece) is carried into the bloodstream.
- Thrombi and emboli can be septic or nonseptic.
- If left untreated or uncontrolled, these hypercoagulable conditions can result in hemorrhagic diathesis and/or disseminated intravascular coagulation (DIC), a life-threatening disorder of hemostasis with deposition of microthrombi with concurrent hemorrhage.

- Horses and cattle are more likely to develop thrombi affecting the postcapillary circulation, while in dogs and cats arterial thrombi are more clinically important.
- 2. Aneurysm
 - is a vascular dilation caused by weakening of the tunica media of blood vessels.
 - The weakness might be primary or caused by degenerative or inflammatory changes progressing from an intimal lesion.
 - Disruption of the endothelium associated with a true aneurysm can cause formation of a thrombus with subsequent embolization; thus, aneurysms, thrombi, and emboli may be recognized simultaneously.
- ✓ In horses, migrating *Strongylus vulgaris* larvae can cause arteritis with development of thrombi and verminous aneurysms in the aorta, cranial mesenteric, or iliac artery.
In some horses, emboli develop and partially or completely occlude terminal branches of the mesenteric arteries.
Affected intestinal segments show changes ranging from passive congestion to hemorrhagic infarction.
- ✓ In dogs, and less commonly in cats, heartworm disease may lead to pulmonary arterial thrombosis; pulmonary embolism is a major secondary effect.
- ✓ Pulmonary thromboemboli most commonly produce dyspnea and tachypnea, and abnormal lung sounds sometimes can be heard during thoracic auscultation.
- ✓ In dogs, other diseases associated with pulmonary thromboembolism include ones that result in systemic or metabolic disorders (eg, diabetes mellitus, glomerulonephropathy, hyperadrenocorticism, immune-mediated hemolytic anemia, neoplasia, renal amyloidosis).
- ✓ In cats, aortic thromboembolism is a frequent complication of cardiomyopathy
- ✓ Hypertrophic and dilated cardiomyopathy, create abnormal circulatory patterns, which predispose to intracavitary thrombus formation.

g. The Inflammatory Process

Inflammation Defined

Inflammation is the vascular and cellular responses of living tissue to injury.

A definition of inflammation is complicated because the local vascular and tissue reactions may be accompanied by systemic effects that include malaise, fever, leukocytosis metabolic disturbances and shock.

Inflammation is the directed tissue response to noxious and injurious external and internal stimuli.

Causes of Inflammation

The following are general etiologies of inflammation.

1. Pathogenic microorganisms – (the toxic and injurious substances produced by microbes).

Included are bacteria, viruses, protozoa, fungi and parasitic metazoa.

2. Chemical injuries – toxins, free radicals, drugs, acids, alkalis etc.
3. Mechanical and thermal injuries (physical) – burns, heat, irradiation, excessive cold as well as trauma, blows, lacerations, pressure.
4. Immune reactions – antigen-antibody complexes, hypersensitivity reactions, immune depositions etc.

Functions of the Inflammatory Response

To minimize the effect of an irritant in the injured tissue is the goal of inflammatory response. This is done by accumulation of fluids and cells in the injured area. The overall plan for this fluids and cells are to:

1. to dilute
2. to localize
3. to destroy
4. to remove

Advantages and Disadvantages of Inflammation

ADVANTAGES

1. It protects the surrounding healthy tissue by localizing and isolating the injured or infected tissue.
2. Inflammatory processes neutralize and inactivate toxins.
3. It destroys and inhibits the growth of pathogenic microorganisms.
4. It readies the injured area for healing and repair by eliminating damaged tissue and necrotic cell debris.

DISADVANTAGES

1. It can result to excessive scar tissue formation as with keloids, contractures, adhesions etc.
2. Varying degrees of disabilities as result of pain and swelling.
3. Tissue compression, vessel rupture and hemorrhage.
4. Formation of cavity, sinus and fistula.
5. Aggravates inflammation by destruction of surrounding intact tissues.
6. Development of inflammatory diseases such as glomerulonephritis, hypersensitivity illness.

Cardinal Signs of Inflammation

Cornelius Celsus (30BC to 30 AD) formulated the 4 cardinal features of inflammation:

1. *rubor* - REDNESS
2. *tumor* - SWELLING
3. *calor* - HEAT
4. *Dolor* - PAIN
5. *functio laesa* - LOSS OF FUNCTION

DEFINITION OF TERMS

Exudation. The escape of fluid and blood cells from the vascular system into the interstitial tissue or body cavities.

Exudate. An inflammatory extravascular fluid that has a high protein concentration, much cellular debris, and a specific gravity above 1.020.

Transudate. A fluid with low protein content and a specific gravity of less than 1.012. It is essentially an ultra filtrate of blood plasma and results from hydrostatic imbalance across the vascular endothelium.

Edema. Denotes an excess of fluid in the interstitial tissue or serous cavities; it can be either an exudates or a transudate.

Pus. A purulent inflammatory exudates rich in leukocytes and parenchymal cell debris.

MEDIATORS OF INFLAMMATION

A. Vasoactive amines (i.e., histamines and serotonin) are responsible for hemodynamic and vascular changes.

1. Histamine

a. **Source.** Most of the body's histamine is stored in the granules of mast cells. Also found in basophils and platelets.

b. **Release.** Histamine is released by degranulation in response to various stimuli such as, physical factors (heat, cold, trauma, radiation), type 1 hypersensitivity reactions, C3a and C5a (referred to as anaphylatoxins), and cationic lysosomal proteins.

c. Actions

(1) Once released, histamine causes direct vascular effect. Some degree of vasoconstriction (which varies according to animal species) almost always occurs, followed by vasodilation (which is the stage of observable hyperemia). Histamine also causes an increase in the vascular permeability of small veins and venules.

(2) Histamine also has been shown to be chemotactic for eosinophils.

2. Serotonin

a. **Source.** Most of the body's serotonin is stored in the gastrointestinal tract and central nervous system; a much smaller proportion exists in the dense granules of platelets.

B. Plasma factors

1. The kinin system, when activated, leads to the formation of bradykinin.

a. **Generation of bradykinin.** When plasma comes in contact with collagen, endotoxin, or basement membrane proteins, a there is an activation of clotting factor XII (Hageman factor). This is followed sequentially by Kallikrein formation, which then converts high molecular-weight kininogen (HMMK) to bradykinin.

2. The complement system, an important mediator of the inflammatory process, contains 9 major plasma proteins, termed complement components.

a. **Activation of complement.** Critical to the biologic action of the complement system is the activation, or cleavage, of complement component C3, which forms C3a. This can occur in two pathways.

1. In the classical pathway, circulating antigen-antibody complexes activate the system and by successive steps of cleavage and combination, generate complement components C3a and C5a.

2. In the alternate pathway, nonimmunologic stimuli (e.g. bacterial endotoxin) activate the system and lead to cleavage of C3.

b. Actions

1. Both C3a and C5a are chemotactic for neutrophils and play an important role in the increased vascular permeability caused by histamine release from mast cells.

2. Following complement cascade activation (by either pathway), C5, C6, and C7 in combination also become chemotactic.

3. C5b through C9 (termed the membrane attack sequence) appears to be involved in injury to parenchymal cells.
(C5b6789 – called the “MEMBRANE ATTACK COMPLEX” or MAC).

C. Arachidonic acid metabolite

1. Prostaglandins are a group of compounds derived from arachidonic acid via the cyclooxygenase pathway.

Prostaglandins E₂ (PGE₂) and PGI₂ (prostacyclin) are potent vasodilators; involved in edema formation by potentiating the effects of histamines. PGE₂ produces pain; potentiating the effects of bradykinin, and acts on the hypothalamic mechanism of fever production.

PGI₂ inhibits platelet aggregation.

PGD, PGF_{2a} are also vasodilators and vasoconstrictor and agents of platelet aggregation (PGG, PGH, thromboxaneA₂)

2. Leukotrienes, derived from arachidonic acid metabolite but by the lipoxygenase pathway.

Leukotriene B₄ (LTB₄) is a potent chemotactic agent for neutrophils and monocyte-macrophages. LTC₄, LTD₄ and LTE₄ are powerful stimulator of vascular permeability, with a 1000 times the potency of histamine. They also cause vasoconstriction and bronchoconstriction.

D. Leukocyte substances, such as proteases, hydrolytic enzymes and cationic proteins are activators of inflammation.

E. SRS-A (slow reacting substances of anaphylaxis), a low molecular weight lipid found in mast cells.

- Vasoconstriction and bronchoconstrictor.

F. Lymphokines are biologically active substances produced by T cells during immune reactions, particularly cell-mediated immune reactions and antibody responses.

1. Chemotactic factors

- Macrophage chemotactic factor (MCF)
- Neutrophil (NCF)
- Eosinophils (ECF)

2. Migration inhibition factor (MIF)

3. Macrophage activating factor (MAF)
4. IL-2 (interleukin 2), produced by T cells that has been stimulated by IL-1 released by macrophages.
5. Interferon are glycoproteins that have varied antiviral and antitumor effects.

Classification of Inflammatory Lesions

Inflammation are classified according to:

1. Degree of Severity
 - a. *mild* – presents little or no tissue destruction.
 - b. *moderate* – usually contain some damage to host tissue, and an easily visible host reaction to the injury manifest by leukocytic accumulation and vascular phenomena.
 - c. *severe* – are extensions of moderate reactions in which considerable tissue damage is present along with abundant exudation.
2. Duration
 - a. *peracute* – manifested very soon after initiation; perhaps only a few hours and is usually caused by a potent stimulus.
 - b. *acute* – usually begins within 4-6 hours and can remain fairly constant in appearance, depending on the initiator, for several days.
 - c. *subacute* – may cover a considerable time span between truly acute reactions and those in which evidence of chronicity becomes apparent. It is an intermediate time frame that can vary from a few days to a few weeks, depending on the nature of the inciting stimulus.
 - d. *chronic* – a prolonged inflammation, usually caused by a persistent agent. Conversely, it is more than just a time frame. It represents a rather specific entity in which inflammation is accompanied by tissue reparative processes.
 - chronic inflammation occurs when healing of acute inflammation is incomplete.

KEY FEATURES TO CHRONICITY

- 1) it often is caused by a persistent inflammatory stimuli in which the host failed to completely rid the tissue of the invader.
- 2) the inflammatory response is usually accompanied by an immune response due in part to the persistence of the invader.
- 3) it is usually highlighted by evidence of host tissue contribution in terms of reparative responses, *i.e.*, fibrosis.
- 4) it is characterized histologically by both mononuclear cell infiltrates and by connective tissue cells such as fibroblasts.

CELLULAR PHASE OF INFLAMMATORY RESPONSE

1. Margination and pavementing
2. Diapedesis (emigration)
3. Chemotaxis
4. Phagocytosis

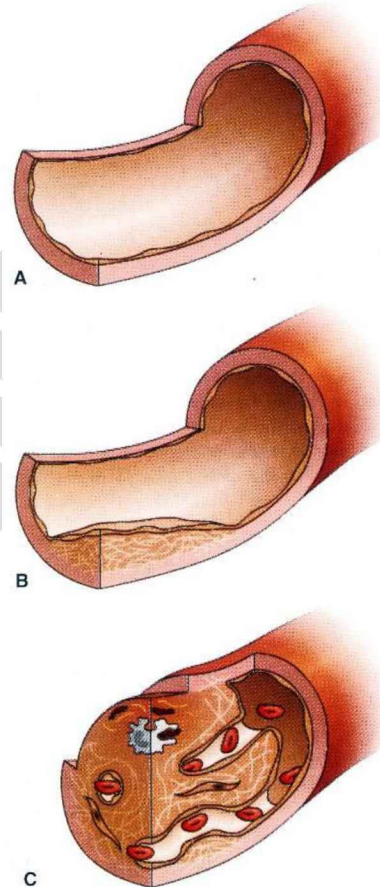
Examples in use:

Mild acute diffuse serous mesenteric lymphadenitis

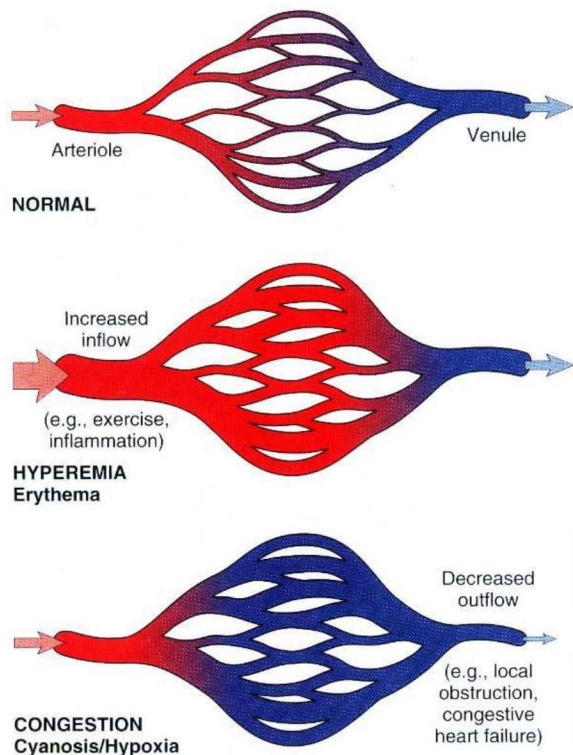
Severe extensive lymphoproliferative proventriculitis
Moderate chronic-active multifocal granulomatous segmental bronchitis

Classification of Inflammatory Lesions Distribution

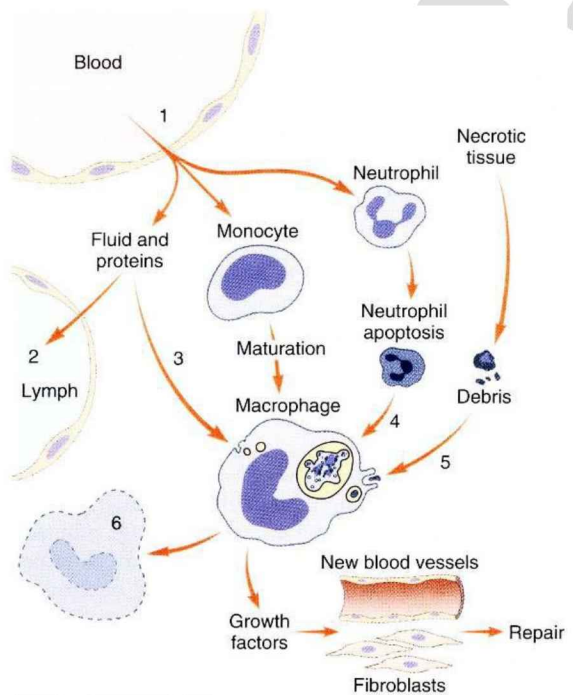
- a. *Focal*
- b. *Multifocal*
- c. *Locally extensive*
- d. *Diffuse*



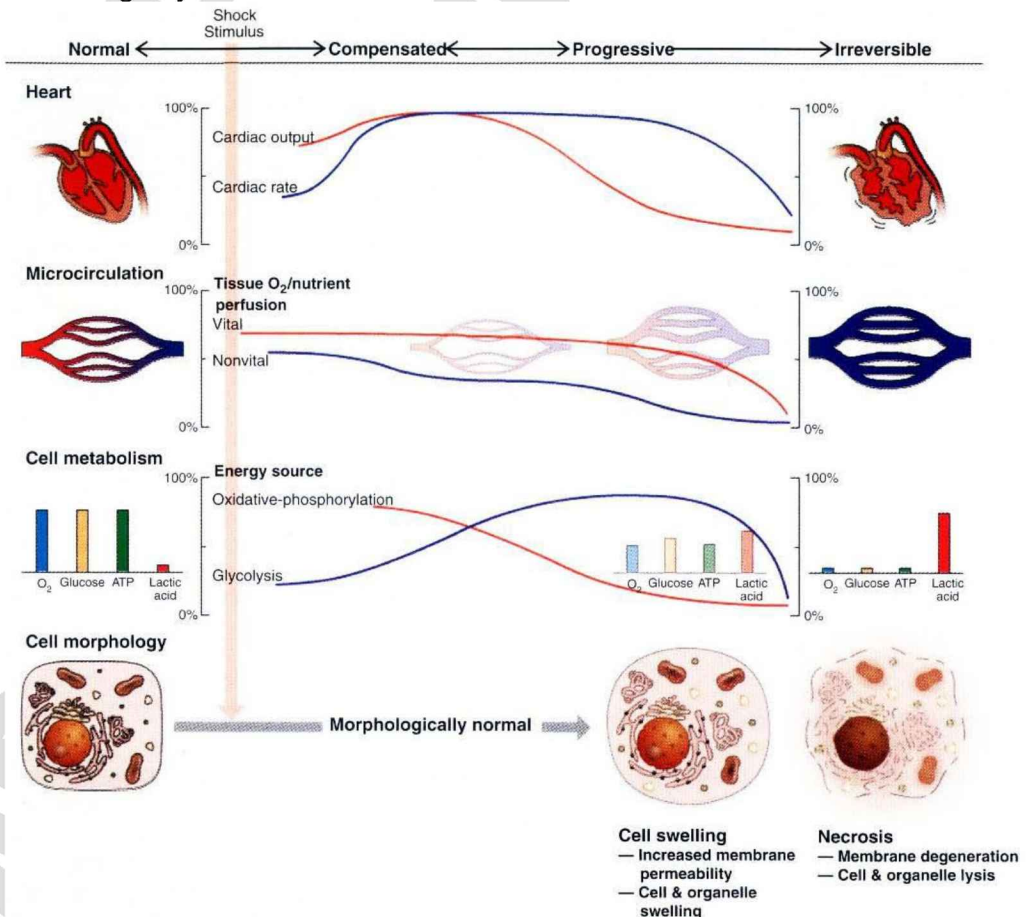
Thrombus resolution. A, Small thrombi are removed by thrombolysis, and the blood vessel returns to normal structure and function. B, Larger, more persistent thrombi are resolved by removal of thrombotic debris by phagocytes with subsequent granulation tissue formation and fibrosis with regrowth of endothelium over the surface to incorporate the affected area into the vessel wall. C, In large mural or occlusive thrombi that are not removed by thrombolysis or phagocytosis of the thrombotic debris, the thrombus is organized by the invasion of fibroblasts and later by the formation of new vascular channels (recanalization), which provides alternate routes for blood flow through and around the site of the original thrombus.



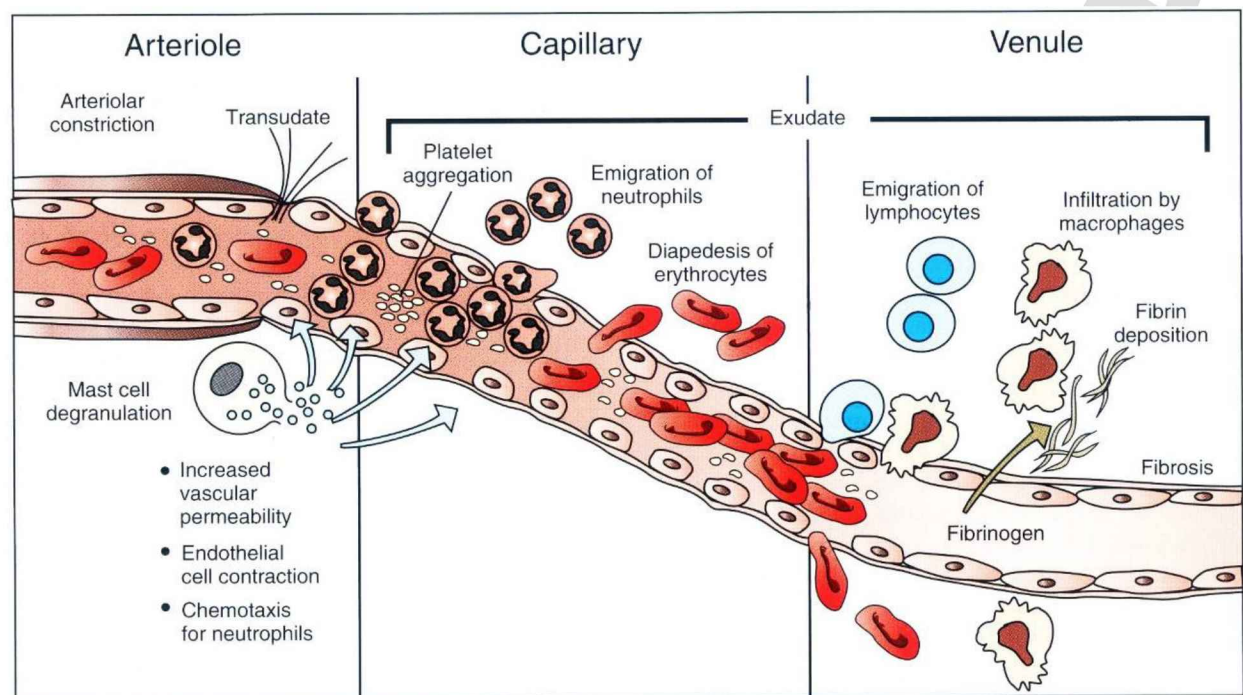
Hyperemia versus congestion. In both cases, there is an increased volume and pressure of blood in a given tissue with associated capillary dilation and a potential for fluid extravasation. In hyperemia there is increased inflow leading to engorgement with oxygenated blood. In congestion, diminished outflow leads to a capillary bed swollen with deoxygenated venous blood resulting in cyanosis.



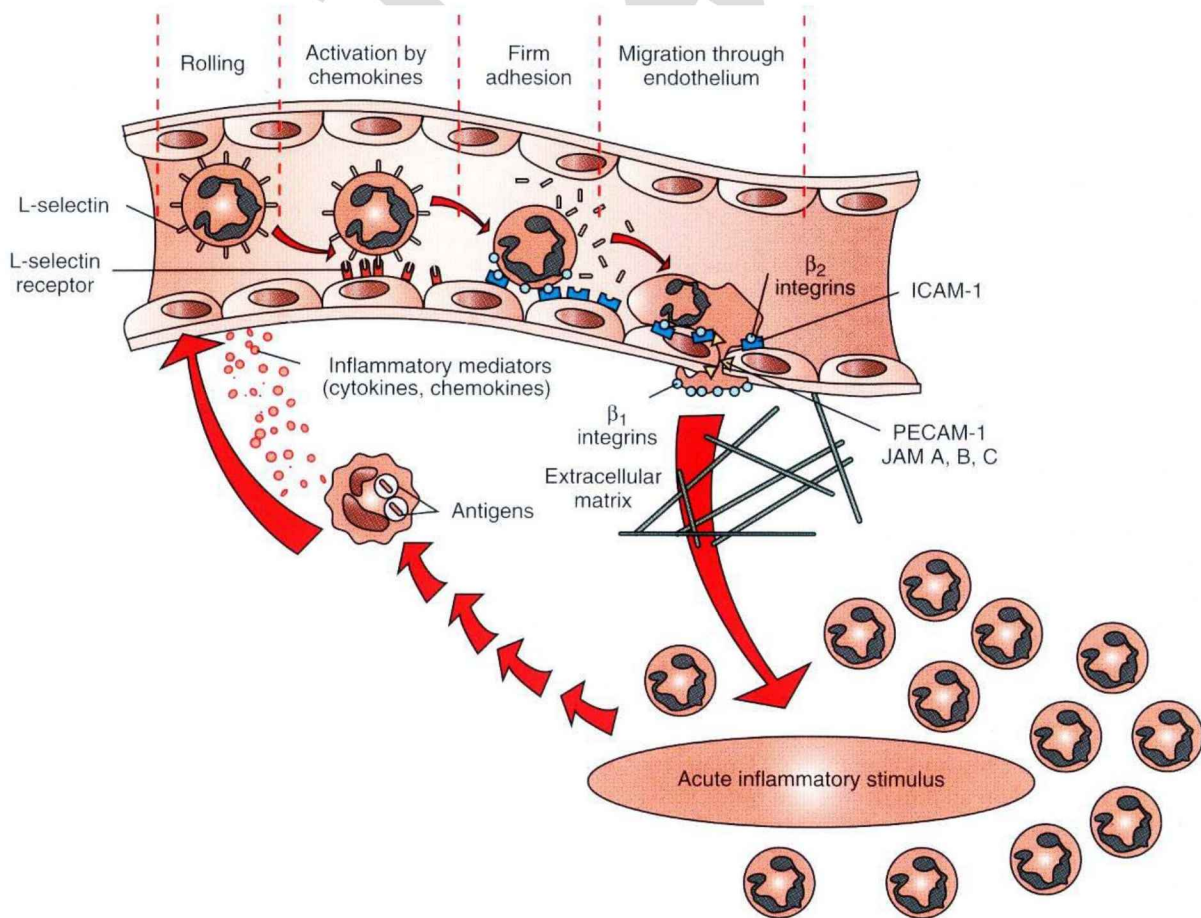
Events in the resolution of inflammation. (1) Return to normal vascular permeability; (2) drainage of edema fluid and proteins into lymphatics or (3) by pinocytosis into macrophages; (4) phagocytosis of apoptotic neutrophils and (5) phagocytosis of necrotic debris; and (6) disposal of macrophages. Macrophages also produce growth factors that initiate the subsequent process of repair. Note the central role of macrophages in resolution.



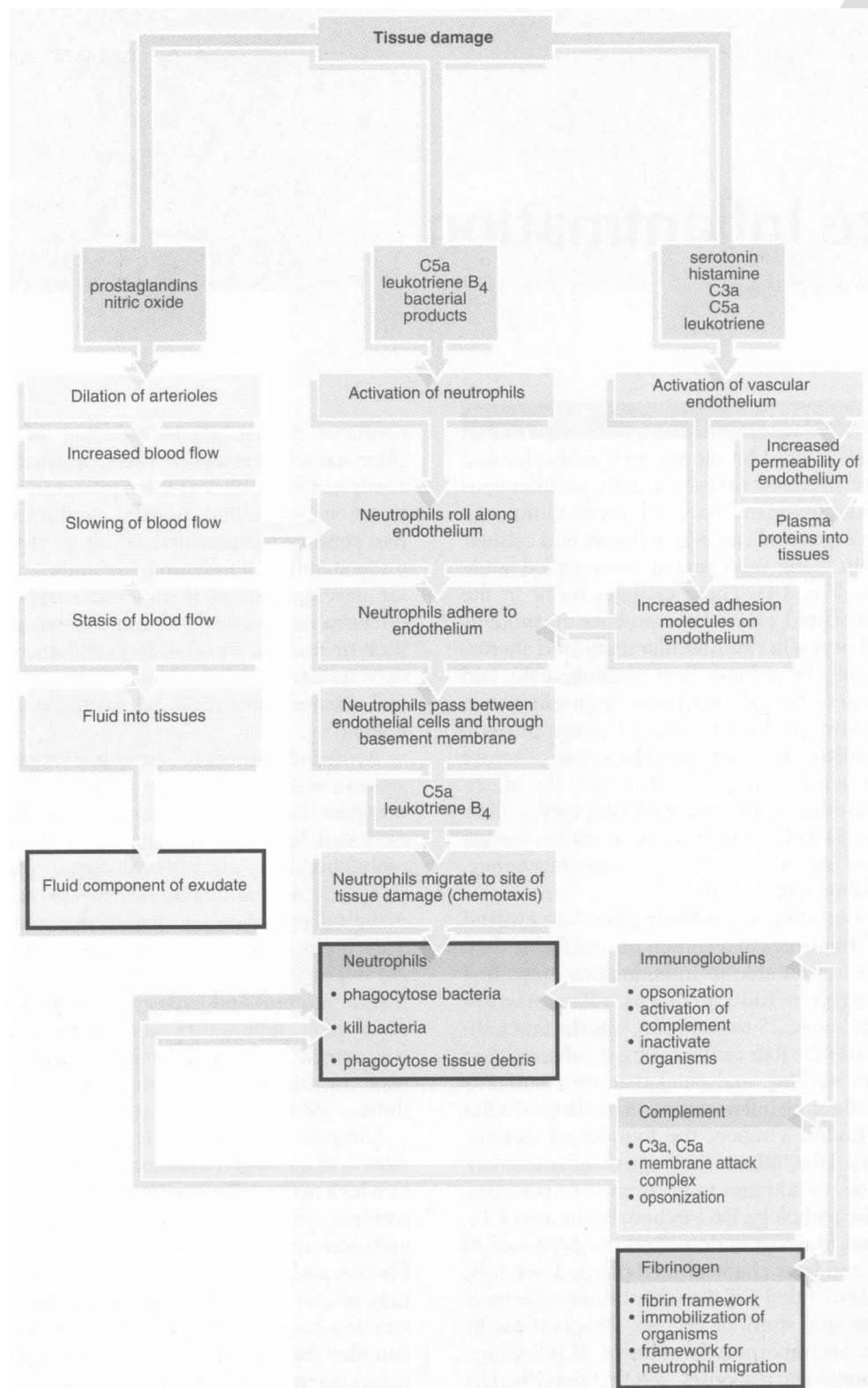
Shock. In hypovolemic shock, there is initially compensation characterized by increased cardiac rate and output, vasoconstriction of nonessential vascular beds, and predominantly oxidative metabolism by morphologically normal cells. With progression, cardiac output falls as peripheral vasodilation occurs and cell metabolism shifts to glycolysis with progressive morphological changes in cells.



The principal cellular and vascular responses during the inflammatory response. The majority of leukocyte transmigration and hemorrhage occurs in the capillaries and postcapillary venules.

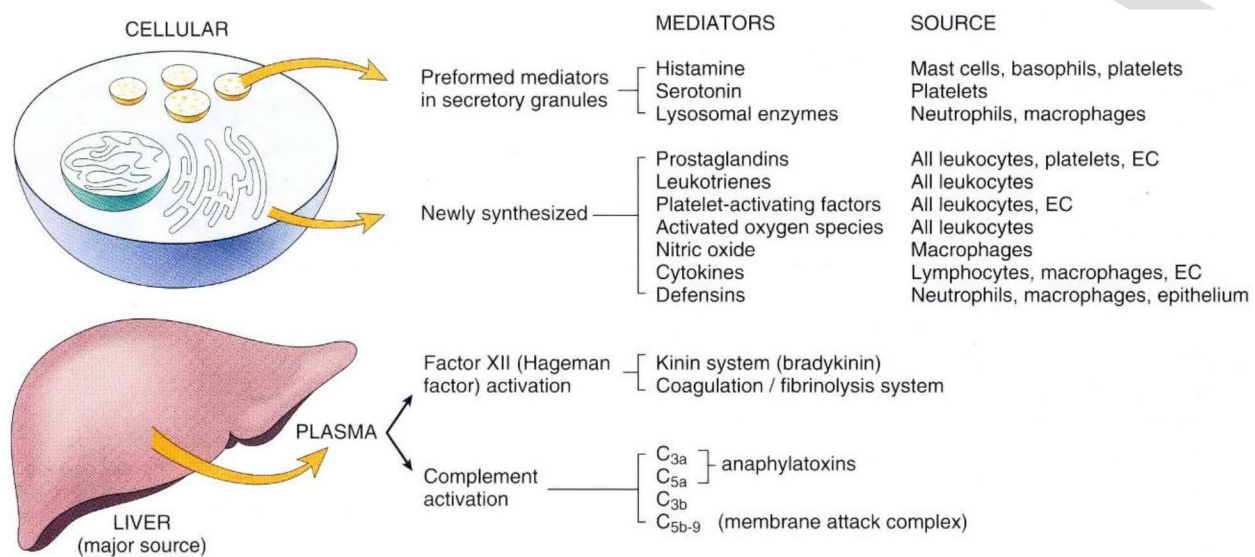


Leukocyte adhesion cascade. The leukocyte adhesion cascade includes tethering (capture) and rolling, which are largely mediated by L- and P-selectins and their receptors.



The major steps of the acute inflammatory process.

Endothelial Cell/Neutrophil Adhesion Molecules		
Endothelial Molecule	Leukocyte Receptor	Major Role
P-selectin	Sialyl-Lewis X PSGL-1	Rolling (neutrophils, monocytes, lymphocytes)
E-selectin	Sialyl-Lewis X ESL-1, PSGL-1	Rolling, adhesion to activated endothelium (neutrophils, monocytes, T lymphocytes)
ICAM-1	CD11/CD18 (integrins) (LFA-1, Mac-1)	Adhesion, arrest, transmigration (all leukocytes)
PECAM-1	PECAM-1	Transendothelial cell migration
JAM A	JAM A, LFA-1	Transendothelial cell migration
JAM C	JAM B, Mac-1	Transendothelial cell migration



Chemical mediators of inflammation. EC, Endothelial cells.

Morphologic Features and Function of Eosinophilic Granules

Granule Type	Morphology	Content	Function
Small granules	Few, small, homogeneous	Acid phosphatase, arylsulfatase	Inactivate leukotrienes
Primary granules	Few, round, electron-dense	Major basic protein	Toxic to parasites, tumor cells, host tissue; causes histamine release; inhibits heparin activity
Secondary granules (specific granules)	Electron-dense, crystalline core		
	Electron-lucent matrix	Eosinophil cationic protein	Toxic to parasites, causes histamine release, antiparasitic
		Eosinophil-derived neurotoxin	Neurotoxic with H ₂ O ₂ /halide, microbicidal
		Eosinophil peroxidase	Microbicidal
		Catalase	Inactivates leukotrienes

Examples of Differing Types of Inflammatory and Clinical Responses to Stimuli

TYPE OF INFLAMMATORY STIMULI			
	Skin Allergen	Gram-Negative Bacterial Infection in Dermis	Gram-Negative Septicemia
Stimulus	Allergen	LPS, toxins	LPS, toxins
Site	Epidermis/dermis	Dermis	Blood
Molecular trigger	Immunoglobulin E-cross-linking, dendritic cell binding	TLR4, CD14	Hageman factor, complement, TLR4
Major response	Histamine, leukotrienes	IL-1, TNF, prostaglandins, PAF, neutrophil products	Kinins, bradykinin, PAF, prostaglandins, IL-1, TNF
Extent of response	Local	Local	Systemic
Clinical finding	Swelling, pruritus (bronchoconstriction)	Swelling, exudate (pus)	Fever, nausea, malaise
Desired resolution	Limited, resolves in hours/days	Limited, resolves in days	Transient, resolves
Possible sequelae	Severe wheal and flare, anaphylaxis	Cellulitis leading to ulceration, eventual fibrosis/granuloma	Septic shock

CD14 = receptor for LPS-binding protein.
Hageman factor = clotting factor.
IL-1, Interleukin-1; LPS, lipopolysaccharide (endotoxin); PAF, platelet-activating factor; TLR4, Toll-like receptor 4; TNF, tumor necrosis factor.

Summary of Various Leukocyte Adhesion Molecules

Common Name	CD	Expressed on	Binds	Expressed on
INTEGRINS				
β_1 integrins	CD29			
VLA-1	CD49a/CD29	EC	Collagen	ECM
VLA-2	CD49b/CD29	EC	Collagen	ECM
VLA-3	CD49c/CD29	EC	Fibronectin	ECM
VLA-4	CD49d/CD29	L (except PMNs)	VCAM-1	EC
VLA-5	CD49e/CD29	EC	Fibronectin	ECM
VLA-6	CD49f/CD29	EC	Laminin	ECM
β_2 integrins	CD18			
LFA-1	CD11a/CD18	L	ICAM-1	EC
Mac-1	CD11b/CD18	L	ICAM-1	EC, L
gp150,95	CD11c/CD18	L	ICAM-1	EC
$\alpha_4\beta_2$	CD11d/CD18	Mac, CD8 ⁺ T lymphocytes	ICAM-3	L, EC
β_3 integrins	CD61			
$\alpha_{IIb}\beta_3$	CD41/CD61	Platelets	Fibrinogen	EC
$\alpha_v\beta_3$	CD41/CD61	EC, Mac, M	Fibronectin	ECM
β_4 integrins				
$\alpha_6\beta_4$		EC, SC	Laminin	ECM
β_5 integrins				
$\alpha_v\beta_5$		EC, epithelia	Vitronectin	ECM
β_6 integrins				
$\alpha_v\beta_6$		Epithelia	Fibronectin	ECM
β_7 integrins				
α_4		EC, lympho	MAdCAM-1, VCAM-1	EC
α_e		Intraepithelia, lympho	E-cadherin	EC
β_8 integrins				
$\alpha_v\beta_8$			Laminin	ECM
IMMUNOGLOBULIN SUPERFAMILY				
ICAM-1	CD54	EC, epithelia, SC, PMN, MQ	β_2 integrins	L
ICAM-2	CD102	EC, lympho	β_2 integrins	L
ICAM-3		EC, lympho, PMN, M	β_2 integrins	L
ICAM-4		Red blood cells	β_2 integrins	L
ICAM-5		Subset of neurons	β_2 integrins	L
VCAM-1	CD106	EC	VLA-4	L (except PMNs)
PECAM-1	CD31	EC, L	PECAM-1	EC, L
MAdCAM-1		EC (mucosal)	L-selectin	PMN, lympho, $\alpha_4\beta_7$ integrin
Selectins				
L-selectin	CD62L	L, trophoblasts, blastula	GlyCAM-1, CD34, MAdCAM-1	EC, uterus
E-selectin	CD62E	EC	ESL-1, sLe ^x	L
P-selectin	CD62P	EC, platelets	PSGL-1, GlyCAM-1, sLe ^x	EC, P
OTHER				
Hyaluronic acid receptor	CD44	L	Hyaluronic acid	ECM
JAM A	CD321	EC junction, L, platelets	JAM A, LFA-1	L
JAM B	CD322	HEV	JAM B, JAM C, VLA-4	L, DC
JAM C		EC junction, L, platelets	JAM B, Mac-1	
CD99	CD99	L, M, EC		EC

This table is not comprehensive for cellular expression and binding activity.
DC, Dendritic cells; EC, endothelial cells; ECM, extracellular matrix; ESL-1, E-selectin ligand; GlyCAM-1, glycoprotein cell adhesion molecule-1; HEV, high endothelial cell venule; L, leukocytes; lympho, lymphocytes; M, monocytes; Mac, macrophages; MAdCAM-1, mucosal addressin cell adhesion molecule-1; PMN, polymorphonuclear cells (neutrophils); PSGL-1, P-selectin glycoprotein ligand-1; SC, Schwann cells; sLe^x, Sialyl-Lewis X.

Key Responses of Acute Inflammation
and the Principal Inflammatory
Mediators That Mediate These Processes

VASODILATION

Nitric oxide
Prostaglandins: PGD₂
Leukotrienes: LTB₄

INCREASED VASCULAR PERMEABILITY

Vasoactive amines: histamine, substance P
Complement factors: C5a, C3a
Prostaglandins: PGE₂
Leukotrienes: LTC₄, LTD₄, LTE₄
Platelet-activating factor, substance P

CHEMOTAXIS, LEUKOCYTE ACTIVATION

Complement factors: C5a
Leukotrienes: LTB₄
Chemokines: IL-8
Defensins: α- and β-defensins
Bacterial products: lipopolysaccharide, peptidoglycan, teichoic acid
Surfactant proteins A and D

FEVER

Cytokines: IL-1, TNF, IL-6
Prostaglandins: PGE₂

NAUSEA

Cytokines: IL-1, TNF, high mobility group factors

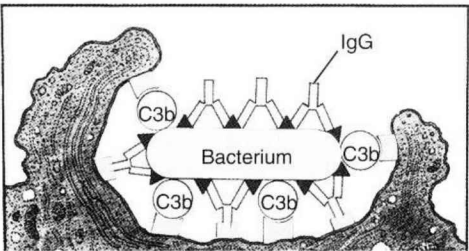
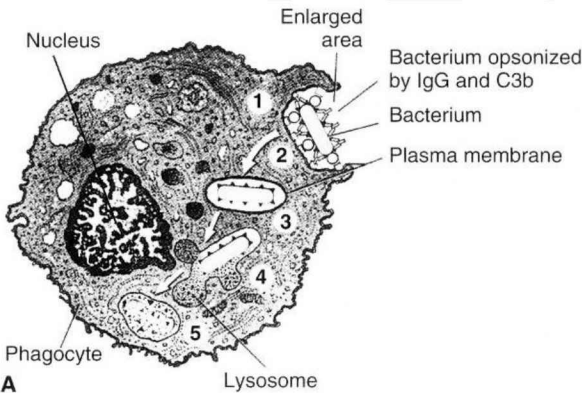
PAIN

Bradykinin
Prostaglandins: PGE₂

TISSUE DAMAGE

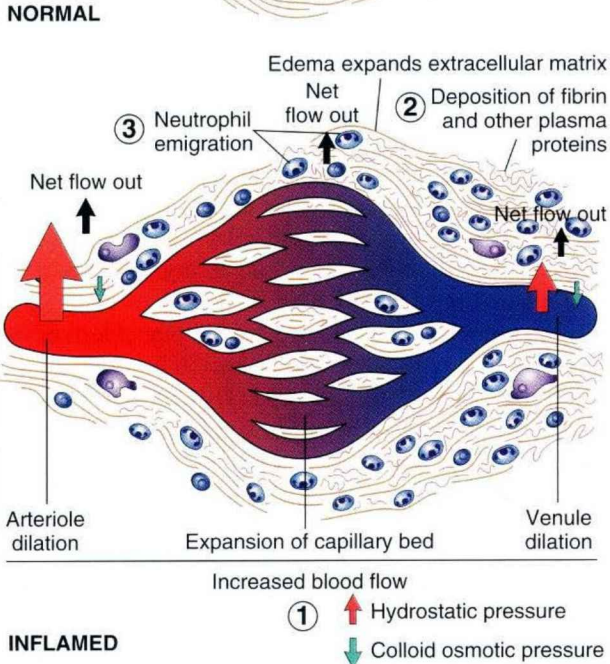
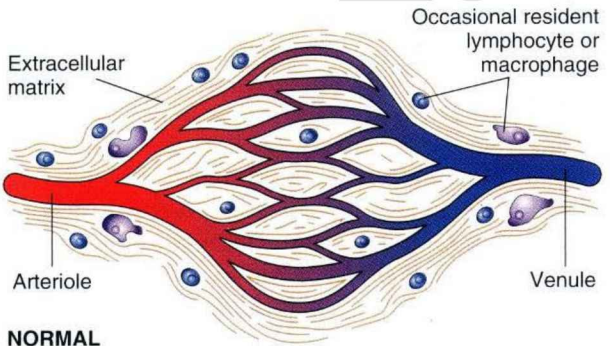
Neutrophil and macrophage lysosomal/granule contents:
matrix metalloproteinases
Reactive oxygen species: superoxide anion,
hydroxyl radical, nitric oxide

C3a, Complement factor C3a; C5a, complement factor C5a; IL-1, IL-6, IL-8, interleukins 1, 6, and 8, respectively; LTB₄, LTC₄, LTD₄, LTE₄, leukotrienes B₄, C₄, D₄, and E₄, respectively; PGD₂, PGE₂, prostaglandins D₂ and E₂, respectively; TNF, tumor necrosis factor.



Phases of phagocytosis. A, Opsonized microbes (1) bind to the surface of a phagocyte and (2) are ingested into a phagocytic vacuole or phagosome (3). Lysosomes fuse with the phagosome (4),

releasing their digestive enzymes into the vacuole. This process results in the formation of a phagolysosome (5), within which the microbe is killed and digested. B, Enlargement showing microbe opsonization. IgG, Immunoglobulin G; C3b, complement component



The major local manifestations of acute inflammation compared with normal. (1) Vascular dilation (causing erythema and warmth), (2) extravasation of plasma fluid and proteins (edema), and (3) leukocyte emigration and accumulation in the site of injury.

Some Terminologies of Inflammatory Conditions

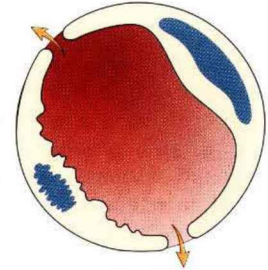
Inflammatory Term	Organ / Tissue Involved
Abomasitis	Abomasum
Arteritis	Artery
Arthritis	Joints
Balanitis	Glans penis
Blepharitis	Eyelid
Bursitis	Bursa
Carditis	Heart
Chelitis	Lip
Cholangitis	Bile Ducts
Cholecystitis	Gall bladder
Colitis	Colon
Conjunctivitis	Conjunctiva
Cystitis	Bladder
Dacryoadenitis	Lacrimal gland
Dermatitis	Skin

Desmitis	Ligaments
Encephalitis	Brain
Endocarditis	Endocardium
Eustachitis	Eustachian tube
Enteritis	Intestine
Funiculitis	Spermatic cord
Gastritis	Stomach
Glomerulitis	Renal glomeruli
Glossitis	Tongue
Hepatitis	Liver
Iritis	Iris
Keratitis	Cornea
Laminitis	Limbs
Lymphadenitis	Lymph nodes
Lymphangitis	Lymph vessels
Meningitis	Meninges
Metritis	Uterus
Myositis	Muscle (Skeletal)
Myocarditis	Myocardium
Neuritis	Nerve
Nephritis	Kidney
Otitis	Ear
Ophthalmitis / ophthalmia	Eye
Osteitis	Bone
Osteomyelitis	Bone marrow
Oophoritis; ovaritis	Ovary
Orchitis	Testide
Pachymeningitis	Dura Mater
Pericarditis	Pericardium
Peritonitis	Peritoneum
Phlebitis	Veins
Pleuritis	Pleura
Pneumonitis	Lung
Polyneuritis (numerous)	Nerves
Posthitis	Prepuce
Pyelitis	Renal pelvis
Radiculitis	Spinal nerve root
Rhinitis	Nasal mucosa
Salpingitis	Oviduct
Sialoadenitis	Salivary gland
Sinusitis	Sinuses
Splenitis / Lienitis	Spleen
Spondylitis	Vertebrae
Steatitis	Fat
Stomatitis	Oral mucosa
Telangitis	Capillaries
Typhlitis	Cecum
Tracheitis	Trachea
Tympanitis	Tympanum
Uveitis	Uvea
Vaginitis	Vagina
Vasitis	Vas deferens
Vasculitis	Blood vessels

MECHANISMS OF VASCULAR LEAKAGE
IN ACUTE INFLAMMATION

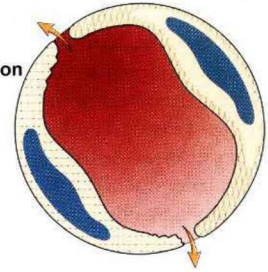
Gaps: Endothelial contraction

- Venules
- Vasoactive mediators (histamine, leukotrienes, etc.)



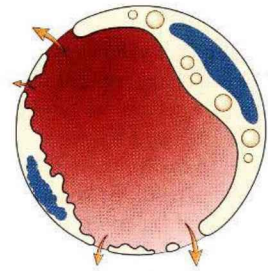
Gaps: Cytoskeletal reorganization

- Mostly venules; capillaries
- Cytokines (e.g., interleukin-1 and tumor necrosis factor)
- Hypoxia



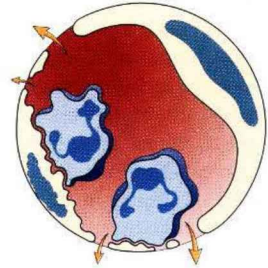
Direct injury

- Arterioles, capillaries, and venules
- Toxins, burns, chemicals



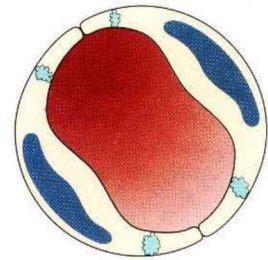
Leukocyte-dependent injury

- Mostly venules
- Pulmonary capillaries
- Late response



Increased transcytosis

- Venules
- VEGF; Other mediators?



Diagrammatic representation of five mechanisms of increased vascular permeability in inflammation. VEGF, Vascular endothelial growth factor.

h. Healing and Repair

Tissue restoration begins almost at the onset of inflammation itself.

a. Repair by regeneration of cells

- occurs in injured tissues that have retained the ability for cell division.

The ability of the tissues to regenerate is described in three ways:

1. *Labile cells* have constant capacity to regenerate.

Lymphoid and hematopoietic cells, epithelial cells of the GI, urinary, male, and female reproductive tracts and skin are labile cells.

2. *Stable cells* have limited regrowth capacity.

Liver, pancreas, kidneys, endocrine cells and blood cells compose the stable cells.

3. *Permanent cells* do not regenerate and once destroyed, cannot be replaced.

Neurons and myocardial cells are permanent cells.

b. Repair by granulation tissue formation

1. First intention healing

- complete apposition of clean and neatly sutured wounds.

2. Second intention healing

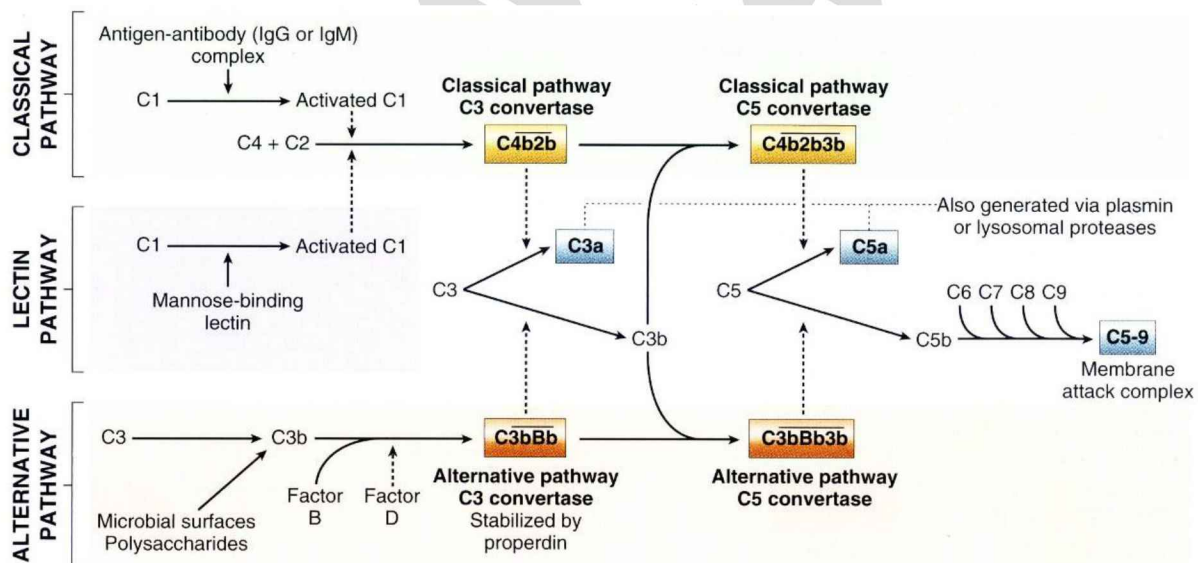
- areas of extensive tissue damage take longer to heal, as infection (abscess) and necrotic debris must be diminished before granulation tissue occur.

Features of second intention healing:

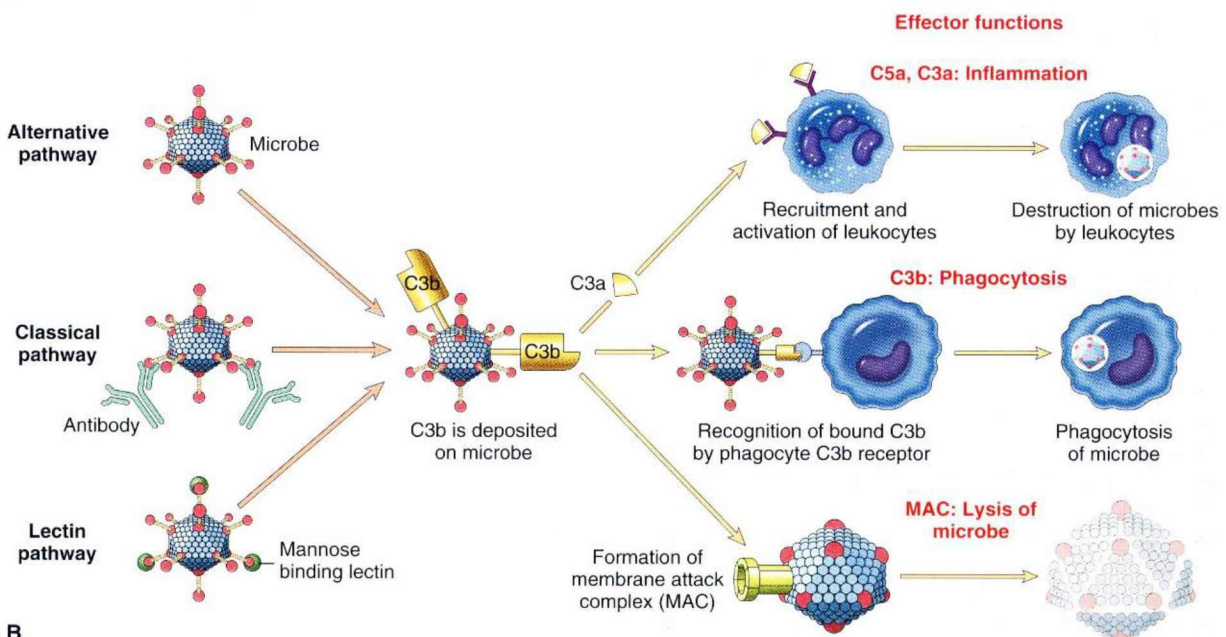
1. Neovascularization (new capillary growth and endothelial cell proliferation)
2. Granulation tissue formation
3. Fibroblasts synthesize collagen and glucose aminoglycan ground substance.
4. Eventually, fibrosis (scarring) occupies defect left by inflammation.

REGENERATION implies that lost cells are replaced by cells of the same kind. Not all tissues are capable of this feat and some are capable of regeneration only under specific conditions.

REPAIR – defined as the restoration of damaged tissue by replacement. Such replacement is either of the same type, as in proliferation of parenchymal tissue (i.e., liver cells, renal epithelia) or by scar replacement (fibrosis or cicatrization).



A



B

A, Components and pathways of the complement cascade. B, Effector functions of the complement system.

Inflammatory and Other Activities of Antimicrobial Peptides and Surfactant Proteins		
Antimicrobial Peptide/Protein	Major Cell of Production	Activity
α -Defensins	Enterocytes, leukocytes	Microbicidal activity, induce interleukin-8 production (cryptidins), inhibit angiogenesis (neutrophil α -defensins)
β -Defensins	Epithelia, leukocytes	Microbicidal activity, chemotactic for neutrophils, dendritic cells, other leukocytes, induce cell proliferation
Cathelicidins	Leukocytes, epithelia	Microbicidal activity, induce cytokine and histamine release, regulate cell proliferation, angiogenesis, wound healing, prevent apoptosis (PR-39)
Surfactant proteins A and D	Epithelia	Opsonization of pathogens, macrophage activation

Cryptidins = a type of α -defensin produced by Paneth cells; neutrophil α -defensins = α -defensins produced by human neutrophils; PR-39 = a cathelicidin molecule produced by porcine neutrophils.

The Nomenclature of a Morphologic Diagnosis					
Degree	Duration	Distribution	Exudate	Modifier	Tissue
Minimal	Acute	Focal	Serous	Necrotizing	Nephritis
	Subacute	Multifocal	Catarrhal	Bronchointerstitial	Cystitis
Mild	Chronic	Locally	Fibrinous	Hemorrhagic	Enteritis
Moderate	Chronic-active	extensive	Suppurative	Embolic	Pneumonia*
Marked (severe)		Diffuse (interstitial) Cranioventral†	Granulomatous		Hepatitis

This table provides an example of how nomenclature can be used to construct a morphologic diagnosis. It is not intended to be all inclusive and may vary from schemes used in other veterinary colleges.

*In the lung, it is customary to use the term *pneumonia* to indicate inflammation of the lung.

†Used only for diseases of the lungs.

i. Immunopathology

The recognition or discrimination between the so called “self” and “non-self” is the primary role of the immune system. This recognition of non-self is important to protect against invading microorganisms, chemical agents, or other foreign substances. Elimination of foreign or non-self of the immune system involves a variety of mechanisms such as:

1. Inactivation of biologic agents
2. Lysis of foreign cells
3. Agglutination of molecules
4. Precipitation of molecules or cells
5. Phagocytosis of foreign materials

The reaction of tissues to antigen (Ag) is mediated by two cell types:

B LYMPHOCYTES (Bursa-derived)

- Secrete **ANTIBODIES** after conversion to **PLASMA CELLS**.

T LYMPHOCYTES (Thymus-derived)

- Responsible for cell-mediated immunity. It does not secrete antibodies. Rather, releases **LYMPHOKINES**.

IMMUNOPATHOLOGIC REACTIONS

A. HYPERSENSITIVITY REACTIONS

TYPE I. Immediate Hypersensitivity or Anaphylaxis

This is mediated by IgE antibodies bound to mast cells and basophils that is formed in response to a particular antigen (or allergen). In this type of hypersensitivity, clinical signs/symptoms occur after the release of pharmacologically active compounds from mast cells and basophils. These cells (basophils and mast cells) possess receptors capable of binding the Fc portion of the IgE molecule. Mast cell and/or basophil degranulation releases the following pharmacologically and biologically active compounds:

1. histamine
2. leukotrienes
2. eosinophil chemotactic factor
3. platelet activating factor
4. kallikrein
5. platelet aggregating factor
6. kinins
7. serotonin
8. proteolytic substances

Agents that cause **ANAPHYLAXIS** are numerous and include:

- a. venom or stings of biting insects
- b. vaccines
- c. variety of drugs
- d. food substances
- e. blood donors/blood products

Clinical signs can be localized or generalized. Symptoms include:

1. restlessness and excitement

2. facial edema
3. pruritus on affected area
4. salivation
5. lacrimation
6. vomiting
7. diarrhea
8. abdominal pains
9. dyspnea
10. cyanosis
11. shock
12. incoordination
13. convulsions
14. death

In domestic animal species, the symptoms of anaphylaxis vary depending in part to the distribution of mast cells in the animal body.

- In DOGS, the major organ affected is the LIVER. Constriction of hepatic veins due to concentrations of mast cells result to portal hypertension and visceral pooling of blood. Therefore, clinical signs in dogs is gastrointestinal rather than respiratory.
- Anaphylaxis in CATS is characterized by respiratory signs, bronchoconstriction and pulmonary edema. Other signs in the cat include dyspnea, facial itching, salivation, incoordination, collapse, shock and even death.
- In PIGS and HORSE, anaphylaxis are manifested as pulmonary emphysema, peribronchiolar edema and edematous hemorrhagic enterocolitis.
- Systemic hypotension, with dyspnea, urination, defecation and bloating are the presenting signs involving the RUMINANTS.

TYPE II HYPERSENSITIVITY: (Cytotoxic/cytolytic reactions or Autoimmunity).

- Autoimmunity is defined as the immune response against individual's own tissue antigens.
- This is mediated by antibodies against intrinsic antigens or extrinsic antigens adsorbed on the cell surface or on other tissue components.

This type of reaction can be produced subsequent to:

1. Complement – dependent reactions

Occur either by direct lysis via the C5-9 (membrane attack complex) or by opsonization (or enhanced phagocytosis).

Examples:

Transfusion reactions from unmatched donor.
Hemolytic disease of the newborn
Thrombocytopenic purpura

2. Antibody-dependent cell-mediated cytotoxicity (ADCC).

In this, reactions can be produced through antibody dependent cell mediated cytotoxicity. In this process, antibody attaches to the target antigen through Fab (fragment antibody-binding) antigen combining sites. The Fc (fragment cell-binding) end of the antibody is free to interact with cytotoxic cells

having an Fc receptor such as macrophages, polymorphonuclear cells, and natural killer lymphocytic cells.

Example:

Autoimmune hemolytic anemia

- own's tissue or (own rbc) cell has been recognized as "NON-SELF"

Immune mediated anemia in events of trypanosomiasis, babesiosis

Drug-induced - (penicillins, aminosalicylates, phenacetin)

Thrombocytopenic (aminopyrine, phenothiazine, chloramphenicol sulfonamide, phenylbutazone).

Systemic lupus erythematosus

- presence of anti-DNA antibody;

TYPE III HYPERSENSITIVITY

Immune complex reactions

This is mediated by antigen-antibody complexes

– IMMUNE COMPLEX.

This complex will induce complement activation either by classical or alternate pathway. There would be a resulting intense inflammatory reactions due to deposition or precipitation of immune complexes in and around blood vessels, attraction of phagocytes (neutrophils) that release tissue destructing substances.

E.g. Immune-mediated GLOMERULONEPHRITIS

In chronic diseases (dirofilariasis, swine fever, equine infectious anemia, bacterial endocarditis, canine distemper), in neoplasia (lymphosarcoma)

TYPE IV HYPERSENSITIVITY:

Delayed type hypersensitivity

This is cell-mediated tissue destruction by specifically sensitized T-lymphocytes.

DTH yields a classic response

In Type IV reactions, reactions require cells to produce effect. The reaction to an antigen is usually delayed and is not clinically detectable until 24 to 72 hours after exposure to a specific antigen. Complement does not play role in this type. Cytotoxicity is a prominent component of delayed type hypersensitivity reaction, and is an important process on host defense against viral and fungal infections, and in spontaneous tumors rejection.

Type IV - Involved clinically in conditions such as

allergic contact dermatitis

tuberculin hypersensitivity

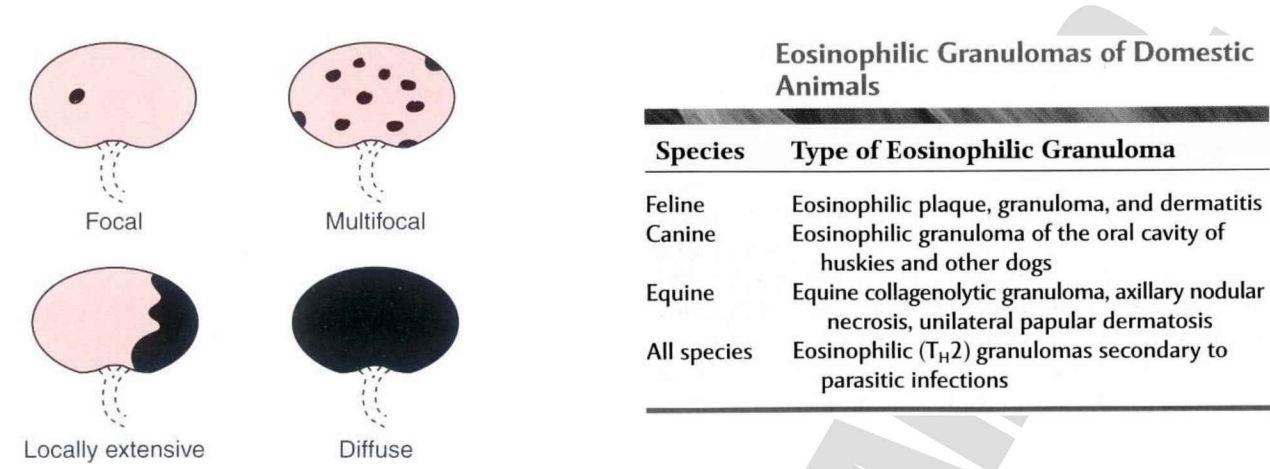
organ or tissue transplant rejection, and graft-vs.-host disease.

flea allergy and allergic contact dermatitis in dogs and cats.

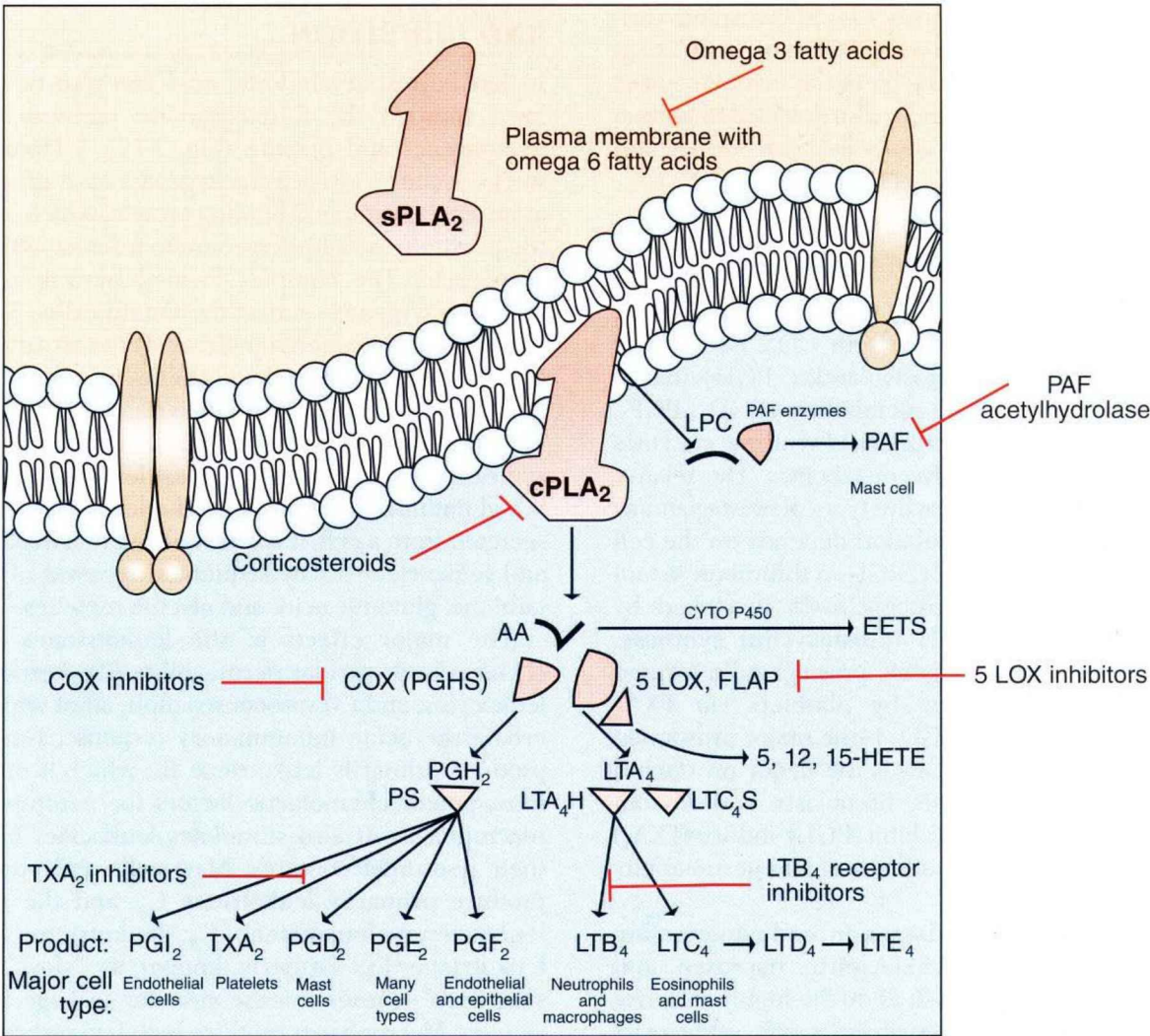
GRANULOMATOUS DISEASES

- Mycobacterial diseases

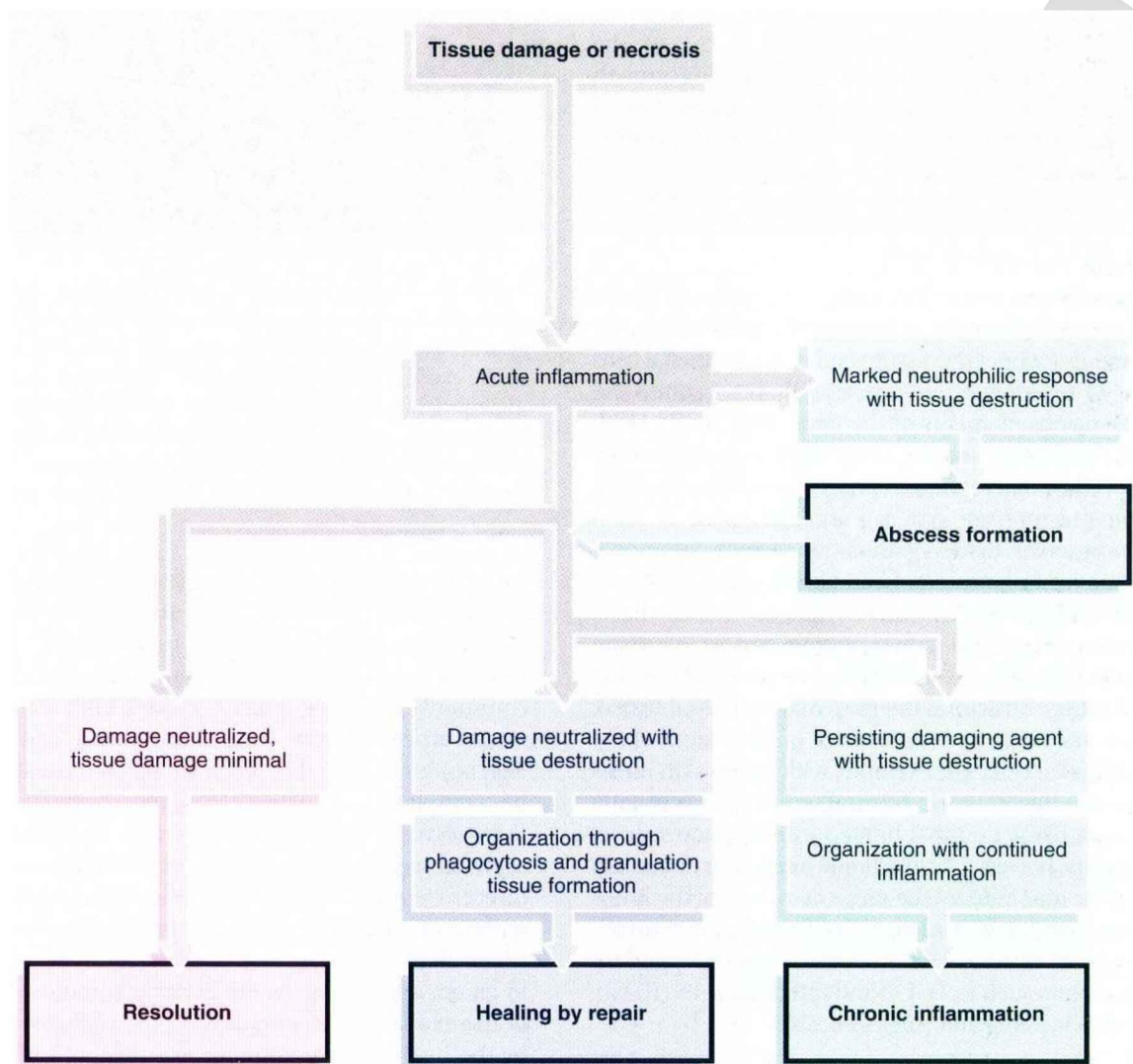
- o Tuberculosis (*M. tuberculosis*, *M. avium*, *M. bovis*)
- o Johne's disease (*M. paratuberculosis*)
- o Leprosy (*M. leprae*)



Patterns of lesion distribution used to construct morphologic diagnosis, as an example, in the kidney.



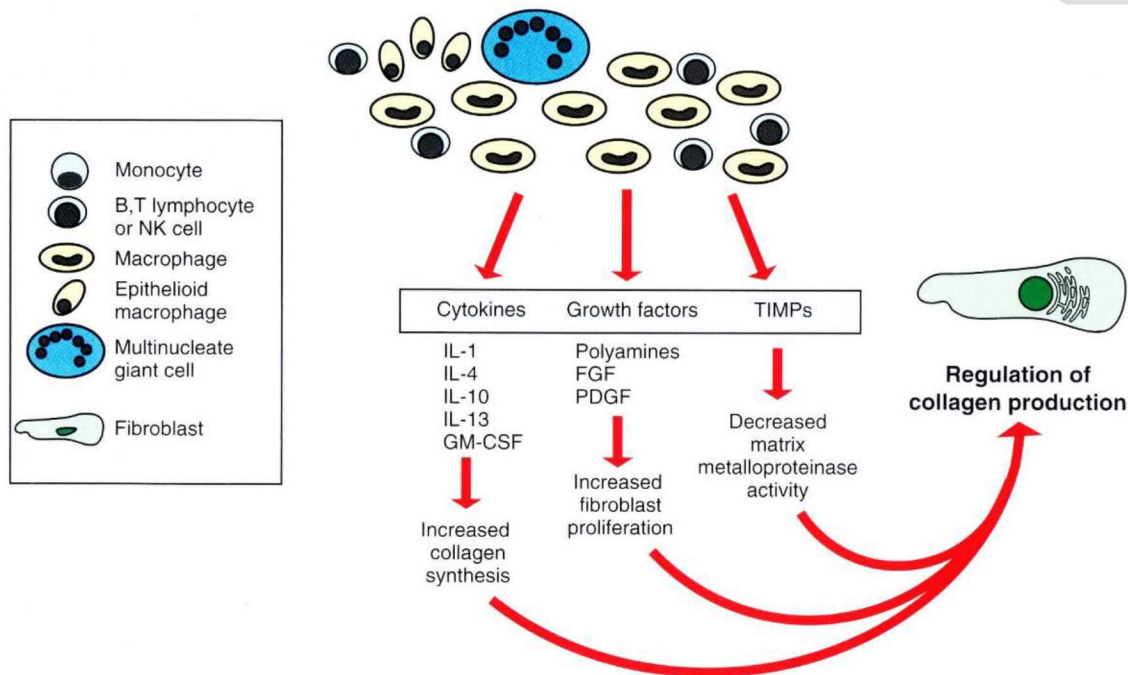
Key inflammatory mediators derived from the plasma membrane. Cytoplasmic phospholipase A₂ (cPLA₂) activity on the plasma membrane leads to free arachidonic acid (AA) and lysophosphatidylcholine (LPC). Arachidonic acid metabolites include prostaglandins and leukotrienes, and LPC is a substrate for platelet activating factor (PAF). The type of prostaglandin formed by a cell is dependent on the cell type. Platelets, for example, form thromboxane, whereas endothelial cells form prostacyclin. Leukotrienes are formed by leukocytes. Inhibitors specific to the various enzymes or products are listed (light lines). COX, Cyclooxygenase; EETs, epoxyicosatrienoics; FLAP, 5-lipoxygenase-activating protein; HETE, hydroxyicosatetraenoic acid; LOX, lipoxygenase; LTA₄, LTB₄, LTC₄, LTE₄, leukotrienes A₄, B₄, C₄, and E₄, respectively; LTA₄H, leukotriene A₄ hydrolase; LTC₄S, leukotriene C₄ synthase; PGD₂, PGE₂, PGF₂, PGH₂, prostaglandins D₂, E₂, F₂, H₂ and I₂, respectively; PGHS, prostaglandin H synthase; PS, polysaccharides; sPLA₂, soluble phospholipase A₂; TXA₂, thromboxane A₂.



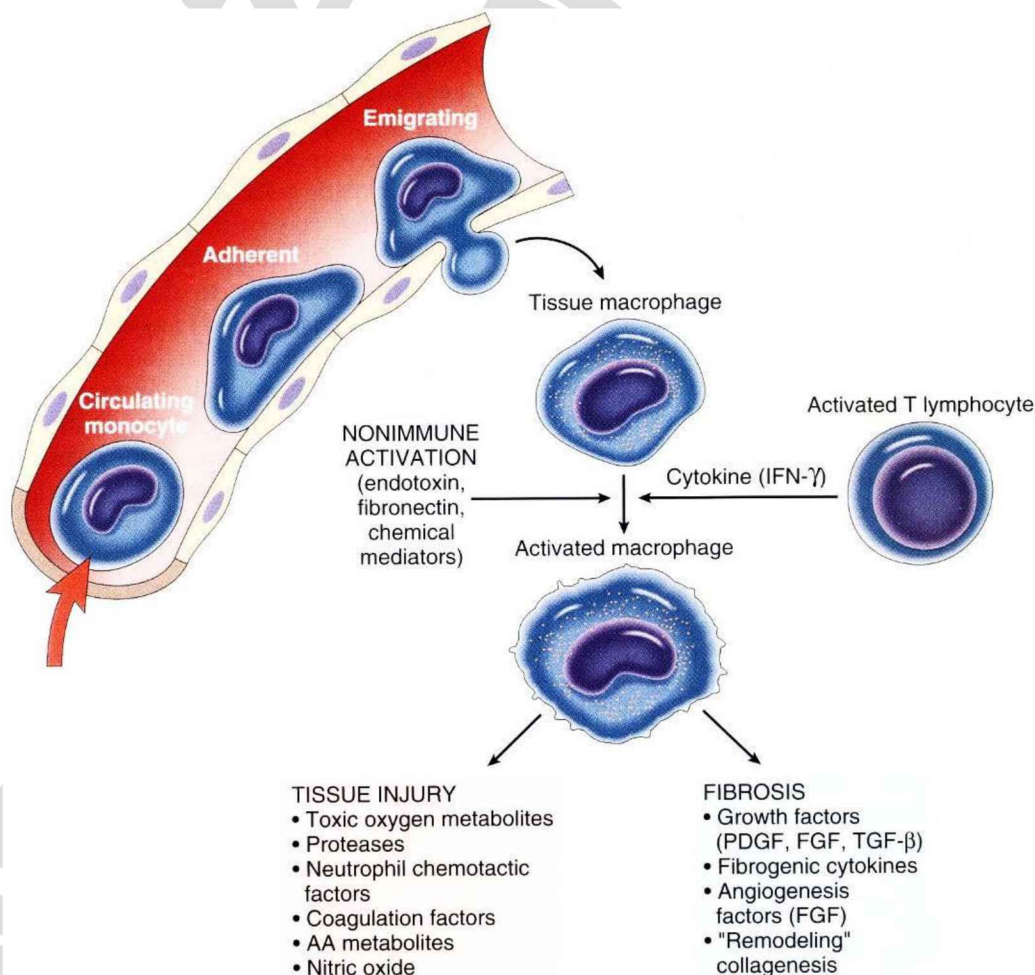
The outcomes of tissue injury and unresolved acute inflammation.

Stimuli that Affect the Activation Status of Macrophages			
Type of Activation	Activating Factor	Macrophage Response	Macrophage Activity
Innate activation to microbes	Toll-like receptor CD14 (LPS binding) β-Glucan receptor TREM	Co-stimulatory expression ROS, NO expression Cytokine release	Inflammation, antigen presentation to memory T lymphocytes
Humoral activation	Fc receptor Complement receptors	Ig/Fc internalization Cytolytic activity Cytokine release	Inflammation, antigen presentation to memory T lymphocytes
Classical activation T _H 1	IFN-γ	MHC II expression Cytokine release (IL-1, IL-6, TNF) Respiratory burst NO release	Cell-mediated immunity Microbial killing DTH
Alternative activation T _H 2	IL-4 IL-13	MHC II expression Mannose receptor expression	Humoral immunity Allergic response Response to parasites Arginase repair Immunosuppression
Deactivation by innate/ adaptive stimuli	IL-10 TGF-β IFN-α, IFN-β GM-CSF CD47 CD200R CD36 (scavenger receptor) α ₅ β ₃ -Integrin Glucocorticoid receptor Internalized ox LDL	MHC II down-regulation PGE ₂ release IL-10 release TGF-β release PPAR inhibition of NF kappa B	

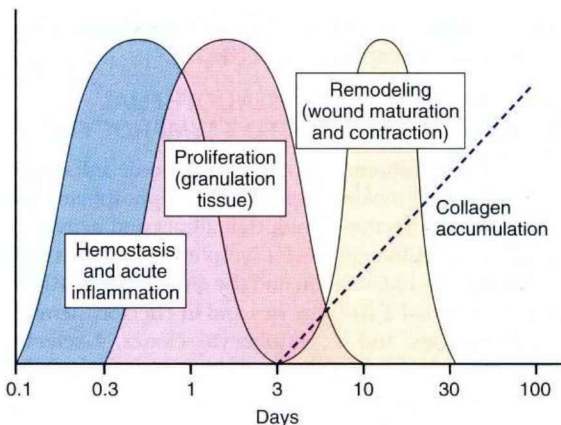
DTH, Delayed type hypersensitivity; IFN, interferon; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; NF, nuclear factor; NO, nitric oxide; ox LDL, oxidized low-density lipoprotein; PGE₂, prostaglandin type E₂; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; TGF, transforming growth factor; T_H1, T helper cell type 1 lymphocyte response; T_H2, T helper cell type 2 lymphocyte response; TREM, triggering receptor expressed on myeloid cells.



Development of fibrosis in chronic inflammation. In most chronic inflammatory lesions, activated macrophages, lymphocytes and other cells secrete cytokines, growth factors, and tissue inhibitors of matrix metalloproteinases (TIMPs) that lead to fibroblast proliferation and collagen synthesis. FGF, Fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, Interleukin; NK, Natural killer; PDGF, Platelet-derived growth factor.



The roles of activated macrophages in chronic inflammation. Macrophages are activated by cytokines from immune-activated T lymphocytes or by nonimmunologic stimuli, such as endotoxin. The products made by activated macrophages that cause tissue injury and fibrosis are indicated. AA, Arachidonic acid; FGF, Fibroblast growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β.



Temporal phases of wound healing.

Enzymes Responsible for Degradation of the Extracellular Matrix (ECM) Proteins and Proteoglycans

PROTEINASES THAT DEGRADE ECM PROTEINS:

- Matrix metalloproteinases
- Cathepsin G
- Cysteine protease
- Urokinase-PA
- Serine protease

PROTEOGLYCANS ARE DEGRADED BY:

- Lysosomal uptake
 - Heparinases—an endoglucuronidase that degrades hyaluronates, chondroitins, heparans, and heparins
 - Galactosidases—degrades dermatans and keratans

Summary of Mast Cell Mediators and Their Actions

Action	Mediator
Vasodilation, increased	Histamine
Vascular permeability	PAF Leukotrienes C ₄ , D ₄ , E ₄ Neutral proteases that activate complement and kinins Prostaglandin D ₂
Smooth muscle spasm	Leukotrienes C ₄ , D ₄ , E ₄ Histamine Prostaglandins PAF
Cellular infiltration	Cytokines (e.g., TNF) Leukotriene B ₄ Eosinophil and neutrophil chemotactic factors (not defined biochemically) PAF

PAF, Platelet-activating factor; TNF, tumor necrosis factor.

j. Disturbance of Growth

I. FORMS OF DEVELOPMENTAL ANOMALIES

- 1) Agenesis- this is a congenital absence of an organ or part.
- complete failure of organ or tissue to develop
 - e.g. congenital absence of one kidney at birth.

- 2) Aplasia – this is defective development or production of a tissue or organ.
- this implies further development and means that some of the organ is present but markedly reduced in size from normal.
 - e.g. Absence of the intestine's lumen or the uterine horn over a short span and is referred to as segmental aplasia.
 - implies a presence of rudimentary organ .
 - Aplastic is sometimes used to mean that there is no tendency to form new tissue, as in failure to regenerate bone marrow in aplastic anemia.
- 3) Atresia - means absence or closure of a normal body opening
- e.g. atresia ani - if there is no external anal opening (common in pigs).
- 4) Hypoplasia - means underdevelopment or incomplete growth of a tissue or organ, usually this is associated with decreased number of cells.
- In hypoplasia, the tissue or organ did not reach its normal size or structure.
 - also refers to failure of organ to reach normal size.
 - a range of incomplete growth occurs, and the term refers to anything from just short of normal development to agenesis.

II. ACQUIRED DEFECTS /ANOMALIES

- 1) Atrophy – this refers to an acquired local reduction in size of a cell, tissue, organ, or region of the body. It may be physiological or pathological.
- Also defined as a decrease in the amount of tissue after normal growth has been achieved.
- Causes of atrophy:

- decreased workload
- deficient nutritive supply
- lack or loss of innervation
- necrosis of cell
- pressure
- disuse
- loss of endocrine feedback mechanisms
- aging

ATROPHY CAN OCCUR UNDER PHYSIOLOGICAL OR PATHOLOGICAL CONDITIONS

A) Physiological atrophy

- occurs in many tissues as a normal condition
- e.g. complete atrophy of chicken bursae, regression of corpus luteum involution of fetal structures such as ductus arteriosus uterine involution after birth.

Note: INVOLUTION is also termed as COMPLETE ATROPHY.

B) Pathological Atrophy

1. nutritional atrophy – during starvation or malnutrition.
2. vascular atrophy – in localized loss or deprived blood supply (ischemia).

3. disuse atrophy – due to lack or reduction of usual functional activity (e.g. a paralyzed limb)
4. pressure atrophy – a persisting pressure in an organ or tissue may contribute to ischemia of an area being pressed or pushed (e.g. as in an enlarging benign tumor, a surgical cast or a parasitic mass).
2. hormonal atrophy – loss of endocrine stimulation from trophic hormones.
(e.g., failure of growth and development of secondary sexual characteristics due to lack of growth hormones, and gonadotrophic hormones)
3. miscellaneous atrophy – as seen in some metabolic, neoplastic, genetic and infectious diseases.

Hypertrophy - is an increase in tissue resulting from an increase in the size of individual cells.

- In the pure form, hypertrophy occurs only in muscle and is usually a response to an increased demand for work (physiologic) or enlargement of cardiac muscle as in ventricular hypertrophy (pathologic).
- loss of an organ or in paired organs such as kidneys may lead to enlargement of the remaining kidney (compensatory hypertrophy).
- uterine hypertrophy during pregnancy

Hyperplasia - means an increase in the number of cells in a tissue or an organ and is usually accompanied by hypertrophy.

- because of increase in number of cells there would be resultant increase in size of tissue or organ.

Note: Hypertrophy and hyperplasia are best differentiated histologically.

Hypertrophy and hyperplasia often occur simultaneously in the tissues, but hypertrophy may occur alone in those tissues which are not capable of regeneration (i.e. cardiac muscles). Both of these processes may be physiological or pathological, and the major contributory factors are increased workload, endocrine and immunologic stimulation.

Dysplasia - refers to a microscopic lesion in which there is a loss of architectural orientation of cells or a loss in uniformity of individual cell in both.

- usually is used with reference to epithelium.
- Dysplasia means an abnormally developed tissue and may refer to an anomaly, as in renal dysplasia. It is considered reversible if the etiological factor is removed.

Metaplasia – means the transformation of a fully differentiated normal adult tissue into a related type of adult tissue (a reversible change).

- it involves mesenchymal and epithelial tissues.
- caused by chronic irritation as in bronchial epithelium, vitamin A deficiency in the urinary tract or salivary duct epithelium, chlorinated

hydrocarbon toxicity in the genital tracts in the urinary cattle and estrogen toxicity in the urinary tract of mink.

TERATOLOGY

TERATOLOGY - the study of anomalies.

- Anomalies and malformation are common and important aspects of disease.
- Anomalies occur at any stage of development; major defects are lethal in embryonic life. Some defects may permit survival in utero but not postnatally.

Hamartomas - these are improper mixture of tissues, usually with excess of a part, and grossly may resemble tumors.

- e.g. the well-known nevus or mole in humans, as well as angioma and some lipoma.
- Generalized defects in the development of the skeleton may occur, as in chondrodystrophy or dwarfism.

Arthrogryposis - is a disease in which an animal is born with flexed, absolutely rigid limbs, but this is a primary problem not with bones or joints but rather with innervation of muscles because of dysraphism in the spinal cord.

CYTOGENETICS

Polygenic inheritance involves many physiological characteristics of an individual.

- may be defined as a physiological or pathological trait governed by the additive effect of many genes of small effect but conditioned by nongenetic environmental influence.
- another group of disorders relates to chromosomal aberrations and involves a change in number or morphological state of chromosome, and thus a change in karyotype. Abnormalities in chromosomes tend to resulting decreased viability and fertility mental deficiency and structural abnormalities.
- Each somatic cell contains homologous pairs of **DIPLOID CHROMOSOMES**, one derived from each parent.
- The germ cells contain half this number called

HAPLOID.

- chromosomes are called autosomes when they include all except the one pair of sex chromosomes.

HETEROPLOIDY – refers to an abnormal number of chromosomes.

EUPLOIDY - if the chromosomes are the exact multiples of the haploid number, the cells are called euploid and the condition is called euploidy.

ANEUPLOID – are abnormalities that do not exact multiples.

TRISOMY - if three chromosomes occur instead of two.

MONOSOMY - if only one chromosome occurs, it is monosomy.

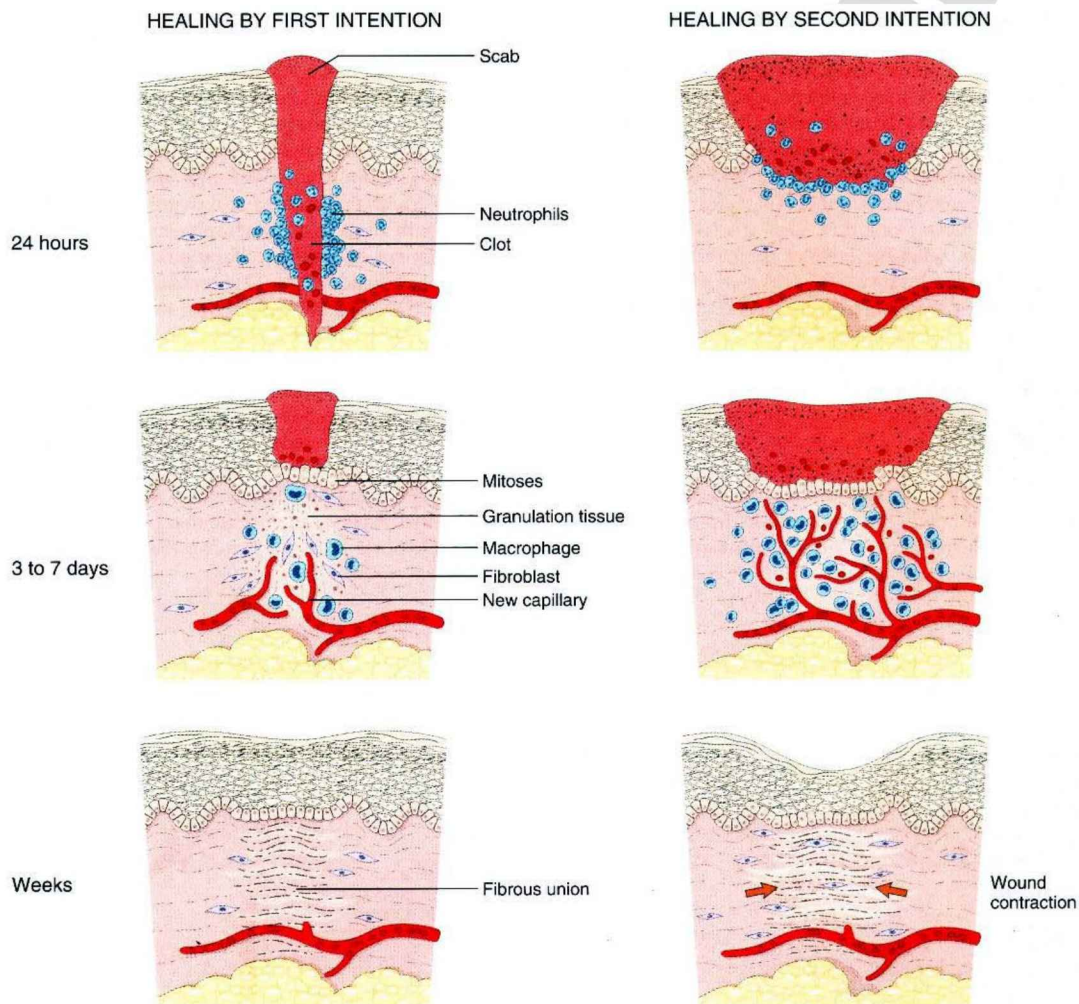
AGING

TWO MAIN THEORIES OF AGING

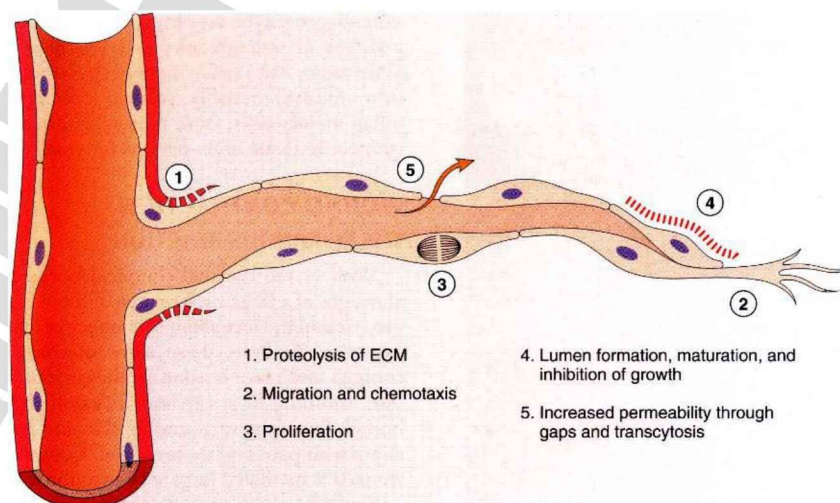
1. Cellular Theory
 2. Immune Theory
- The essence of these theories involves error in protein production that leads to changes in functions and aging. The errors may occur by

mutation, in transcript or in synthesis and lead to further self-perpetuating defects. The term for this overall mechanism is "error catastrophe".

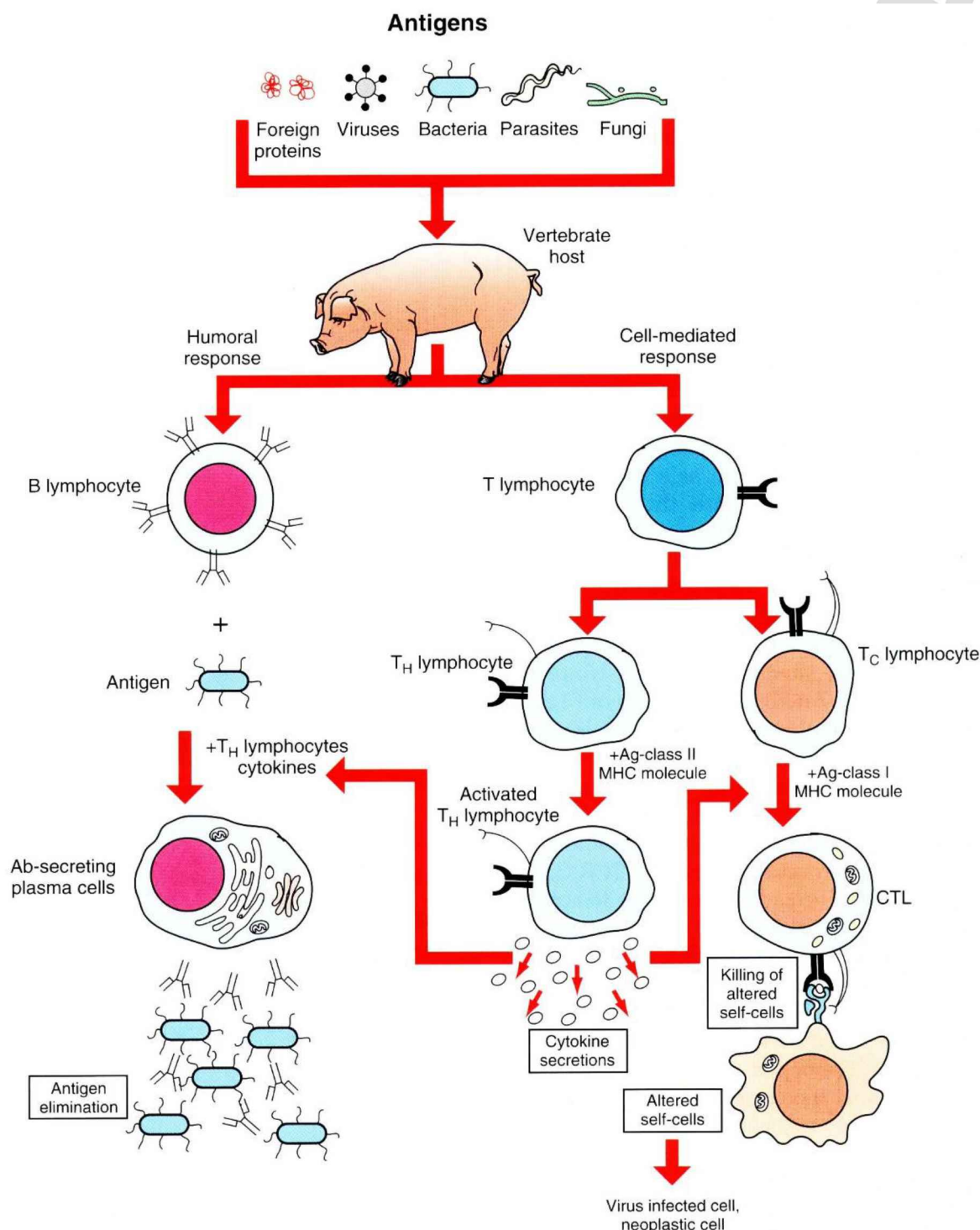
The second main theory concerning aging is the immune theory. It is known that immune functions decrease with age. This in part accounts for autoimmune disease and cancer in older individuals.



Wound healing. Steps in wound healing by first intention (left) and second intention (right). Note large amounts of granulation tissue and wound contraction in healing by second intention.



Steps in the process of angiogenesis. ECM, Extracellular matrix.



Overview of humoral and cell-mediated arms of adaptive immunity. CTL, Cytotoxic T lymphocyte.

k. Neoplasia and Tumor Biology

NEOPLASIA

Neoplasia occurs when a group of cells becomes free of normal growth control mechanisms, grows without regard for the normal structural and functional aspects of a tissue or an organ and excessive growth becomes autonomous.

Neoplasia literally means "new growth", and this tissue growth is called neoplasms. A neoplasm or a TUMOR is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissues, and persists in the same excessive manner even after stoppage of the stimulus which evoked the change. The key

features of neoplasia that distinguishes it from other forms of cell proliferation include the following:

- 1) Excessive tissue growth
- 2) Lack of responsiveness to normal control mechanisms
- 3) Lack of dependence on the continued presence of the stimulus.

TUMOR - means tissue swelling or mass, but by common usage has come to mean neoplasm.

CANCER is a common term used to mean malignant neoplasm.

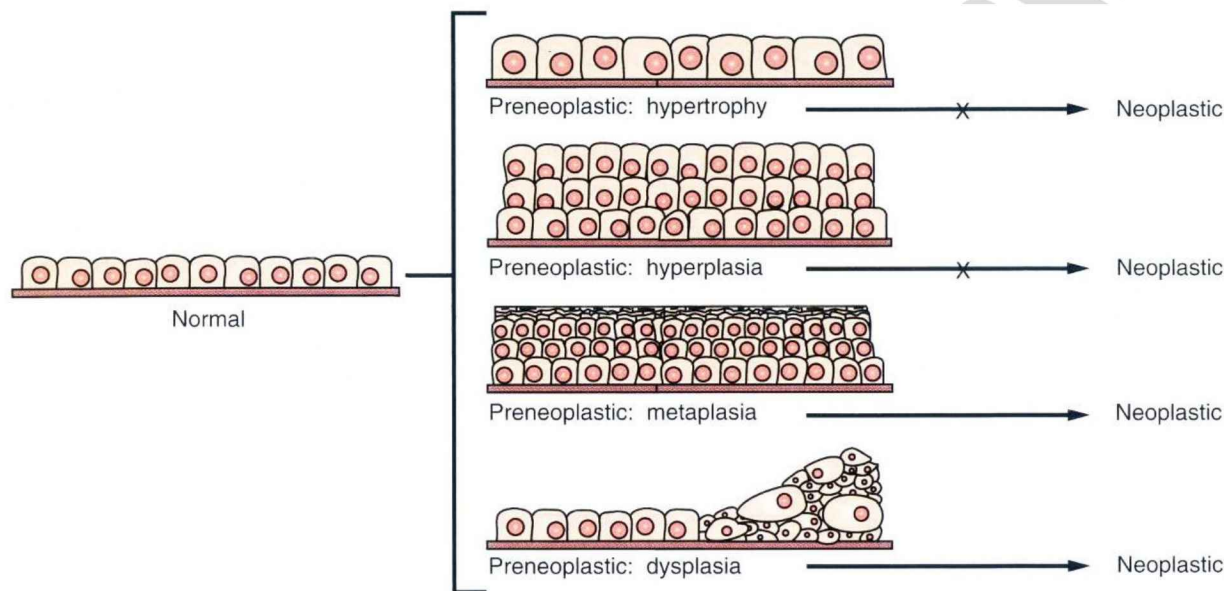
ONCOLOGY is the study of neoplasia, and this word is the basis of oncogenesis and oncogenic,

which relate to the induction of neoplasia. The common term for a neoplasm is cancer, or tumor, and both of these tend to be used all-inclusively.

A neoplasm or a tumor is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner

after cessation of the stimuli which evoked the change.

Hyperplasia occurs in response to loss of tissue, increased functional demands, disturbed hormonal activity and immunologic stimulation (i.e., lymphoid hyperplasia following active vaccination).



Preneoplastic changes that may precede tumor emergence. Preneoplastic changes in tissues include alterations in cell number, size, and organization. Some of these terms can also be applied to neoplastic tissues, as indicated. In this example, preneoplastic changes are illustrated in simple cuboidal epithelium, although such changes may also occur in other epithelial and mesenchymal cell types.

Comparisons between Benign and Malignant Tumors		
Characteristic	Benign	Malignant
Differentiation	Well-differentiated appearance Structure similar to tissue of origin Little or no anaplasia	Usually some lack of differentiation Structure often atypical Variable degree of anaplasia
Growth rate	Slow, progressive expansion Rare mitotic figures Normal-appearing mitotic figures	Slow to rapid growth; erratic growth rate Mitotic figures often numerous Mitotic figures sometimes abnormal
Local invasion	No invasion Cohesive and expansile growth Capsule often present	Local invasion Infiltrative growth Usually no capsule
Metastasis	No metastasis	Frequent metastasis (definitive criterion for malignancy)

CLASSIFICATION OF NEOPLASM

Neoplasms are classified in several ways.

1. **Histogenic** – this is based on the tissue origin (histogenic) as mesenchymal or epithelial in origin. Most are of one neoplastic cell type and fit into one or the other of these two groups. A few types of neoplasm contain more than one neoplastic cell type. When they are derived from one embryonic germ layer, they are called mixed neoplasm (e.g., mammary tumors in dogs in which proliferating epithelial tissue is intermixed with mesenchymal components, bone and cartilage). A **TERATOMA** is a neoplasm containing tissues derived from more than one germ cell layer, and may contain any number of tissues of any type

including bone, skin, nervous tissue, muscle, hair and other.

2. **Behavioral** – this is another classification that is based on the growth behavior of neoplastic cells.
 - benign neoplasm - describes those which are relatively inoffensive.
 - neoplasms that are confined, slow growing and noninvasive.
 - malignant neoplasm - which are aggressive and potentially life threatening.
 - tumors that are invasive, rapidly growing and dangerous are called malignant and carry the suffix sarcoma if derived form mesenchymal tissue or the suffix carcinoma if derived from epithelial tissue.

TUMOR SUFFIXES:

“OMA” - a suffix that refers to a BENIGN TUMOR and is used for neoplasms that are confined, slow growing and noninvasive. Benign tumors of either mesenchymal or epithelial origin carry the suffix “OMA”.

CARCINOMA – a suffix used for malignant tumor of epithelial origin.

SARCOMA – a suffix for malignant tumor of mesenchymal origin.

Usually, a tumor is first classified as either epithelial or mesenchymal. Such tumors are said to be poorly differentiated or anaplastic.

Tumor Nomenclature

	ORIGIN	Tissue of Origin	Cell of Origin	Benign	Malignant
MESENCHYMAL	Connective tissue and related tissue	Fibrous connective tissue	Fibroblast	Fibroma	Fibrosarcoma
		Fat	Adipocyte	Lipoma	Liposarcoma
		Cartilage	Chondrocyte	Chondroma	Chondrosarcoma
		Bone	Osteoblast	Osteoma	Osteosarcoma
	Endothelium and related tissue	Blood vessel	Vascular endothelium	Hemangioma	Hemangiosarcoma
		Lymphatic vessel	Lymphatic endothelium	Lymphangioma	Lymphangiosarcoma
		Synovium	Synovial lining cell	Synovioma	Synovial sarcoma
		Mesothelium	Mesothelial cell		Mesothelioma
		Meninges	Meningeal connective tissue cell	Meningioma	Malignant meningioma
	Hematopoietic and lymphoid tissue	Ovary	Modified mesothelium	Adenoma	Adenocarcinoma
		Lymphoid tissue	Lymphocytes	*	Lymphoma
		Bone marrow	Leukocytes and erythrocytes	*	Leukemia
		Connective tissue	Mast cell	Mast cell tumor	Malignant mast cell tumor
EPITHELIAL	Muscle	Smooth muscle	Histiocytes	Histiocytoma	Malignant histiocytosis
		Skeletal muscle	Smooth muscle cell	Leiomyoma	Leiomyosarcoma
	Lining or covering epithelia	Skin	Skeletal muscle cell	Rhabdomyoma	Rhabdomyosarcoma
			Squamous epithelial cell	Papilloma	Squamous cell carcinoma
			Adnexal cells	Adenoma	Adenocarcinoma
			Melanocyte	Benign melanoma	Carcinoma
		Upper alimentary tract	Squamous epithelial cell	Papilloma	Carcinoma
		Lower alimentary tract	Columnar epithelium	Adenoma	Adenocarcinoma
		Upper respiratory tract	Columnar epithelium	Adenoma	Carcinoma
		Lung	Columnar epithelium of bronchi and bronchioles	Adenoma	Adenocarcinoma
					Carcinoma

*Not generally recognized.

Kinds of Tumors

Papilloma(s) - usually occur on skin and may have a variety of forms from pedunculated to flat, smooth or villous.

e.g. warts or “kulugo” (this occur in many species).

Adenomas - occur in glands.

e.g., common in dogs as circumanal gland adenoma
sebaceous gland adenoma and
mammary gland adenoma
thyroid gland adenoma

Polyp – a smooth, spherical or membranous mass projecting on a mucosal surface; may be broad-based or pedunculated.

e.g.,
nasal polyp
rectal polyp

A common group of epithelial tumors found in dogs is the basal cell group – derived from the basal layer of the squamous epithelium.

e.g.
sweat gland adenoma
sebaceous gland adenoma
hair follicle tumor (trichoepithelioma) or sometimes designated as basal cell tumors – sebaceous gland type or ribbon-type (without using words of either adenoma or carcinoma)

Carcinoma – should carry the name of the tissue of origin, of example, squamous cell carcinoma, transitional cell carcinoma, adrenal cortical carcinoma, hepatocellular carcinoma, pancreatic carcinoma, intestinal carcinoma, renal carcinoma, mammary carcinoma and uterine carcinoma.

Hemangiomas are common in the skin of dogs.

LYMPHOSARCOMA – the proper term for malignant tumor of lymphocytes. It has been called various names, such as leukemia, leukosis, lymphoma, malignant lymphoma and lymphomatosis.

Leukemia – a clinical term for malignant cells circulating in the blood stream.

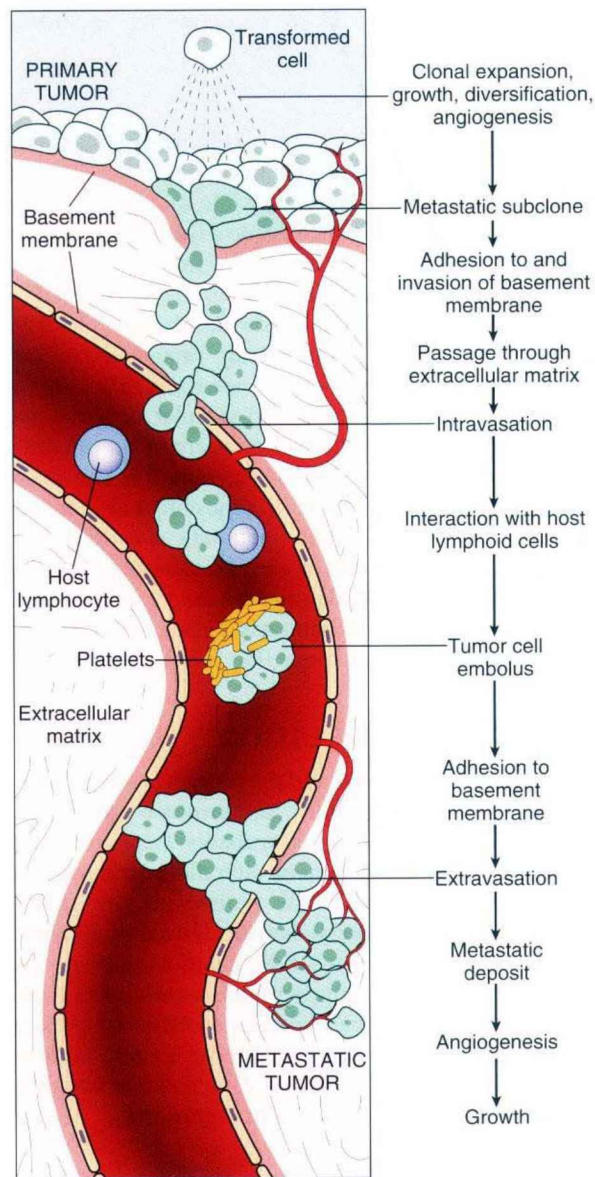
- also mean that there are abnormal malignant cells present in the circulating blood, and it may occur in about half of the cases of lymphosarcoma, but this feature (of leukemia) is more consistent in myelogenous leukemia.

Myelogenous leukemia - malignancy usually involving the granulocytic group (neutrophils, basophils, eosinophils) and may also involve the red cells and the megakaryocytes.

Reticuloendotheliosis and myeloproliferative disorder are the proper terms that can be used when non-specificity of lesion arising from the bone marrow is described.

Tumor Nomenclature–Cont'd

ORIGIN		Tissue of Origin	Cell of Origin	Benign	Malignant
EPITHELIAL–Cont'd	Solid epithelial organs	Urinary tract	Alveolar epithelium	Adenoma	Adenocarcinoma
			Transitional epithelium	Papilloma	Transitional cell carcinoma
		Uterus	Columnar epithelium	Uterine polyp	Endometrial carcinoma
					Endometrial adenocarcinoma
		Lining of glands or ducts	Prostate, thyroid, bile ducts of liver, etc.	Adenoma	Adenocarcinoma
		Glands	Pancreas, salivary gland, etc.	Adenoma	Adenocarcinoma
		Liver	Hepatocyte	Hepatoma	Hepatocellular carcinoma
		Kidney	Renal tubular cell	Renal tubular adenoma	Renal cell carcinoma
		Testicle	Sertoli cell	Sertoli cell tumor	Sertoli cell tumor
			Interstitial cell	Interstitial cell tumor	
		Ovary	Stromal cell	Germ cell	Seminoma
				Seminoma	Teratocarcinoma
				Teratoma	*
				Granulosa cell tumor	*
NERVOUS TISSUE	Glial cells	Central nervous system	Astrocyte	Luteoma	*
				Thecoma	*
			Oligodendrocyte	Dysgerminoma	Dysgerminoma
				Teratoma	Teratocarcinoma
		Peripheral nervous system	Schwann cell	*	Astrocytoma
				Schwannoma	Glioblastoma
	Neural cells	Central nervous system	Neuron	*	Oligodendroglioma
					Microgliomatosis
		Peripheral nervous system	Neuron		Malignant schwannoma
				Ganglioneuroma	
MIXED TUMORS	Various	Mammary gland	Epithelium and myoepithelium	Benign mixed mammary tumor (dog)	Malignant mixed mammary tumor (dog)
				Adenoma	Adenocarcinoma
		Testicle	Germ cell	Teratoma	Teratocarcinoma
		Ovary	Germ cell	Teratoma	Teratocarcinoma



The metastatic cascade. This figure illustrates the sequential steps involved in the hematogenous spread of a tumor. Similar events occur during lymphatic spread.

GROSS DESCRIPTION OF TUMORS

Abnormal mass – is the common descriptive term used for unusually or greatly enlarged organ.

Persistent non-healing ulcerating lesion – ulcerated lesion particularly on body surfaces.

Size is no indication of prognosis; a tiny tumor may be highly malignant and a huge one may be benign. Benign tumors tend to be discrete masses.

Microscopic patterns of growth are variable, but general patterns are useful for purposes of recognition and description.

Microscopic Descriptions:

1. **Sheets of cells** – term that is used to describe a monotonous pattern of masses of cells with

similar appearance and very little apparent stromal support, just cell after cell after cell.

2. **Acinar arrangements** – these are characterized by cells forming or attempting to form acinar units, as in a secretory gland like the thyroid or mammary gland.
3. **Nests of cells** are typical of endocrine tumors in which a clump or nests of cells is surrounded by a narrow band of connective tissue stroma.
4. **Palisading or trabecular patterns** occur when cells line up in a picket fence-type arrangement along a strand of connective tissue, such as in the testicular interstitial cell tumor.
5. **Tubular arrangements** occur when a single, double or finger-like projection of tumor cells invade surrounding tissue. Examples are basal cell tumors or anal gland tumors.

When there is little apparent stroma, stromal arrangements may be described as:

1. **scant**, as in sheets of cells
2. **locular**, as in the case of nests
3. **scirrhous**, the reaction when the stroma is very dense and perhaps even predominating over actual tumor cells.

Terminologies for sarcomas:

1. **Solid or loose arrangements**
2. **Whorls**
3. **Sheets**
4. **Localized around blood vessels**
5. **Spindly cells**
6. **Fleshy cells**
7. **Well or poorly-differentiated**
8. **Monotonous**
9. **Variable**

Necrosis is prominent in many tumors, particularly in the center of a large mass, and the tissue becomes pale and soft.

Chalones – chemical messengers that regulate growth and mitosis

SPREAD OF TUMORS: INVASION AND METASTASIS

Four main mechanisms for the spread of tumors:

1. **by infiltration**
2. **by spreading via blood vessels**
3. **by spreading via the lymphatics**
4. **by implantation**

METHODS OF TUMOR DIAGNOSIS

1. **Histologic Examination** – the most important method

by biopsy method – fine needle aspiration
by exfoliative cytologic examination

2. **Immunocytochemical Examination**
by use of monoclonal antibody

by immunofluorescence method

3. DNA Probe Analysis and DNA Flow Cytometry Comparison between Benign and Malignant Neoplasm

4. TUMOR MARKER Detection

1. Alpha fetal globulin – detected in patients with hepatocellular carcinoma.

- abnormal antigen detected in blood of patient with neoplastic condition.
- produced by fetal hepatocytes but normally disappears late in fetal life.

2. Carcinoembryonic antigen - widely used for cancer detection particularly in respiratory and gastrointestinal tumors.

- normally made by intestinal epithelium in fetal life. Appear in adult life in events of tumor.

ETIOLOGY OR CAUSES OF TUMORS

The main etiological factors or CARCINOGENS:

1. IRRADIATION - induces mutation

- UV rays from sunlight; X and Gamma rays
- electromagnetic and ionizing radiation (i.e. nuclear radiation)

2. CHEMICAL - mutagenic effect

- polycyclic aromatic hydrocarbons (i.e. cigarette smoke)
- azo dyes (i.e., beta-naphthylamine, an aniline dye used in rubber industries)
- aromatic amines
- alkylating agents such as cyclophosphamide and busulfan used in cancer treatment.
- Aflatoxins from aspergilli
 - hormones (i.e. estrogen) that induces endometrial cancer.

3. VIRAL

DNA viruses

- Hepatitis B virus

- Papillomaviruses

- adenovirus, herpes virus, papovavirus, and poxvirus

- Herpesvirus (which causes Marek's disease in chickens, malignant lymphoid neoplasms in guinea pigs, rabbits etc.

RNA viruses

All oncogenic RNA viruses belong to the Retroviruses. Called as retrovirus because it possesses an enzyme called *reverse transcriptase* or RNA-dependent DNA polymerase. This enzyme can form DNA using an RNA template.

- RNA genome contains three sets of genes: 1) *gag*, encoding viral coat proteins; 2) *pol*, encoding the reverse transcriptase and 3) *env*, encoding envelop glycoproteins.

- causes lymphosarcoma in several species of non-human primates, cats, cattle, chickens, mice etc.

ONCOGENES AND CANCER

- oncogenes are genes whose products are associated with neoplastic transformation
- proto-oncogenes (*proto-oncs*) are normal cellular genes that affect growth and differentiation.

Proto-oncs can be converted to into oncogenes by:

- (1) transduction into retroviruses (*v-oncs*)
- (2) changes in situ that affect their expression and/or function, thereby converting them into *c-oncs*.

v-oncs – viral oncogenes

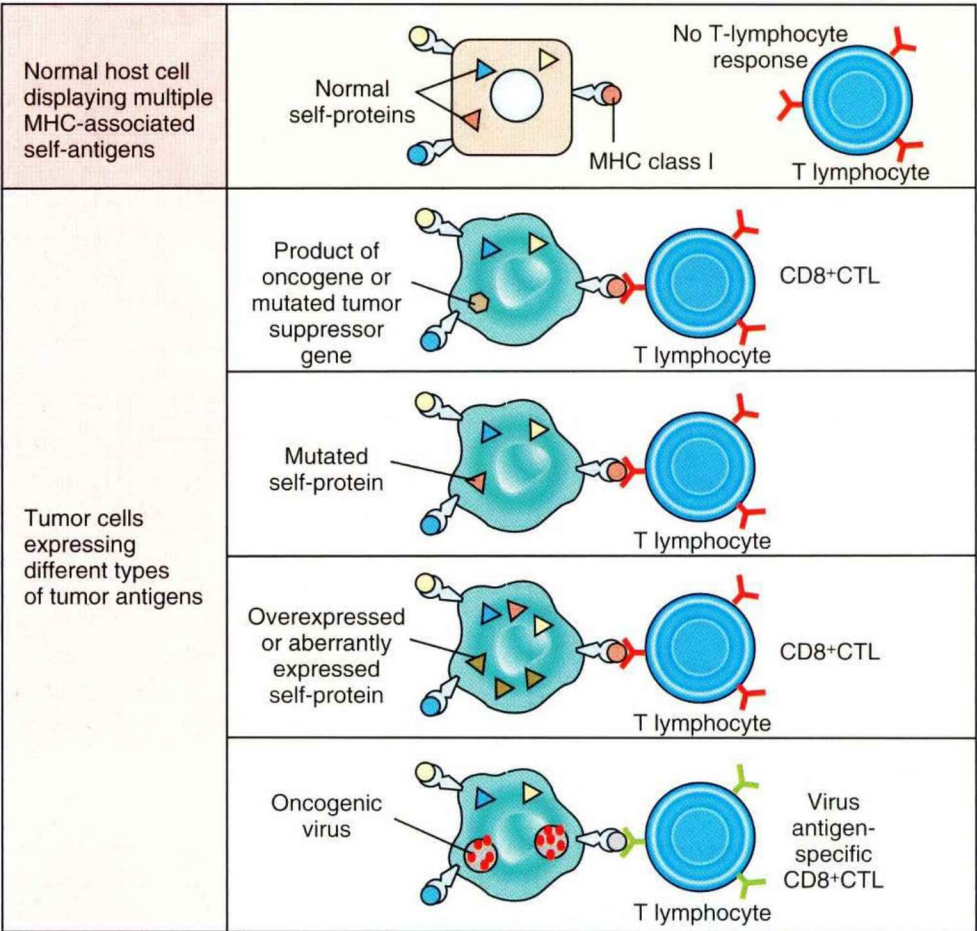
c-oncs – cellular oncogenes

TREATMENT OF TUMORS

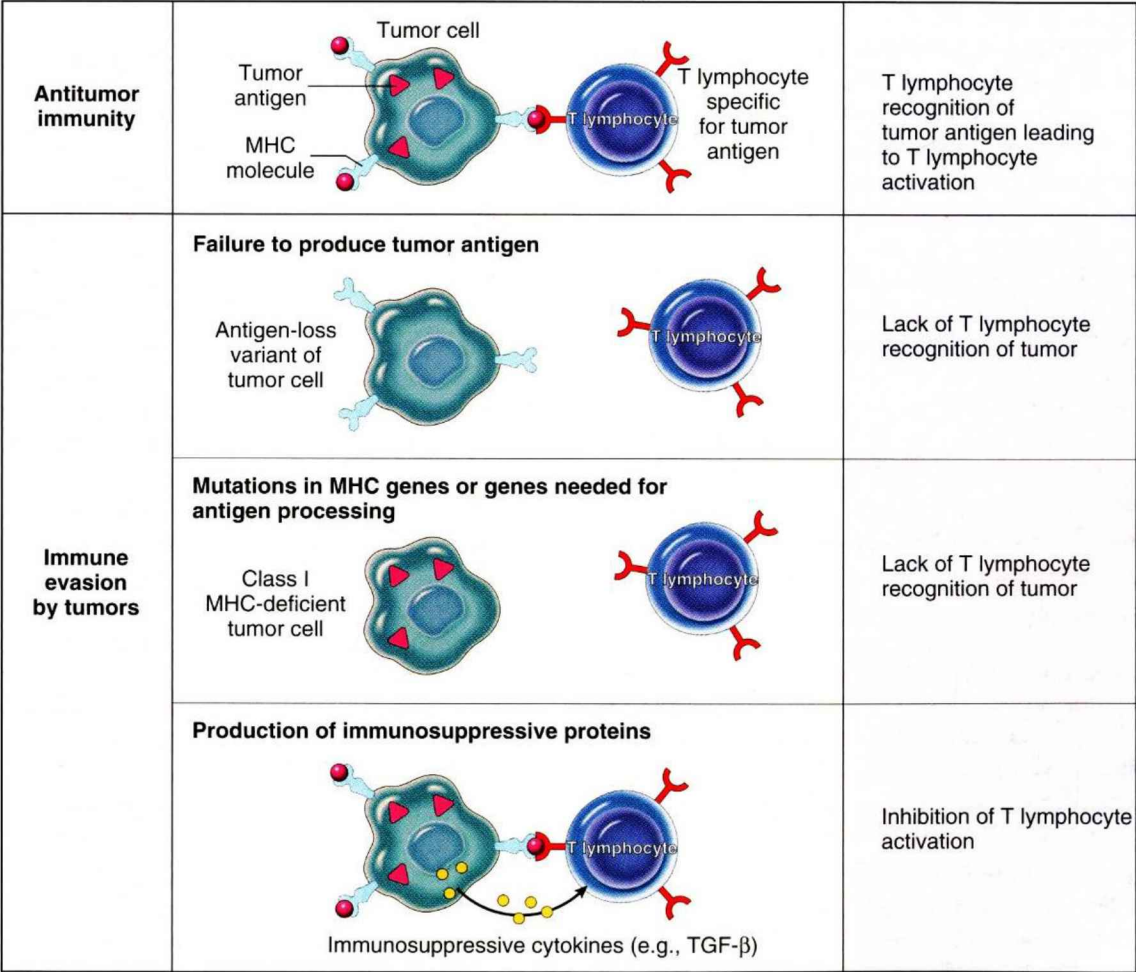
1. by surgery
2. by irradiation
3. by chemotherapy
4. by immunotherapy

Cancer Susceptibility in Dogs

Tumor Site	Tumor Type	Susceptible Breeds	Resistant Breeds
Hematopoietic system	Lymphoma	Boxer	Crossbreeds
Brain	Malignant histiocytosis	Bernese mountain dog	
Skin	Various	Boston terrier, boxer, bulldog	
	Mast cell tumor	Boxer, bulldog, retriever	
	Vascular tumor		
	Hemangiosarcoma	German shepherd	
Mammary gland	Various	Boxer, Brittany spaniel, dachshund, English setter, Labrador retriever, pointer, Springer spaniel	Boxer,* German shepherd, crossbreeds
Nose and sinuses	Various	Airedale, collie, Scottish terrier	
Oropharynx	Various	Boxer, cocker spaniel, golden retriever	Beagle, dachshund
Ovary	Carcinoma	Pointer	
Pancreas	Carcinoma, insulinoma	Airedale terrier, poodle	
Thyroid	Carcinoma	Beagle, boxer, retriever	Poodle
Skeleton	Osteosarcoma	Giant breeds, boxer, Danish dog, German shepherd, rottweiler	Crossbreeds
Testis		Boxer, collie, German shepherd	
Urinary bladder	Carcinoma	Beagle, collie, Scottish terrier	



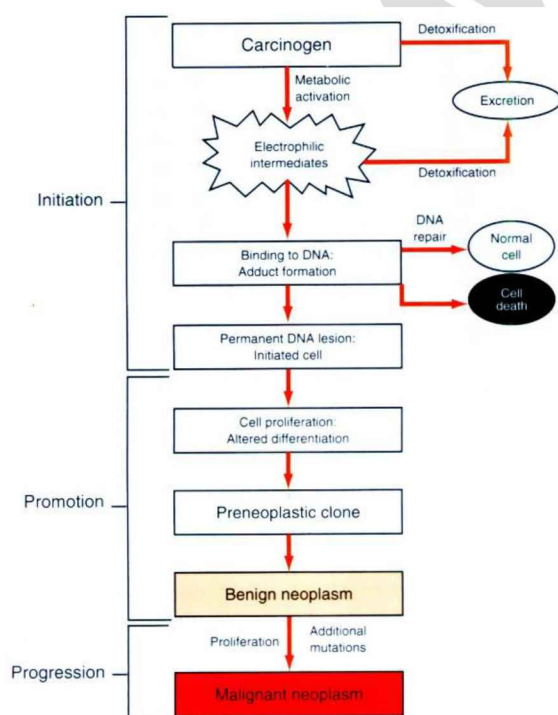
Tumor antigens recognized by CD8⁺ lymphocytes. Note that all tumor antigens are presented to CD8⁺ T lymphocytes by major histocompatibility (MHC) class I molecules. CTL, Cytotoxic T lymphocyte.



Mechanisms by which tumors evade the immune system. Tumor cells employ a variety of mechanisms to avoid attack by cytolytic T lymphocytes. MHC, Major histocompatibility complex; TGF-β, transforming growth factor-β.

Oncogenic Viruses of Animals

Classification	Virus	Species Affected	Associated Tumors
Retrovirus	Mouse mammary tumor virus	Mouse	Mammary adenocarcinomas
	Avian sarcoma-leukosis virus complex	Fowl	Various sarcomas, carcinomas, lymphomas, leukemias
	Avian reticuloendotheliosis virus complex	Fowl	Lymphomas, leukemias
	Mouse leukemia and sarcoma viruses	Mouse	Various sarcomas, carcinomas, lymphomas, leukemias
	Feline leukemia virus	Cat	Leukemias, lymphomas
	Bovine leukosis virus	Cattle	Leukemias, lymphomas
	Primate leukemia and sarcoma viruses	Primate	Fibrosarcomas, leukemias
	Mason-Pfizer monkey virus	Primate	Fibrosarcomas
	Feline immunodeficiency viruses	Cat	Lymphomas
	Maedi-Visna virus	Sheep	Pulmonary carcinomas
Hepadnavirus	Hepatitis B group	Primate, rodent, duck	Hepatocellular carcinomas
Papovavirus	Polyoma	Mouse	Various carcinomas, sarcomas
	SV40	Primate	Sarcomas (in rodents)
	Papilloma	Many species	Papillomas, carcinomas
Adenovirus	Types 2, 5, 12	Human	Sarcomas (in hamsters)
Herpesvirus	Frog herpesvirus	Frog	Adenocarcinomas
	Marek's disease	Fowl	Lymphoproliferative disease
	Herpesvirus ateles	Primate	Lymphomas, leukemias
	Herpesvirus saimiri		
Poxvirus	Various	Various	Fibromas, papillomas



General schema of events in chemical carcinogenesis. Note that promoters cause clonal expansion of the initiated cell, thus producing a preneoplastic clone. Further proliferation induced by the promoter leads to formation of a benign neoplasm. Accumulation of additional mutations during the phase of tumor progression results in emergence of a malignant tumor.

I. Host-Parasite Relationship

Infectious disease results from the interaction of an infectious agent with the host in its particular environment.

The Host

Primary protective factor is RESISTANCE:

Four Types of Resistance

- 1) Genetic or natural resistance

- 2) Species resistance
- 3) Age and Sex resistance
- 4) Immune resistance
 - a. passive Immunity
 - b. active Immunity
- 5) Nutritional

The Agent

Influential Factors

- 1) Virulence
- 2) Tropism
- 3) Ability to persist or to spread in the host

The Environment

Influential Factors

- 1) Ambient temperature
- 2) Humidity
- 3) Spacing
- 4) Housing/Shelter
- 5) Moisture
- 6) Ventilation
- 7) Lighting
- 8) Feeds
- 9) Various environmental pollutant

WAY BY WHICH THE FOLLOWING CAUSE A DISEASE:

BACTERIA generally cause disease: (singly or in combination)

- 1) invasion
- 2) production of toxins
- 3) by attaching or colonizing
- 4) by evading hosts defenses

VIRUSES generally cause disease:

- 1) by cytolysis
- 2) by maintaining steady state with the host
- 3) by integrating into the genome of the host

PARASITES generally cause disease by:

- 1) local destruction of cells/tissues

- 2) by their effects on blood circulation
- 3) by their effects as space-occupying lesions
- 4) by nutritive competition

FUNGI generally cause disease by:

- 1) invasion of living tissue
- 2) inducing allergies or hypersensitivities
- 3) toxicosis

TOXINS or POISONS generally produce disease by:

- 1) by direct contact (causing sudden degeneration and necrosis)
- 2) by absorption (striking lesion produced and derangement of metabolism)

Symbiosis – the general term for living together or co-existence of two organisms. Such “living together” or “co-existence” maybe mutualistic, commensalistic or parasitic.

Types of Relationships:

Parasitic Relationship or Parasitism

- one partner lives at the expense of another.

Commensalism

- there is advantage to one partner but no real disadvantage to the other.

Mutualism

- two organisms live together without disadvantage nor harm to one another.

II. SYSTEMIC PATHOLOGY

a. Digestive System

DISEASES OF THE MOUTH

1. Cleft Palate or Cleft Lip (Harelip) Complex:

- ✓ This is due to a disturbance of the processes that form the jaw and face during embryonic development.
- ✓ Cleft of the lower lip is rare and usually occurs on the midline.
- ✓ Clefts of the upper lip, usually at the junction of the premaxilla and maxilla, may be unilateral or bilateral, complete or incomplete, and often are associated with clefts of the alveolar process and palate.
- ✓ The defect may also involve the palate alone, affecting the hard or soft components of the palate, or both.
- ✓ Developmental anomalies affecting other organ systems are seen in ~8% of dogs and cats with cleft palate or lips.
- ✓ The primary etiology is hereditary, although maternal nutritional deficiencies, drug or chemical exposure, mechanical interferences with the fetus, and some viral infections during pregnancy have also been implicated.
- ✓ Ingestion of toxic agents may also play a role; eg, ingestion of lupines (*Lupinus sericeus* and *L. caudatus*) during the second and third months of gestation in cattle can potentially result in “crooked calf disease,” of which cleft abnormalities may be a component.

- ✓ Initial signs reflect the extent of the malformation but may include difficulty suckling, dysphagia, and evidence of milk dripping from the nostrils when the newborn attempts to nurse.

- ✓ Respiratory infection due to aspiration of food is common and a grave consequence with a poor prognosis.

2. Brachygnathia

- ✓ (overshot, short lower jaw, or parrot mouth in horses) is manifest when the mandible is shorter than the maxilla.

- ✓ In cattle, it is inherited as a polygenetic factor and can be associated with other anomalies such as impacted molar teeth and osteopetrosis in Angus calves and Simmental cattle, or with chromosomal aberrations such as trisomy, which is lethal.

- ✓ In small animals, mild forms may be of no clinical significance; however, more severe forms may result in trauma to the hard palate or the restriction of normal mandibular growth secondary to erupting adult mandibular canine teeth.

3. Craniofacial dysplasia

- ✓ of Limousin cattle is characterized by a convex profile of the nose, short lower jaw, deficient ossification of frontal sutures, exophthalmos, and a large tongue;
- ✓ it is thought to be due to homozygosity of a simple autosomal recessive gene.

4. Prognathia (undershot, or monkey or sow mouth in horses)

- ✓ is found when the mandible is longer than the maxilla.
- ✓ It is identified on oral examination by finding the mandibular incisors in contact with or rostral to the maxillary incisors.
- ✓ In brachycephalic dogs and Persian cats, it is considered a normal breed characteristic.

TONGUE ANOMALIES:

1. Ankyloglossia or microglossia

- ✓ refers to incomplete or abnormal development of the tongue.
- ✓ It is often referred to as “bird tongue” in dogs and may be a component of the fading puppy syndrome.
- ✓ Affected puppies have difficulty nursing and do poorly. Oral examination reveals missing or underdeveloped lateral and rostral thin portions of the tongue that result in prehensile and motility disturbances.
- ✓ It is generally lethal.

2. Macroglossia, or large tongue, is seen in belted Galloway cattle but resolves with age and is rarely clinically significant.

3. Epitheliogenesis imperfecta,

- ✓ or “smooth tongue,” is a condition of incomplete development of the lingual filiform papillae that is transmitted as an

- autosomal recessive trait in Holstein, Friesian, and Brown Swiss cattle.
- ✓ It results in excessive salivation and an unthrifty condition.

TIGHT-LIP SYNDROME OF CHINESE SHAR-PEIS:

- ✓ Some Shar-Peis have a small or absent lower anterior lip vestibule.
- ✓ The lower lip covers the lower teeth and folds over the lower incisor teeth toward the tongue.
- ✓ Contact between the palatal surface of the upper incisors and the lower lip worsens the lip position and may contribute to the lingual displacement of the lower incisor teeth

DISEASES OF THE TEETH**1. Abnormal Number:**

- ✓ In most species, a reduction in the number of teeth (termed anodontia) is rare, although in dogs, molars and premolars may fail to develop or erupt.
- ✓ Supernumerary teeth occasionally are found in the incisor or molar regions of horses; in dogs, they are usually unilateral and most often in the upper jaw.
- ✓ In dogs, although rare, improper germination of the permanent dental arcade may lead to splitting of the tooth bud to form 2 teeth.
- ✓ The result may be crowding and subsequent rotation of the teeth, which necessitates extraction to prevent or correct occlusal abnormalities.

2. Irregularities of Shedding:

- ✓ In premolar teeth of ruminants, the root of the temporary tooth may be absorbed, but the crown may persist as a covering or "cap" to the erupting permanent tooth.
- ✓ These caps are readily removed with forceps if they have not separated spontaneously.
- ✓ Delayed shedding of deciduous teeth in dogs is common and secondary to the failure of the periodontal ligament to detach from the deciduous tooth, with the permanent canine teeth erupting rostrally.
- ✓ This may cause permanent tooth displacement, which can occur within 2-3 wk, and result in malocclusion or food entrapment and subsequent periodontal disease.
- ✓ Therefore, retained deciduous teeth should be removed as soon as possible, taking care not to damage the underlying permanent tooth bud.

3. Abnormalities in Position, Shape, and Direction:

- ✓ In horses, this may affect the incisors and result in long-axis rotation or overlapping of adjacent teeth.

- ✓ In brachycephalic dogs, the upper third premolar and occasionally other premolar or molar teeth may rotate.
- ✓ Usually, this is of no clinical significance but may require extraction of some involved teeth if crowding or occlusal abnormalities occur.
- ✓ Abnormalities in shape, including dens in dente, are reported in various species and breeds.

4. Enamel Lesions:

- ✓ Hypoplasia or disruption in enamel formation can occur in both large and small animals.
- ✓ Common causes are pyrexia, trauma, malnutrition, toxicosis (eg, fluorosis in cattle), and infections (eg, distemper virus in dogs).
- ✓ Lesions vary, depending on the severity and duration of the insult, from pitted enamel to the absence of enamel with incomplete tooth development.
- ✓ Affected teeth are prone to plaque and tartar accumulation and subsequent bacterial penetration and formation of caries.
- ✓ In small animals, resin restoration has been used to cover defects, although diligent dental hygiene and home care is critical in reducing the incidence of complications.
- ✓ Enamel may also develop discoloration. In small animals, administration of tetracyclines to pregnant females or to puppies <6 mo old may result in a permanent brownish yellow discoloration of the teeth.
- ✓ In ruminants, the enamel of some teeth may demonstrate flecks of varying color.
- ✓ The condition is thought to have a genetic etiology but generally is of no clinical significance; however, some believe affected teeth may be prone to more rapid wearing.

CYSTS AND SINUSES OF THE HEAD AND NECK**Thyroglossal duct cyst**

- ✓ is the result of postnatal persistence of the early embryonic thyroglossal duct.
- ✓ This rare cyst is always single and found in the middle of the neck, usually at the level of the hyoid bone and larynx.
- ✓ It is smoothly rounded with a well-defined border, anchored to the hyoid bone and deep tissues.
- ✓ Unless infection is superimposed, it is seldom attached to the skin. It is not tender and contains fluid.

Branchial (or lateral cervical) cyst

- ✓ develops from branchial apparatus malformation, usually of the second branchial cleft.
- ✓ Unilateral or bilateral branchial cysts occupy a lateral position in the upper neck and are usually only slightly mobile.
- ✓ Their size varies considerably, and an individual cyst may change size periodically as its contents escape through a small opening into the throat or through a small cutaneous fistula (branchial or lateral cervical fistula).

Dentigerous cysts

- ✓ are of epithelial origin and arise from abnormal tooth development.
- ✓ They often contain tooth fragments and usually involve the maxilla and mandible to varying degrees.
- ✓ These cysts can be found in young (<3 yr) horses or ruminants (primarily sheep). In young horses, they may be difficult to differentiate from cystic sinuses (osteitis fibrosa cystica), which also typically result in facial or mandibular distortion.

ESOPHAGUS**Congenital megaesophagus**

- ✓ is thought to result from developmental anomalies in esophageal neuromuscular innervation.
- ✓ Incidence is increased in Chinese Shar-Peis, Fox Terriers, German Shepherds, Great Danes, Irish Setters, Labrador Retrievers, Miniature Schnauzers, Newfoundlands, and Siamese cats.
- ✓ In Fox Terriers, it is an autosomal recessive trait, whereas in Miniature Schnauzers, it is an autosomal dominant.

Vascular ring entrapment anomalies

- ✓ most commonly result from persistence of the right fourth aortic arch during embryonic development, which results in esophageal entrapment at the heart base by the right fourth aortic arch, left atrium, pulmonic artery, and the ligamentum arteriosum.
- ✓ This obstructs food passage and results in food retention and subsequent esophageal dilation anterior to the anomaly. Boston Terriers, German Shepherds, and Irish Setters have higher breed incidences.

Cricopharyngeal achalasia

- ✓ is a failure, or asynchrony, of the cricopharyngeus muscle to relax during swallowing, thereby preventing the normal passage of a food bolus from the caudal pharynx to the cranial

esophagus. It has been mainly identified in toy breeds and rarely in cats.

Lower esophageal sphincter achalasia

- ✓ is now considered to be a component of a more generalized esophageal motor disturbance (ie, megaesophagus) and no longer a distinct entity.
- ✓ Identification of an esophageal disorder is generally based on characteristic clinical signs (eg, regurgitation) and contrast radiography or fluoroscopy of the swallowing reflex.

Esophageal diverticula

- ✓ may involve the cervical esophagus just cranial to the thoracic inlet or be epiphrenic (just cranial to the diaphragm).
- ✓ Clinical signs depend on severity and are seen in only 10-15% of cases but may include impaction, esophagitis, and rarely rupture or tracheoesophageal fistula formation.

Hernias

- ✓ Hernias involving the abdomen are seen when abdominal contents protrude through a natural or abnormal opening in the body wall.
- ✓ They may be congenital or acquired. In acquired hernias, there is usually a history of trauma.
- ✓ Congenital hernias may involve the diaphragm or the abdominal wall.
- ✓ Hernias involving the diaphragm are of 3 main types:
 1. peritoneopericardial, in which abdominal contents are found extending into the pericardial sac;
 2. pleuroperitoneal, in which abdominal contents are found within the pleural cavity; and
 3. hiatal, in which the abdominal esophagus, gastroesophageal junction, and/or portions of the stomach protrude through the esophageal hiatus of the diaphragm into the thoracic cavity. Hiatal hernias may be "sliding" and result in clinical signs of reflux esophagitis (anorexia, salivation, and/or vomiting) that may be intermittent.
- ✓ Hernias involving the abdominal wall include umbilical, inguinal, or scrotal.
- ✓ Umbilical hernias are secondary to failure of the normal closure of the umbilical ring and result in protrusion of abdominal contents into the overlying subcutis.
- ✓ Size varies depending on the extent of the umbilical defect and the amount of abdominal contents contained within it.

- ✓ The etiology in both large and small animals is likely to have a genetic component; however, excess traction on an oversized fetus or cutting the umbilical cord too close to the abdominal wall are other possible causes.
- ✓ Inguinal hernias in male pigs are common, and they usually extend into the scrotum.
- ✓ In female pigs, this defect is invariably accompanied by arrested genital development; such animals are sterile, and surgery is indicated only when the size of the defect is a threat to the growth of the pig to market weight.
- ✓ Inguinal hernias in male foals often resolve spontaneously during the first year of life.
- ✓ For this reason, early corrective surgery is not indicated unless the hernia is strangulated or of such magnitude that it interferes with gait.
- ✓ Strangulated inguinal hernia in stallions is fairly frequent and is characterized by signs of constant and severe abdominal pain.

STOMACH

- ✓ Besides hiatal hernia the most common abnormality involving the stomach with a suspect heritable etiology is pyloric stenosis.
- ✓ Pyloric stenosis or hypertrophy results from muscular thickening of the pyloric sphincter, which obstructs pyloric outflow.
- ✓ Affected breeds include brachycephalic and smaller breeds, especially Boxers and Boston Terriers, as well as Siamese cats.
- ✓ Clinical signs reflect delayed gastric emptying and usually manifest as vomiting of food several hours after a meal.

SMALL AND LARGE INTESTINE

- ✓ Maldigestion or malabsorption disorders usually manifest as chronic, persistent GI signs including vomiting, weight loss, small- and/or large-intestinal diarrhea, or a combination of the above.
- ✓ There are many potential etiologies, both heritable and acquired, and most are associated with inflammatory bowel disease (IBD).
- ✓ Congenital conditions may have specific breed predilections. Soft-coated Wheaten Terriers have a high incidence of concurrent protein-losing enteropathy and nephropathy.

- ✓ Both IBD and food allergies are considered to be a component of this syndrome.
- ✓ Irish Setters are reported to have a familial tendency for a gluten-sensitive enteropathy, with clinical signs beginning as early as 6 mo of age.
- ✓ The wheat sensitivity is both confirmed and treated through the use of gluten-free diets.
- ✓ Basenjis are prone to an immunoproliferative enteropathy of unknown mode of inheritance; severe lymphocytic-plasmacytic enteritis is a component, and the condition may progress to lymphoma.
- ✓ Lymphangiectasia is a malformation of the intestinal lymphatic system that results in a protein-losing enteropathy that may be congenital or acquired.
- ✓ The impaired lymphatic drainage results in dilated lacteals and lymphatics of the intestinal wall
- ✓ Exocrine pancreatic insufficiency (EPI) has a higher incidence in German Shepherds and is due to pancreatic acinar atrophy; it is an acquired disease (secondary to pancreatitis) in cats.
- ✓ The lack of pancreatic enzymes results in an osmotic diarrhea, in which steatorrhea is a prominent feature. Affected animals either fail to gain weight or, if EPI is acquired later in life, show a dramatic weight loss..
- ✓ Ileocolonic agangliosis has been reported in white foals produced by matings of Overo horses to each other.
- ✓ Although the foals appear normal at birth, they soon develop colic and die on the second day.
- ✓ The affected horses are white and have blue irises.
- ✓ Inherited atresias of the small- and large-intestinal tracts are relatively common in large animals.
- ✓ Atresia coli has been reported in Percheron horses and involves the ascending colon at the pelvic flexure.
- ✓ In Swedish Highland cattle, atresia ilei has been recorded, and atresia of the small intestine is seen in lambs.
- ✓ These conditions are invariably fatal.
- ✓ Anal atresia has been reported in sheep, pigs, and cattle; it results when the dorsal membrane separating the rectum and anus fails to rupture.
- ✓ Segmental aplasia (rectal agenesis) is seen when the rectum terminates in a blind pouch before reaching the anus.

- ✓ Surgical correction is difficult because the location of the terminal section varies, and iatrogenic damage to nerves in the area may occur.
- ✓ Colonic and rectal duplications are rare, and affected animals generally show signs of large-bowel disease.
- ✓ Rectourethral fistula has been reported in English Bulldogs and is seen clinically as simultaneous urination from both the urogenital and anal orifices along with a history of chronic urinary tract infections.
- ✓ Rectovaginal fistula is a fistulous tract that connects the vagina and rectum and usually is seen in conjunction with imperforate anus.
- ✓ Passage of feces through the vulva or signs of colonic obstruction are suggestive.

ANAL SAC DISEASE

- ✓ Anal sac disease is the most common disease entity of the anal region in dogs. Small breeds are predisposed; large or giant breeds are rarely affected. In cats, the most common form of anal sac disease is impaction.

Etiology and Pathogenesis:

- ✓ Anal sacs may become impacted, infected, abscessed, or neoplastic.
- ✓ Failure of the sacs to express during defecation, poor muscle tone in obese dogs, and generalized seborrhea (which produces glandular hypersecretion) lead to retention of sac contents. Such retention may predispose to bacterial overgrowth, infection, and inflammation.

Clinical Findings and Lesions:

- ✓ Signs are related to pain and discomfort associated with sitting.
- ✓ Scooting, licking, biting at the anal area and painful defecation with tenesmus may be noted.
- ✓ Induration, abscesses, and fistulous tracts are common.
- ✓ In impaction, hard masses are palpable in the area of the sacs; the sacs are packed with a thick, pasty, brown secretion, which can be expressed as a thin ribbon only with a large amount of pressure.
- ✓ When the sacs are infected or abscessed, severe pain and often discoloration of the area are present.
- ✓ Fistulous tracts lead from abscessed sacs and rupture through the skin; these must be differentiated from perianal fistulas.
- ✓ Anal sac neoplasms are usually nonpainful and are associated with perineal edema, erythema, induration, or fistula formation.

- ✓ Apocrine gland adenocarcinomas of the anal sac are typically seen in older female dogs.

- ✓ These dogs are presented for signs secondary to hypercalcemia, such as polyuria and polydipsia, or for problems related to the perineal mass.

Perianal Fistula

- ✓ Perianal fistula is characterized by chronic, purulent, malodorous, ulcerating, sinus tracts in the perianal tissues.
- ✓ It is most common in German Shepherds and is also seen in Setters and Retrievers. Dogs >7 yr old are at higher risk.

Etiology and Pathogenesis:

- ✓ The cause is unknown, although many theories have been proposed.

Perineal Hernia

- ✓ Perineal hernia is a lateral protrusion of a peritoneally lined hernial sac between the levator ani and either the external anal sphincter muscle or the coccygeus muscle.

Etiology and Pathogenesis:

- ✓ Many factors are involved, including breed predisposition, hormonal imbalance, prostatic disease, chronic constipation, and weakness of the pelvic diaphragm due to chronic straining.
- ✓ The higher incidence among sexually intact males is evidence that hormonal influences probably play a primary role.
- ✓ Prostatic hypertrophy attributed to sex-hormone imbalance has been strongly implicated.
- ✓ Both estrogens and androgens have been cited as causative agents.

Clinical Findings and Diagnosis:

- ✓ Common signs include constipation and obstipation, tenesmus, and dyschezia. Stranguria and urinary obstruction may develop secondary to retroflexion of the bladder and prostate.
- ✓ The mass is soft and fluctuant and may be reduced digitally.
- ✓ A firm, painful swelling may be compatible with retropulsion of the bladder and prostate.
- ✓ Determination of contents is often made by rectal examination and perineal centesis (to determine if urine is present).
- ✓ Over 90% of perineal hernias contain a rectal deviation, which is a sacculation of the rectum into the hernial sac, where the layers of the rectal wall remain intact.

Rectal Neoplasms

- ✓ Malignant rectal neoplasms are usually adenocarcinomas in dogs and lymphosarcomas in cats.
- ✓ Adenocarcinomas are slow growing and infiltrative.

- ✓ Local or systemic metastasis may develop before tenesmus, dyschezia, hematochezia, or diarrhea is seen.
- ✓ Surgery is the treatment of choice for adenocarcinomas, but it may be unrewarding because metastasis has usually occurred before the diagnosis.
- ✓ Cats with rectal lymphosarcoma are treated medically with antineoplastic drugs.

Rectal Polyps

- ✓ Rectal adenomatous polyps are an infrequent, usually benign disease, primarily of small animals.
- ✓ The larger the polyp, the greater the potential for malignancy.

Rectal Prolapse

- ✓ In rectal prolapse, one or more layers of the rectum protrude through the anus due to persistent tenesmus associated with intestinal, anorectal, or urogenital disease.
- ✓ Prolapse may be classified as incomplete, in which only the rectal mucosa is everted, or complete, in which all rectal layers are protruded.

Etiology:

- ✓ Rectal prolapse is common in young animals in association with severe diarrhea and tenesmus.
- ✓ Perineal hernia, or other interruption of normal innervation of the external anal sphincter, may also produce prolapse.
- ✓ In cattle, it may be associated with coccidiosis, rabies, or vaginal or uterine prolapse; occasionally, excessive "riding" and associated traumatic injury may be causative in young bulls.
- ✓ It is common in sheep with short tail docking and especially in feedlot lambs, in which high-concentrate rations may be causative.

Clinical Findings, Lesions, and Diagnosis:

- ✓ An elongated, cylindrical mass protruding through the anal orifice is usually diagnostic.
- ✓ However, it must be differentiated from prolapsed ileocolic intussusception by passing a probe, blunt instrument, or finger between the prolapsed mass and the inner rectal wall.
- ✓ In rectal prolapse, the instrument cannot be inserted due to the presence of a fornx.

LIVER

- ✓ The most common congenital liver anomaly is portosystemic shunt (PSS).
- ✓ Breeds with a reported increased incidence include Yorkshire Terriers, Miniature Schnauzers, and Himalayan and Persian cats.
- ✓ PSS results in portal blood bypassing the liver and gaining direct access to the systemic vascular system.

- ✓ Shunts may be:
 1. single and intrahepatic (most often secondary to a patent fetal ductus venosus),
 2. single and extrahepatic (with various possible vascular routes between the portal and postcava or azygous vein), or
 3. multiple and secondary to intrahepatic arterioportal fistulas.
- ✓ Hepatoportal microvascular dysplasia is an intrahepatic circulatory disorder that results in the shunting of portal blood to the systemic circulation.
- ✓ The syndrome is well defined in Cairn Terriers and Yorkshire Terriers, although it has also been reported in Maltese, Dachshunds, Toy and Miniature Poodles, Bichon Frise, Pekingese, Shih Tzus, and Lhasa Apsos.
- ✓ It is generally asymptomatic, with its predominant clinical significance being its differentiation from PSS, as bile acid testing is abnormal in both; this can be done only through the exclusion of a definable macroscopic shunting vessel(s).
- ✓ Copper-associated hepatopathy is a metabolic derangement of hepatic copper storage resulting in progressive hepatocellular copper accumulation and the subsequent development of chronic hepatitis and hepatic cirrhosis.
- ✓ This condition is well defined in Bedlington Terriers, in which 3 clinical variations are described: acute hepatic necrosis in young (<6-yr-old) dogs; chronic progressive hepatic failure in older dogs; and asymptomatic but affected (carrier) dogs.
- ✓ Elevated copper levels have also been identified in the familial hepatic disease of West Highland White Terriers, Skye Terriers, and Doberman Pinschers, although a causal relationship, as demonstrated in the Bedlington, has not been defined.

DISEASES OF THE MOUTH IN LARGE ANIMALS**Lip Lacerations:**

- ✓ Wounds of the lips and cheeks are most common in horses.
- ✓ They may be caused by a fall, a kick, or the use of inappropriate bits or restraint devices or, more commonly, from the horse having its lips and sometimes mandible caught as it "plays" in its stall.
- ✓ Lip lacerations may be accompanied by mandibular or incisive bone and dental fractures and avulsions in some cases (eg, if the horse panics).
- ✓ Because of the vascularity of the region, healing is usually rapid.

- ✓ However, once the wound has penetrated into the mouth, careful management is needed to avoid formation of a fistula.
- ✓ First-stage healing is best achieved by the construction of intraoral mucosal flaps to achieve an oral seal.
- ✓ Subsequent skin or mucosal grafts may be necessary to correct large defects or fistulae.

Glossoplegia (Paralysis of the Tongue):

- ✓ This may be seen in newborns as a result of the placement of obstetric snares.
- ✓ Such neonates need to be managed carefully to ensure that they are able to eat; ingestion of colostrum is particularly important. Fluid therapy (IV) and anti-inflammatory treatments are required.
- ✓ If the condition persists for >10 days after birth, the likelihood of regaining normal function is slight.
- ✓ Inflammatory diseases and trauma may also result in transient glossoplegia.
- ✓ Glossoplegia of central origin may accompany or follow such conditions as strangles, upper respiratory infections, meningitis, botulism, encephalomyelitis, leukoencephalomalacia, or cerebral abscessation in horses.
- ✓ In cattle, glossoplegia may accompany severe actinobacillosis.
- ✓ There may be complete paralysis of the tongue accompanied by necrosis of the tip.
- ✓ Such conditions are occasionally seen in outbreaks in feedlot cattle and may follow an initiating viral stomatitis.

Neoplasia

- ✓ Neoplasia of the mouth and lips other than viral papillomas are uncommon in younger animals.
- ✓ In gray horses, melanomas may develop and infiltrate the commissures of the mouth and cause hard, thickened, tumorous plaques that may not be detected until well advanced.

Saframine Toxicosis:

- ✓ The causes are ingestion of forages, particularly clovers, infected with the fungus *Rhizoctonia leguminicola*, which produces the toxic alkaloid saframine.
- ✓ The only clinical signs that may be diagnostic are profuse salivation; no lesions have been described within the mouth.
- ✓ Usually, there is complete recovery. Differential diagnoses in large animals, particularly in ruminants, include bluetongue, vesicular stomatitis, vesicular exanthema, and foot-and-mouth disease.
- ✓ Removal of infected forages results in rapid recovery.

Stomatitis:

- ✓ Inflammation of the mouth is a clinical sign of many diseases in large animals.

- ✓ Oral trauma or contact with chemical irritants (eg, horses that lick at their legs after having been blistered) may result in transient stomatitis.
- ✓ Traumatic injury from the ingestion of the awns of barley, foxtail, porcupine grass, and spear grass, as well as feeding on plants infested with hairy caterpillars, also will result in severe stomatitis in horses and cattle.

Papillar Stomatitis:

- ✓ Viral papillomas are found around the lips and mouths of all young animals, particularly in cattle from 1 mo to 2 yr old. In some instances, the rate of occurrence may be 100%.
- ✓ The lesions are characteristic and usually resolve spontaneously.
- ✓ However, in some cases, the lesions may coalesce to form cosmetically unacceptable masses around the muzzles of young horses, and owners may request therapy.

Diseases of the Abomasum

- ✓ Abomasal disorders include
 1. left displaced abomasum (LDA),
 2. right displaced abomasum (RDA),
 3. abomasal volvulus, ulcers, and
 4. impaction.
- ✓ Displacement or volvulus is seen most commonly in dairy cows, but can also be seen in dairy bulls and calves.
- ✓ Except for abomasal volvulus, abomasal displacement is rare in beef cattle and essentially undiagnosed in small ruminants.
- ✓ Ulcers are seen in dairy and beef cattle and in calves and lambs;
- ✓ they are rarely diagnosed in small ruminants.
- ✓ Impactions can be primary, which is most frequent in beef cattle, or secondary, which develop most often in dairy cows as a form of vagal indigestion.
- ✓ Impactions may have a hereditary basis in some black-faced sheep.

Left or Right Displaced Abomasum and Abomasal Volvulus

- ✓ Because the abomasum is suspended loosely by the greater and lesser omenta, it can be moved from its normal position on the right ventral part of the abdomen to the left or right side (LDA, RDA), or it can rotate on its mesenteric axis while displaced to the right (abomasal volvulus).
- ✓ It can shift from its normal position to left displacement or to right displacement over a relatively short period.
- ✓ Abomasal volvulus can develop rapidly or slowly from an uncorrected RDA.

Pathophysiology

- ✓ In LDA, as a result of abomasal hypomotility and gas production, the partially gas-distended abomasum

- becomes displaced upward along the left abdominal wall lateral to the rumen.
- ✓ It is primarily the fundus and greater curvature of the abomasum that become displaced, which in turn causes displacement of the pylorus and duodenum.
 - ✓ The omasum, reticulum, and liver are also rotated to varying degrees.
 - ✓ The abomasal obstruction is partial, and although the segment contains some gas and fluid, a certain amount can still escape, and the distention rarely becomes severe.
 - ✓ Because there is no interference with blood supply, the effects of displacement are entirely due to interference with digestion and passage of ingesta, which lead to decreased appetite and dehydration.
 - ✓ A mild metabolic alkalosis with hypochloremia and hypokalemia are common. The hypochloremic metabolic alkalosis is due to abomasal hypomotility, continued secretion of hydrochloric acid into the abomasum, and the partial abomasal outflow obstruction, with sequestration of chloride in the abomasum and reflux into the rumen.
 - ✓ Hypokalemia is due to decreased intake of feeds high in potassium, sequestration of potassium in the abomasum, and dehydration.
 - ✓ Secondary ketosis is common and may be complicated by development of fatty liver disease.
 - ✓ In RDA, hypomotility, gas production, and displacement of the partially gas-filled abomasum occur as in LDA.
 - ✓ Mild hypokalemic, hypochloremic, metabolic alkalosis develops as well.
 - ✓ After this dilatation phase, rotation of the abomasum on its mesenteric axis leads to volvulus and local circulatory impairment and ischemia (hemorrhagic strangulating obstruction).
 - ✓ The volvulus is usually in a counterclockwise direction when viewed from the rear and the right side of the animal.
 - ✓ The omasum is displaced medially and can be involved in the volvulus with occlusion of its blood supply (called an omasal-abomasal volvulus).
 - ✓ The liver and reticulum usually are displaced also.
 - ✓ In rare cases, the reticulum can be involved (called a reticular-omasal-abomasal volvulus).
 - ✓ A large quantity of fluid accumulates in the abomasum; chloride is sequestered there as well.
 - ✓ Hypochloremic, hypokalemic metabolic alkalosis develops.

- ✓ The blood supply to the abomasum, and often the omasum and proximal duodenum, is compromised, eventually resulting in ischemic necrosis of the abomasum as well as dehydration and circulatory failure.
- ✓ As this progresses, a metabolic acidosis is superimposed on the metabolic alkalosis.

Abomasal Ulcers

- ✓ Abomasal ulcers affect mature cattle and calves and have several different manifestations.
- ✓ Except for lymphosarcoma of the abomasum and the erosions of the abomasal mucosa that develop in viral diseases such as bovine viral diarrhea, rinderpest, and bovine malignant catarrhal fever, the causes of abomasal ulceration are not well understood.
- ✓ Many different causes have been suggested.
- ✓ Although abomasal ulcers can be seen any time during lactation, they are common in high-producing, mature dairy cows within the first 6 wk after parturition.
- ✓ The most likely cause is prolonged inappetence, which results in sustained periods of low abomasal pH.
- ✓ Abomasal ulcers are very common in milk-fed calves after they have consumed milk or milk replacer for 4-12 wk.
- ✓ Most of these are subclinical and nonhemorrhagic.
- ✓ Occasionally, milk-fed calves <2 wk old are affected by acute, hemorrhagic abomasal ulcers that may perforate and cause rapid death.
- ✓ Abomasal trichobezoars are common in these calves, but do not appear to increase the risk of ulcer formation.

Clinical Findings:

- ✓ The syndrome varies, depending on whether ulceration is complicated by hemorrhage or perforation and by the severity of such hemorrhage or peritonitis.
- ✓ A system of classification is based on the depth of penetration or the degree of hemorrhage or peritonitis caused by the ulcer:
- ✓ Type I is an erosion or ulcer without hemorrhage, Type II is hemorrhagic, Type III is perforated with acute localized peritonitis, and Type IV is perforated with acute diffuse peritonitis.
- ✓ There may be only a single ulcer or many acute and chronic ulcers.
- ✓ Calves with abomasal ulceration and hairballs may have a distended gas- and fluid-filled abomasum that is palpable behind the right costal arch.

- ✓ Deep palpation may reveal abdominal pain associated with local peritonitis due to a perforated ulcer.
- ✓ In calves, perforating ulcers are more common than bleeding ulcers.

Lesions:

- ✓ Ulceration is most common in the fundic region in adult cattle and in the pyloric antrum in milk-fed calves.
- ✓ The affected artery is usually visible after ingesta and necrotic tissue are removed from a bleeding ulcerated area.
- ✓ Most cases of perforation are walled off by the omentum, which forms a cavity 12-15 cm in diameter that contains degenerated blood and necrotic debris.

Hepatic Disease in Large Animals

- ✓ Hepatic disease is common in large animals, especially horses.
- ✓ Increases in serum hepatic enzymes and total bile acid concentration may indicate hepatic dysfunction, insult, disease, or failure.
- ✓ Diseases that frequently result in hepatic failure in horses include Theiler's disease, Tyzzer's disease, pyrrolizidine alkaloid toxicosis, hepatic lipidosis, suppurative cholangitis, cholelithiasis, chronic active hepatitis, and ferrous fumarate toxicosis.
- ✓ Obstructive biliary disease associated with intestinal displacement, aflatoxicosis, leukoencephalomalacia, pancreatic disease, duodenal ulcerations, kleingrass or alsike clover poisoning, portal caval shunts, hepatic abscess, hepatic neoplasia, and perinatal herpesvirus 1 infections sporadically result in hepatic failure.

Acute Hepatitis

- ✓ Infectious, toxic, and undefined etiologies may cause acute hepatitis.
- ✓ Increases in serum SDH and AST activities indicate acute hepatocellular injury.
- ✓ GGT is increased with cholestasis secondary to hepatocyte swelling.
- ✓ Cholestasis results in hyperbilirubinemia, with the direct (conjugated) fraction ranging from 15-35% of total in horses.
- ✓ Increased serum total bile acid concentration, decreased glucose and BUN concentrations, and prolonged BSP® clearance and coagulation times become evident as hepatic function progressively worsens.
- ✓ Anorexia can lead to hypokalemia.
- ✓ The CBC is variable because it may reflect an inflammatory response with a neutrophilia or an endotoxemia with a neutropenia, increased band neutrophils, and toxic changes.

Idiopathic Acute Hepatic Disease

(Theiler's disease, Serum hepatitis, Postvaccinal hepatitis, Acute hepatic necrosis, Acute hepatic atrophy)

- ✓ Idiopathic acute hepatic disease (IAHD) is the most common cause of acute hepatitis in horses.
- ✓ About 20% of horses with IAHD show clinical signs of hepatic failure 4-10 wk after receiving an equine origin biologic, such as tetanus antitoxin (TAT).
- ✓ In some cases, the affected horse may not have received TAT but may have been in contact with another horse that received TAT.
- ✓ Others affected have no prior history of exposure to such a product.
- ✓ Most commonly, only one horse on the premises is affected, although outbreaks may occur or other horses on the farm may have evidence of liver disease (increased enzyme levels) without clinical signs.
- ✓ Occurrence of the disease in groups of adult horses during the late summer or early fall (August to November) suggests an infectious (viral) or vector-spread etiology, although supporting evidence is lacking.
- ✓ The seasonal occurrence could reflect the fact that many foaling mares receive TAT in the spring of the year along with their newborn foals.
- ✓ Lactating mares that receive TAT at foaling seem to be more susceptible
- ✓ A Type III (immune-complex mediated) hypersensitivity reaction also has been proposed.
- ✓ At necropsy, icterus and varying degrees of ascites are present.
- ✓ The liver is usually small to normal in size but may be enlarged (peracute cases), with a mottled and bile-stained surface.
- ✓ Histologically, there is marked centrilobular-to-midzonal hepatocellular necrosis, mild to moderate mononuclear infiltrate and a few neutrophils, and moderate bile duct proliferation.

Acute Hepatic Necrosis in Cattle**Epidemiology and Pathogenesis:**

- ✓ Acute hepatic disease and failure in cattle most commonly results from a toxic insult.
- ✓ Hepatocellular necrosis with clinical and laboratory evidence of hepatic failure may develop in cattle after mastitis or metritis with clinical signs of endotoxemia.
- ✓ Endotoxin induces hepatocellular necrosis through both direct and indirect effects on the liver.
- ✓ Endotoxin can cause Kupffer's cells to release lysosomal enzymes, prostaglandins, and collagenase that damage hepatocytes, or it may interact directly with the hepatocytes, causing lysosomal damage,

decreased mitochondrial function, and necrosis.

- ✓ Endotoxin-related hepatocellular necrosis may be due in part to decreased hepatic blood flow and liver hypoxia.

Clinical Findings and Lesions:

- ✓ Clinical signs include weight loss, anorexia, and cessation of milk production.
- ✓ Photosensitization and mild icterus are variable.
- ✓ Serum SDH, GGT, and AST concentrations are mildly to severely increased.
- ✓ Fatty liver or ketosis is not characteristic.
- ✓ The liver may be normal in size or mildly enlarged.

Tyzer's Disease

- ✓ Tyzzer's disease, due to *Clostridium piliforme*, causes an acute necrotizing hepatitis, myocarditis, and colitis in foals 8-42 days old.

Cholangiohepatitis

- ✓ Cholangiohepatitis is a severe inflammation of the bile passages and adjacent liver, which sporadically causes hepatic failure in horses and ruminants.
- ✓ It is occasionally associated with cholelithiasis in horses.

Etiology:

- ✓ Bacteremia due to an organism (eg, *Salmonella*) eliminated in the bile, an ascending infection of the biliary tract after intestinal disturbance, or ileus are thought to be related to the development of cholangiohepatitis.
- ✓ In foals, duodenal ulceration and duodenitis may result in bile stasis, hepatic duct obstruction, and cholangiohepatitis.
- ✓ Parasite migration through the liver may predispose to cholangiohepatitis in some animals.
- ✓ Gram-negative organisms, including *Salmonella* sp, *Escherichia coli*, *Pseudomonas* sp, and *Actinobacillus equuli* are frequently isolated from the liver. *Clostridium* sp, *Pasteurella* sp, and *Streptococcus* sp are less frequently recovered.

Lesions:

- ✓ In acute cases, the liver is swollen, soft, and pale.
- ✓ Suppurative foci may be visible beneath the capsule or on cut surface.
- ✓ Lesions in other systems may reflect septicemia and jaundice.
- ✓ Microscopically in acute cases, neutrophils are present in the portal triads and degenerate parenchyma.
- ✓ Purulent exudate is evident in the ducts. In subacute or chronic cholangiohepatitis, the inflammation is more proliferative and bile duct proliferation more pronounced.

- ✓ Areas of atrophy, regenerative hyperplasia, and periportal fibrosis may be evident.

Hepatic Abscesses

- ✓ The primary etiologic agent of liver abscesses in cattle is *Fusobacterium necrophorum*.
- ✓ In goats, most abscesses are due to *Corynebacterium pseudotuberculosis*. *Arcanobacterium (Actinomyces) pyogenes* and *Escherichia coli* are also common.
- ✓ In horses, hepatic abscesses often contain *Streptococcus*, (*S equi equi*, *S equi zooepidemicus*), *C pseudotuberculosis*, or enterobacteria after ascending cholangiohepatitis or intestinal disease.
- ✓ In pigs, hepatic abscesses develop after migration of ascarids into the bile ducts.
- ✓ The liver is particularly susceptible to abscess formation because it receives blood from the hepatic artery, the portal system, and the umbilical vein in the fetus and the newborn.
- ✓ Hepatic abscesses are most prevalent in ruminants and uncommon in horses.
- ✓ Abscesses are associated with bacteremia, septic portal vein thrombosis, parasite migration, or extension from intestinal disease.
- ✓ In neonates and young animals, abscesses may develop secondary to ascarid migration, bacterial septicemia, or ascending infection of the umbilical vein.
- ✓ In horses and cattle, signs may be similar to those seen with other abdominal abscesses and include intermittent colic, intermittent fever, and weight loss.

Hepatotoxins:

- ✓ Hepatotoxins manifest their toxicity by one or more mechanisms: periportal (centrilobular) necrosis, midzonal necrosis, periportal necrosis, cholestasis, biliary hyperplasia, fatty or hydropic change near necrotic zones, or venous occlusion.
- ✓ Fatal hepatic insufficiency may result if the initial injury is acute and severe.
- ✓ In chronic processes, the longterm result may be cirrhosis.
- ✓ Many hepatotoxins, especially those in plants, exert toxic effects on multiple organs, particularly kidneys, lungs, and the GI tract.

Chemical and Drug-related Causes of Toxic Hepatopathy

Iron Toxicosis:

- ✓ Newborn foals are exceptionally sensitive to iron because of the high serum iron levels, increased ability to absorb iron, and oversaturation of transferrin at birth.

- ✓ In adult horses, injectable iron increases body iron concentration more substantially than most oral supplements.
- ✓ Iron toxicosis has been reported in calves and young bulls injected with a ferric ammonium citrate alone or in combination with ferrous gluconate.
- ✓ Foals given iron at birth, especially before nursing colostrum, develop clinical signs of hepatic encephalopathy in 2-5 days.
- ✓ Concentrations of serum bilirubin (both conjugated and unconjugated) and blood ammonia are high, and prothrombin time is prolonged.
- ✓ Alterations in serum hepatic enzymes are more variable.
- ✓ In foals, acute iron toxicity is commonly fatal; in adult horses, although less commonly a problem, it causes enteric irritation and cardiovascular collapse with sudden death.
- ✓ Calves with iron toxicosis have trembling, vocalizing, bruxism, colic, and convulsions.
- ✓ Hepatic lesions are variable. Most livers are friable and are swollen or shrunken. The liver is pale tan or mottled red-brown in color. Hemorrhages may be present in the stomach, intestines, and bladder.

Copper Toxicosis:

- ✓ Acute copper toxicosis with severe hepatic necrosis and death may be seen in cattle 1-4 days after injection of copper salt.
- ✓ Copper toxicosis is seen in sheep and young calves after excess dietary intake of copper and in young goat kids fed calf milk replacer containing copper.
- ✓ The primary condition associated with copper toxicosis is hemolytic anemia and liver damage.

Miscellaneous Chemicals and Drugs Associated with Hepatotoxicity:

- ✓ Exposure to carbon tetrachloride, chlorinated hydrocarbons, hexachlorethane, carbon disulfide, arsenic, monensin, pentachlorophenols, phenol, paraquat, halothane (goat, llama), isoflurane, phenobarbital, tannic acid, copper disodium edetate, and high doses of ivermectin may cause centrilobular necrosis and hepatic failure.
- ✓ Phosphorus causes primarily periportal changes.
- ✓ Active hepatitis to cirrhosis may be seen after use of isoniazid, nitrofurantoin, halothane, aspirin, or dantrolene in large animals.
- ✓ Erythromycin, rifampin, anabolic steroids, phenothiazine tranquilizers, some diuretics, quinidine sulfate, and diazepam have been associated with cholestasis and icterus.

Mycotoxicoeses

- ✓ Aflatoxins and fumonisins can cause hepatic injury and failure in ruminants, swine, and horses.
- ✓ Fusarium toxicosis is the most common mycotoxicoesis causing liver failure in horses, while aflatoxins only sporadically cause hepatic failure in this species.

Cholelithiasis, Choledocholithiasis, and Hepatolithiasis**Etiology and Epidemiology:**

- ✓ Cholelithiasis in horses may cause biliary obstruction and concurrent liver disease or may be an incidental finding at necropsy.
- ✓ Solitary or multiple calculi may be present in the common bile duct (choledocholithiasis), intrahepatic bile ducts (hepatolithiasis), or bile duct or gallbladder in ruminants (cholelithiasis).
- ✓ The cause of cholelith formation in horses is not known.
- ✓ Ascending biliary tract (cholangiohepatitis), intestinal bacterial infection resulting in bile stasis, and a change in bile composition or cholesterol concentration have been proposed.
- ✓ Choleliths also may form around a foreign body or parasites may occlude the common bile duct.
- ✓ Cholelithiasis and hepatolithiasis reportedly are not recognized as a clinical problem in sheep and goats.
- ✓ Laboratory abnormalities include hyperbilirubinemia with increased direct (conjugated) bilirubin, a marked increase in serum GGT activity, and increased serum total bile acid concentration.
- ✓ SDH and AST activities are increased but to a lesser degree.
- ✓ Serum urea nitrogen, glucose, and potassium concentration may be decreased.
- ✓ Metabolic tests indicate reduced hepatic function.
- ✓ Activated partial thromboplastin time and one-stage prothrombin time may be prolonged.

Chronic Active Hepatitis

- ✓ Chronic active hepatitis describes any progressive inflammatory process within the liver.
- ✓ It is a histopathologic diagnosis in which there is evidence of sustained, aggressive, chronic liver disease.
- ✓ The histologic diagnosis is often cholangiohepatitis because the inflammatory response is mainly in the periportal areas.

Lesions:

- ✓ Grossly, the liver is firm, pale brown to green in color, and often small.

- ✓ Irregular markings may be seen on the cut surface.
- ✓ Histologic lesions are predominantly in the periportal areas.
- ✓ Inflammatory cell infiltration may consist primarily of mononuclear cells, neutrophils with bacteria (often coliforms), or lymphocytes and plasma cells.
- ✓ The character of the infiltrate may indicate the nature of the primary disease process.
- ✓ Biliary hyperplasia may be marked if there is cholangiohepatitis. Variable degrees of necrosis and fibrosis are present.

Hyperlipemia and Hepatic Lipidosis in Horses, Donkeys, and Camelids

- ✓ Poor feed quality or decrease in feed intake, particularly during a period of high-energy requirement (eg, pregnancy, systemic disease), may result in hyperlipemia syndrome.
- ✓ Hyperlipemia is seen most commonly in ponies, miniature horses, and donkeys, and less frequently in standard-size adult horses.
- ✓ Pathogenesis of hyperlipemia is complex, with a negative energy balance triggering excessive mobilization of fatty acids from adipose tissue leading to increased hepatic triglyceride synthesis and secretion of very low density lipoproteins, concomitant hypertriglyceridemia, and fatty infiltration of the liver.
- ✓ The biochemical etiology of hyperlipemia is overproduction of triglyceride, rather than failure of triglyceride catabolism.
- ✓ In ponies, hyperlipemia is usually a primary disease process associated with obesity, pregnancy, lactation, stress, or transportation.
- ✓ Hyperlipemia may develop secondary to any systemic disease that results in anorexia and a negative energy balance.
- ✓ Secondary hyperlipemia is more common than primary hyperlipemia in miniature breeds.
- ✓ Hyperlipemia secondary to a systemic disease can be seen in horses of any age and in any condition.

Lesions:

- ✓ The liver and kidneys are often pale, swollen, and friable with a greasy texture.
- ✓ The hepatic sinusoids may appear compressed and anemic with severe fatty infiltration.
- ✓ Gross and microscopic lesions of the primary disease process in ponies and horses may predominate.

Hepatic Neoplasia

- ✓ Primary hepatic tumors are uncommon in horses and ruminants.
- ✓ They include hepatocellular carcinoma, cholangiocarcinoma, and rarely lymphoma, hepatoblastoma, and mixed hamartoma.
- ✓ Cholangiocarcinoma is the most common and is primarily found in middle-aged or older horses.
- ✓ Hepatic carcinomas arise from hepatocytes, bile ducts, or metastasis.
- ✓ Hepatocellular carcinomas generally are found in yearlings to young adult horses and have also been reported in llamas and goats.
- ✓ Adenomas or adenocarcinomas of the liver have been reported in cattle. Hepatic fibrosarcoma and bile duct carcinoma with metastasis to the lungs have been reported in goats. Erythrocytosis, large areas of extramedullary hemopoiesis, and metastasis to the thoracic cavity have been reported in horses with hepatoblastoma.
- ✓ Lymphosarcoma is the most common neoplasia of the hematopoietic system in horses. As many as 37% of horses with lymphosarcoma have neoplastic involvement of the spleen, and 41% have neoplastic involvement of the liver. Metastasis of lymphosarcoma of the liver has been reported in cattle, llamas, and goats.
- ✓ Cholangiocarcinoma causes pronounced weight loss before the onset of hepatic failure.

Hepatic Failure in Foals

- ✓ Hepatic failure in neonatal foals may follow septicemia endotoxemia, *Leptospira pomona* infection, perinatal asphyxia, biliary atresia, hepatic duct obstruction secondary to gastroduodenal obstruction, and iron toxicity.
- ✓ Gastric ulcers and duodenitis in foals can cause strictures of the duodenum and subsequent cholangiohepatitis due to bile stasis.
- ✓ Neonatal isoerythrolysis and hemolysis may cause hypoxic and cholestatic hepatic disease.
- ✓ Administration of total parenteral nutrition may cause cholestasis and concurrent hepatic disease.

Biliary Atresia

- ✓ Biliary atresia (extrahepatic) has been reported in 2 foals and in a neonatal lamb.
- ✓ Affected foals presented for anorexia, depression, lethargy, poor growth, colic, polydipsia, polyuria, pyrexia, and icterus at 1 mo of age.
- ✓ Markedly increased serum GGT and bilirubin with mildly increased SDH supported biliary obstruction.

Hemochromatosis

- ✓ Hemochromatosis is an iron storage disease in which hemosiderin is deposited

in the parenchymal cells, causing damage and dysfunction of the liver and other tissues.

- ✓ The disease is either primary (idiopathic) or secondary. It is reported in humans, Mynah birds, Salers cattle, and horses.
- ✓ In Salers cattle, the condition appears to be a homozygous recessive condition with inappropriate intestinal absorption of iron, excessive hepatic storage, and eventual loss of hepatic function.

Clinical Findings and Lesions:

- ✓ In horses, primary clinical signs are weight loss, lethargy, and intermittent anorexia.
- ✓ In cattle, signs include decreased weight gain, poor body condition, dull hair coat, and diarrhea. In both species, liver enzymes, including GGT, AP, AST, and SDH are increased.
- ✓ Serum total bile acid concentrations are increased in horses, and serum iron, total iron binding capacity (TIBC), and percent saturation of the TIBC are usually normal.
- ✓ In some cases, serum iron and ferritin may be increased but TIBC is not saturated.
- ✓ In cattle, total serum iron, TIBC, and saturation of transferrin are increased.
- ✓ Iron content of the liver tissue is greatly increased in both horses (normal 100-300 ppm) and cattle (normal 84-100 ppm).

Right Hepatic Lobe Atrophy in Horses

- ✓ The right lobe of the liver is the largest lobe in young horses but frequently atrophies in older animals and becomes fibrous.
- ✓ Right hepatic lobe atrophy was previously considered an incidental postmortem finding, but some consider it to be a pathologic condition.
- ✓ Right hepatic lobe atrophy has been proposed to result from chronic compression of this portion of the liver by the right dorsal colon and base of the cecum.

Hepatic Lobe Torsion

- ✓ Hepatic lobe torsion can cause colic in horses.
- ✓ Liver enzymes and fibrinogen are increased, but abdominal fluid analysis is variable in affected animals.
- ✓ Bacteria, including *Clostridium* sp, may be found in the necrotic portion of liver. Exploratory celiotomy may be required for diagnosis.

Hepatic Amyloidosis

- ✓ Amyloidosis refers to disease characterized by the extracellular deposition of amyloid, a proteinaceous fibril substance, in the tissue.
- ✓ Deposition of amyloid within an organ distorts normal tissue architecture and possibly function.

- ✓ In horses, the liver and spleen are the most common organs affected by systemic amyloidosis.

- ✓ Reactive or secondary systemic amyloidosis with deposition of amyloid A (AA) fibrils in the liver has been associated with severe parasitism and chronic infection or inflammation in horses.

Primary Hyperammonemia of Adult Horses

- ✓ In this syndrome of hyperammonemia, blindness and severe neurologic signs are seen in adult horses.
- ✓ The etiology is unknown, but a primary intestinal problem with overgrowth of urease-producing bacteria within the intestine is suspected.
- ✓ The syndrome is nearly always associated with enteric disease, diarrhea, or colic.
- ✓ Diarrhea and, in some cases, protein-losing enteropathy may persist for several days.
- ✓ In most horses, neurologic signs resolve within 2-3 days with supportive treatment (IV fluids, potassium chloride, glucose, sodium bicarbonate) and administration of drugs to reduce ammonia absorption (lactulose, neomycin).

Portosystemic Shunts

- ✓ Portosystemic shunts are seen in foals and calves.
- ✓ Hyperammonemia and neurologic signs result from liver dysfunction with little laboratory or microscopic evidence of liver disease.

Clinical Findings and Lesions:

- ✓ Clinical signs are first seen when affected foals are ~2 mo of age and start to ingest larger amounts of grain and forage.
- ✓ Neurologic signs include staggering, wandering, blindness, circling, and seizures.
- ✓ The liver is often small with a smooth surface and normal in color and texture.
- ✓ Microscopically, the hepatocytes are small. Portal veins in the triads may be small or absent. Hepatic arteries are often prominent and multiple.

Hyperammonemia of Morgan Weanlings

- ✓ A syndrome of ill thrift and hyperammonemia with variable hepatic involvement are seen in Morgan foals.
- ✓ Affected foals have been related, but the cause of the syndrome is undetermined.
- ✓ Clinical signs are usually first seen around weaning time.

Gilbert's Syndrome

- ✓ Gilbert's syndrome is a congenital hyperbilirubinemia seen in humans, inherited as an autosomal dominant trait, and Southdown sheep.
- ✓ It is an unconjugated hyperbilirubinemia in the presence of normal erythrocyte life span. A

- ✓ Defect in carrier proteins or conjugating enzyme is suspected.
- ✓ Affected Southdown sheep have increased conjugated and unconjugated plasma bilirubin levels.
- ✓ Hepatic bilirubin clearance is defective, and affected sheep cannot excrete BSP® into the bile. Icterus is variable.
- ✓ Histopathologic lesions are absent except for pigment in the hepatocytes.

Dubin-Johnson Syndrome

- ✓ Dubin-Johnson syndrome sporadically is seen in humans and Corriedale sheep.
- ✓ it is a failure of conjugated bilirubin to enter the bile canaliculi. Excretion of bilirubin and other conjugated organic anions may be impaired.
- ✓ Affected sheep may be icteric or hyperbilirubinemic.
- ✓ Histologically, the hepatocytes contain a black melanin-like pigment.

Intestinal Diseases in Cattle**Bovine Viral Diarrhea and Mucosal Disease Complex**

- ✓ Bovine viral diarrhea (BVD) is most common in young cattle (6-24 mo old) and generally is accompanied by typical mucosal lesions;
- ✓ it must be distinguished from other viral diseases that produce diarrhea and mucosal lesions.
- ✓ These include malignant catarrhal fever which usually is a sporadic disease in more mature cattle, and rinderpest which can be seen in outbreak form but is exotic in most countries.
- ✓ Bovine viral diarrhea virus (BVDV), the causal agent of BVD and mucosal disease complex, is classified in the genus Pestivirus in the family Flaviviridae.

Clinical Findings and Lesions:

- ✓ Disease induced by BVDV varies in severity, duration, and organ systems involved.
- ✓ Acute disease results from infection of susceptible cattle with either noncytopathic or cytopathic BVDV.
- ✓ Acute BVD, also termed transient BVD, often is an inapparent to mild disease of high morbidity and low mortality.
- ✓ Gross lesions seldom are seen in cases of mild disease.
- ✓ Lymphoid tissue is a primary target for replication of BVDV, which may lead to immunosuppression and enhanced severity of intercurrent infections.
- ✓ Some isolates of BVDV induce clinically severe disease that manifests as high fever ([41-42°C]), oral ulcerations, eruptive lesions of the coronary band and interdigital

cleft, diarrhea, dehydration, leukopenia, and thrombocytopenia.

- ✓ In thrombocytopenic cattle, petechial hemorrhages may be seen in the conjunctiva, sclera, nictitating membrane of the eyes; and on mucosal surfaces of the mouth and vulva.
- ✓ Prolonged bleeding from injection sites also occurs.
- ✓ Swollen lymph nodes, erosions and ulcerations of the GI tract, petechial and ecchymotic hemorrhages on the serosal surfaces of the viscera, and extensive lymphoid depletion are associated with severe forms of acute BVD.
- ✓ In pregnant cattle, BVDV may cross the placental barrier and infect the fetus. The consequences of fetal infection usually are seen several weeks to months after infection of the dam and depend on the stage of fetal development and on the strain of BVDV.
- ✓ Infection of the dam near the time of fertilization may result in reduced conception rates.
- ✓ Infection during the first 4 mo of fetal development may lead to embryonic resorption, abortion, growth retardation, or persistent infection.
- ✓ Congenital malformations of the eye and CNS result from fetal infections that occur between months 4-6 of development.
- ✓ Fetal mummification, premature birth, stillbirth, and birth of weak calves also are seen after fetal infection.

Mucosal disease

- ✓ a highly fatal form of BVD that may be acute or chronic and is seen infrequently in persistently infected cattle.
- ✓ Mucosal disease is induced when persistently infected cattle become superinfected with cytopathic BVDV.
- ✓ The origin of the cytopathic BVDV is usually internal, resulting from a mutation of the resident persistent, noncytopathic BVDV.
- ✓ In those cases, the cytopathic virus is antigenically similar to the resident noncytopathic virus.
- ✓ External origins for cytopathic BVDV include other cattle and modified live virus vaccines.
- ✓ Cattle that develop mucosal disease due to exposure to a cytopathic virus of external origin often produce antiviral antibody.
- ✓ Intermittent diarrhea and gradual wasting are common.
- ✓ Coronitis and eruptive lesions on the skin of the interdigital cleft cause lameness in some cattle.
- ✓ Lesions found at necropsy are less pronounced than, but similar to, those seen in acute mucosal disease.

- ✓ Often, the only gross lesions seen are focal ulcerations in the mucosa of the cecum, proximal colon, or rectum, and the mucosa over, Peyer's patches of the small intestine may appear sunken.

Winter Dysentery

- ✓ Winter dysentery is an acute, highly contagious GI disorder that affects housed adult dairy cattle, primarily during winter.
- ✓ Clinical features include explosive diarrhea (sometimes accompanied by dysentery), a profound drop in milk production, variable anorexia and depression, and mild respiratory signs such as coughing.
- ✓ The disease has a high morbidity but low mortality, and spontaneous recovery within a few days is typical.

Etiology:

- ✓ The precise etiology of winter dysentery is unclear.
- ✓ In recent years, a bovine coronavirus (BCV), closely related to the virus that causes diarrhea in neonatal calves, has been implicated as the etiologic agent.

Pathophysiology

- ✓ BCV is transmitted via the fecal-oral route through ingestion of feed or water contaminated with feces from clinical cases or clinically normal carrier animals.
- ✓ Viral particles present in respiratory secretions of affected animals may further enhance transmission.
- ✓ Winter dysentery is highly contagious and easily introduced to barns by visitors, carrier animals, and fomites.
- ✓ Coronaviruses survive best at low temperatures and at low ultraviolet light intensities, which can lead to a buildup of virus in the environment during the colder months.
- ✓ Adult lactating cows that have recently calved are most severely affected, but the disease can affect younger or older animals and males.
- ✓ Inflammatory mediators that cause hypersecretion in the small intestine and colon are thought to contribute to the voluminous diarrhea seen in cattle with winter dysentery.
- ✓ In addition, destruction of epithelial cells in the colonic crypts results in transudation of extracellular fluid and blood, explaining the hemorrhagic nature of the diarrhea in some cases.

Lesions:

- ✓ The small intestine may be dilated and flaccid.
- ✓ Lesions are primarily seen in the large intestine and consist of cecal and colonic mucosal hyperemia, linear streaks or pinpoint-sized hemorrhages mostly along

the colonic mucosal ridges, and blood in the lumen of the large intestine.

- ✓ Histologic findings may include widespread degeneration and necrosis of colonic glandular epithelium.

Intestinal Diseases in Sheep and Goats

- ✓ The causes and circumstances of diarrhea in neonatal lambs and kids are similar to those in newborn calves.
- ✓ Intensive lambing practices and shed-lambing increase the potential for disease and buildup of infectious agents and can be associated with serious outbreaks of diarrhea.
- ✓ The serotypes of enteropathogenic *Escherichia coli* that cause secretory diarrhea in calves also do so in lambs, and the approach to diagnosis, treatment, and control is similar.
- ✓ Similarly, rotavirus, coronavirus, and cryptosporidia also cause outbreaks of diarrhea in lambs.
- ✓ Lamb dysentery caused by *Clostridium perfringens* type B is a distinct intestinal disease of lambs in the first week of life.
- ✓ Watery mouth or rattle belly, a disease of uncertain etiology associated with low concentrations of circulating immunoglobulins,
- ✓ It also affects young lambs but is manifest by GI stasis. Coccidiosis and GI helminthiasis except for haemonchosis, are important causes of diarrhea in older nursing and weaned sheep.
- ✓ Terminal ileitis and villous atrophy, both of unknown etiology, are often present in the intestine of lambs culled because of poor growth.
- ✓ GI helminthiasis is the most common cause of diarrhea in pastured sheep.
- ✓ Coccidiosis develops in association with overstocking or intensive indoor housing and poor sanitation.
- ✓ Salmonellosis can cause diarrhea in all ages; the circumstances in young lambs are similar to those in calves.
- ✓ It also can cause outbreaks of diarrhea late in pregnancy and is frequently accompanied by abortion.
- ✓ Salmonellosis is more common when sheep or goats are congregated intensively or stressed, particularly by shipping.
- ✓ *Yersinia pseudotuberculosis* and *Y. enterocolitica* have both been associated with enterocolitis and diarrhea in young sheep at pasture that are debilitated from factors such as starvation and cold weather.
- ✓ Diarrhea may be present in bluetongue in sheep and is accompanied by typical mucosal lesions.

- ✓ In goats, diarrhea is often prominent in enterotoxemia associated with *C perfringens* type D
- ✓ Infection with *C perfringens* type C (struck, manifests with abdominal pain, tenesmus, and rapid death.
- ✓ Sheep with paratuberculosis usually show progressive emaciation without diarrhea.

Watery Mouth Disease in Lambs (Slavery mouth, Slavers, Rattle belly)

Etiology and Pathogenesis:

- ✓ Newborn lambs deprived of adequate colostrum because of sibling competition, weakness, poor mothering, or inadequate maternal supply are at greatest risk.
- ✓ The disease develops after ingestion of gram-negative bacteria, particularly *Escherichia coli*, from contaminated fleece or bedding.
- ✓ The strains of *E coli* involved do not possess the K99 antigen and are normally regarded as nonenteropathogenic and nonenterotoxigenic.
- ✓ The unique digestive physiology of the newborn lamb and absence of gut or systemic antibodies allow ingested bacteria to survive and translocate from the gut to the bloodstream.
- ✓ The resultant bacteremia is initially tolerated by the lamb; however, bacteremias $>10^4$ colony-forming units/mL are associated with the release of free endotoxin, and endotoxic shock rapidly develops.
- ✓ The newborn lamb is particularly vulnerable to disease resulting from ingestion of environmental bacteria for the following reasons.
- ✓ First, it is immunocompromised because it lacks circulating antibodies.
- ✓ Second, neutral conditions in the abomasum may allow viable bacteria to pass to the small intestine.
- ✓ Third, rapid multiplication of bacteria within the gut is enhanced by the normal depression in gut motility that occurs during the first 48 hr of life.
- ✓ Fourth, *E coli* are able to attach to receptors present on the intestinal epithelium and be absorbed into the systemic circulation.
- ✓ Watery mouth disease is more common in twins and triplets than in single lambs, particularly when born to ewes in poor body condition.

Lesions:

- ✓ Necropsy may reveal an inflamed GI tract distended with fluid and gas, retained meconium, pale kidneys and muscle, a dehydrated carcass, and mesenteric lymph nodes that are enlarged and reactive.

Intestinal Diseases in Horses and Foals Salmonellosis

- ✓ Salmonellosis is one of the most commonly diagnosed infectious causes of diarrhea in adult horses.
- ✓ Stress appears to play an important role in the pathogenesis—a history of surgery, transportation, or change in feed; concurrent disease, particularly GI disorders (colic); or treatment with broad-spectrum antimicrobial drugs often precedes the diarrhea.
- ✓ Salmonellae are subdivided into serogroups and then further into types or serovars based on testing with specific antisera.
- ✓ Serovars are named after the clinical condition, host, or geographic region from which the organism was first identified. For example, *Salmonella typhimurium* is now referred to as *Salmonella enteritica serovar typhimurium* or *Styphimurium*.
- ✓ Although the list may vary slightly from year to year, certain types are consistently in the top 10.
- ✓ *Salmonella* of the serogroup B (which includes *S typhimurium* and *S agona*) are consistently in the top 10 isolates from horses with clinical disease.
- ✓ Serogroup C, which is further divided into serogroup C₁ (includes *S infantis*, *S braenderup*, *S montevidео*, *S thompson*, *S ohio*, *S oranienburg*) and serogroup C₂ (includes serovars *S javiana*, *S newport*, *S hadar*, *S muenchen*), appears to be on the increase as a cause of disease in horses.
- ✓ The other serogroup often identified in clinical disease of horses is serogroup E (includes *S krefeld*, *S muenster*, *S anatum*).
- ✓ Some types (eg, *S typhimurium*) appear to be more pathogenic than others.

Potomac Horse Fever

(Equine monocytic ehrlichiosis, Ditch fever, Shasta River crud, Equine ehrlichial colitis)

- ✓ Potomac horse fever (PHF) is an acute enterocolitis syndrome producing mild colic, fever, and diarrhea in horses of all ages, as well as abortion in pregnant mares.
- ✓ The causative agent, formerly known as *Ehrlichia risticii*, has recently been renamed *Neorickettsia risticii* because of its lesser genetic relationships to other *Ehrlichia* groups.
- ✓ The infection of enterocytes of the small and large intestine results in acute colitis, which is one of the principal clinical signs of PHF.
- ✓ The disease is seen in spring, summer, and early fall and is associated with pastures bordering creeks or rivers.

- ✓ Recently, the epidemiology of PHF has been shown to involve a trematode vector.

Etiology and Pathogenesis:

- ✓ *N. risticii* is a gram-negative obligate intracellular bacterium with tropism for monocytes.
- ✓ Initial morphologic studies of this organism isolated from cell culture, as well as the serologic responses of *N. risticii*, caused this bacterium to be assigned to the genus *Ehrlichia*.
- ✓ Recent DNA analyses have revealed *N. risticii* is most closely related to *N. helminthoeca*, the agent of salmon poisoning in dogs, and *Ehrlichia sennetsu*, a disease of humans in Japan.

Clinical Findings and Lesions:

- ✓ The clinical features of PHF are typified initially by mild depression and anorexia, followed by a fever ranging from (38.9-41.7°C).
- ✓ At this stage, intestinal sounds can be decreased.
- ✓ Within 24-48 hr, a moderate to severe diarrhea, with feces ranging in consistency from that usually seen in cows to watery, develops in ~60% of affected horses.
- ✓ The onset of diarrhea is often accompanied by mild abdominal discomfort.
- ✓ Some horses develop severe toxemia and dehydration.
- ✓ Several months following clinical disease in pregnant mares, abortion due to fetal infection with *N. risticii* may occur.
- ✓ The abortion is accompanied by placentitis and retained placenta.
- ✓ Fetal lesions include colitis, periportal hepatitis, and lymphoid hyperplasia of mesenteric lymph nodes and spleen.
- ✓ Necropsy findings in nonpregnant horses with enterocolitis are nonspecific and reveal diffuse inflammation, mainly in the large intestines.

Clostridia-associated Enterocolitis

- ✓ *Clostridium* spp have been incriminated as a cause of enterocolitis in horses and foals and appear to be part of a complex disease process.
- ✓ *Clostridium* spp that have been associated with equine enterocolitis include *C. perfringens* (types A, B, C, and D), *C. sordellii*, *C. difficile*, and *C. cadaveris*.
- ✓ Alteration of the normal intestinal milieu appears to be necessary for this disease to develop.
- ✓ The clinical enterocolitis syndrome due to clostridial infection has been best characterized in foals but appears to occur in adult horses as well.

Parasitism

- ✓ Both large and small strongyles have been incriminated as a cause of chronic diarrhea in horses and foals.
- ✓ The condition associated with small strongyles in horses is termed cyathostomiasis and has been reported to result in recurrent colic, diarrhea, and weight loss.
- ✓ Giardiasis has been reported in a limited number of cases as a cause of intermittent diarrhea in horses.
- ✓ Cryptosporidia have been identified in the feces of both healthy and diarrheic foals.

Colitis-X

- ✓ This peracute, fatal disease of horses is characterized by sudden onset of profuse, watery diarrhea and development of hypovolemic shock.
- ✓ Many affected horses have a history of stress.
- ✓ The cause of colitis-X is unknown, although multiple causes have been proposed, including peracute salmonellosis, clostridial enterocolitis, and endotoxemia.
- ✓ Tachypnea, tachycardia, and marked depression are present.
- ✓ An explosive diarrhea develops, followed by extreme dehydration.
- ✓ At necropsy, edema and hemorrhage in the wall of the large colon and cecum are pronounced, and the intestinal contents are fluid and often blood-stained.

Sand Enterocolopathy

- ✓ Consumption of large amounts of sand, which then accumulates in the large intestine, can produce diarrhea, weight loss, or colic.
- ✓ Sand is ingested when the horse or foal is kept on sandy pasture or is fed hay or grain in a sandy area (paddock, stall, or pasture).
- ✓ Some horses or foals preferentially eat dirt and sand if it is in their environment.

Infiltrative Colonic Disease

- ✓ Any process that causes a thickening of the wall of the large colon may interfere with absorption of fluid and result in chronic diarrhea, weight loss, and sometimes hypoproteinemia.
- ✓ Thickening may be due to neoplasia, inflammatory cells (such as lymphocytes, plasma cells, macrophages, or eosinophils), or scar formation from previous acute colitis.
- ✓ Rectal palpation may help detect bowel thickening and mesenteric lymphadenopathy.

Diarrheal Disease in Foals**Foal Heat Diarrhea:**

- ✓ From 4 to 14 days after birth, foals often develop a mild, self-limiting diarrhea.
- ✓ During this time, the dam is usually undergoing her first estrous cycle, hence the name "foal heat diarrhea." A
- ✓ Although the cause is unknown, it may be associated with alterations in the foal's intestinal microbial flora or alteration in diet as the foal begins to eat small amounts of hay and grain.
- ✓ The foal remains active and alert and has a normal appetite.
- ✓ Vital signs remain normal.
- ✓ Feces are semiformed to watery and not malodorous.

Bacterial Diarrhea in Foals:

- ✓ Bacterial enterocolitis in neonatal foals can be a component of neonatal septicemia.
- ✓ Organisms that may be involved in diarrhea in neonatal foals include *Salmonella* spp, *Escherichia coli*, *Klebsiella* spp, and *Clostridium* spp.
- ✓ An acute, fulminant, hemorrhagic diarrhea syndrome with high mortality in young foals <3 days old has been associated with *Clostridium perfringens* type C infection
- ✓ Enterocolitis has also been associated with *C. perfringens* type A with or without b2 toxin gene.
- ✓ The significance of this association is less clear than with type C, as type A has been identified in the feces in >90% of healthy neonatal foals in a farm-based study.
- ✓ Other bacteria that have been associated with diarrhea in foals are *Bacteroides fragilis*, *Clostridium difficile*, *Aeromonas hydrophila*, and *Rhodococcus (Corynebacterium) equi*.
- ✓ The first 3 are seen in foals <2 wk old and infected foals require intensive supportive care. Although *R. equi* primarily causes respiratory disease, both acute and chronic enteritis can be seen; diarrhea is seen in foals 1-4 mo old.
- ✓ The diagnosis is more straightforward if pneumonia is also present.
- ✓ Erythromycin combined with rifampin is the treatment of choice for *R. equi* infection in foals.

Viral Diarrhea in Foals:

- ✓ Viruses appear to cause diarrhea in foals but not in adult horses.
- ✓ Rotavirus is the main cause of viral diarrhea in foals; however, other viruses (eg, coronavirus) have been implicated.
- ✓ Diarrhea induced by rotavirus is characterized by depression, anorexia, and profuse, watery, malodorous feces.

- ✓ It is usually seen in foals <2 mo old; younger foals typically have more severe clinical signs.
- ✓ Rotavirus destroys the enterocytes on the tip of the villi in the small intestine, which results in malabsorption.
- ✓ Lactase becomes deficient, so lactose passing into the large intestine induces an osmotic diarrhea.
- ✓ Diagnosis is made by identification of virus

Gastrointestinal Neoplasia

- ✓ Squamous cell carcinoma of the stomach and the alimentary form of lymphosarcoma are the most common forms of neoplasia involving the GI tract in horses.
- ✓ Chronic weight loss may be the primary clinical sign.
- ✓ Chronic diarrhea and hypoalbuminemia may develop when lymphosarcoma has infiltrated the wall of the intestine.
- ✓ Because the incidence of GI neoplasia is low, other causes of weight loss should be investigated first.
- ✓ In horses with lymphosarcoma, enlarged mesenteric lymph nodes or thickened bowel may be detected by rectal palpation or by ultrasonographic examination

Inflammatory Bowel Disease (Granulomatous enteritis, Chronic eosinophilic gastroenteritis, Plasmacytic-lymphocytic enteritis)

- ✓ This disease is characterized by infiltration of the small and large intestine and regional lymph nodes with inflammatory cells, including lymphocytes, plasma cells, macrophages, and eosinophils.
- ✓ The inflammatory condition may be limited to only a short segment of the bowel or be more diffuse.
- ✓ Malabsorption and a protein-losing enterocolopathy result.
- ✓ Failure to absorb oral glucose or D-xylose verifies malabsorption from the small intestine.
- ✓ The pathophysiology is not understood. An altered immune response to a common intestinal factor (eg, feed, parasites, and bacteria) has been suggested.

Nonsteroidal Anti-inflammatory Drug Toxicosis

- ✓ Phenylbutazone administered at high doses or for prolonged periods can cause a protein-losing enterocolopathy in horses.
- ✓ Toxicosis can develop from oral or parenteral administration of NSAID.
- ✓ Hypoproteinemia is seen due to loss of protein into the intestinal lumen, which can occur without visible ulceration.
- ✓ Gastric and colonic ulceration are potential sequelae of phenylbutazone toxicosis.
- ✓ Scarring of the right dorsal colon with subsequent recurrent colic and hypoproteinemia is also a sequela.
- ✓ Renal papillary necrosis may be seen.

- ✓ Administration of flunixin meglumine at high doses or for prolonged periods can result in a similar toxicosis.

DIGESTIVE SYSTEM

Defense Mechanisms in the Oral Cavity

- Taste buds that reject potentially toxic materials based on taste and tongue feel
- Indigenous bacterial flora that occupy attachment sites of pathogens
- Saliva
 - Flushing action so potential pathogens are cleared from the oropharynx
 - Protective coating of the mucosa
 - Contains antimicrobial lysozyme and immunoglobulins

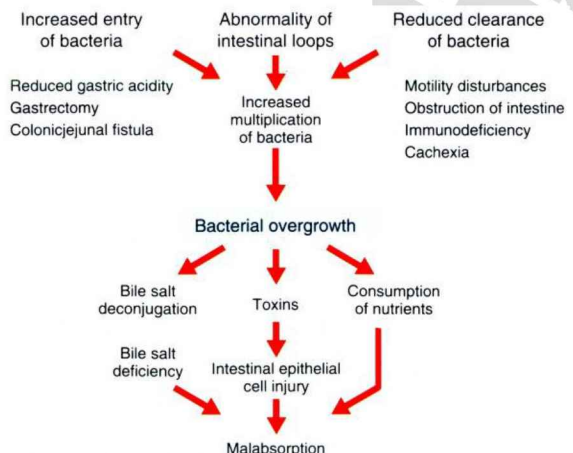
Laboratory Findings in Diseases of the Ruminant Stomach:

- Acute Rumen Engorgement
 - increased PCV – hemoconcentration
 - increased serum total protein and albumin
 - animal becomes acidotic → acidic urine pH
- Traumatic Reticuloperitonitis
 - absolute increase in circulating neutrophils and a left shift (usually lymphopenia and eosinopenia)
 - increased fibrinogen

Vesicular Stomatitides

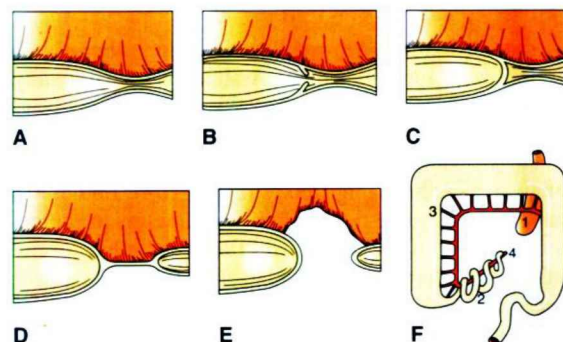
Disease	Cause	Ruminant	Pigs	Horses
Foot-and-mouth disease	Picornavirus	+	+	–
Vesicular stomatitis	Rhabdovirus	++	+	+
Vesicular exanthema of swine	Calicivirus	–	++	–
Swine vesicular disease	Enterovirus	–	++	–

+ = Species in which disease occurs; – = species in which disease does not occur.

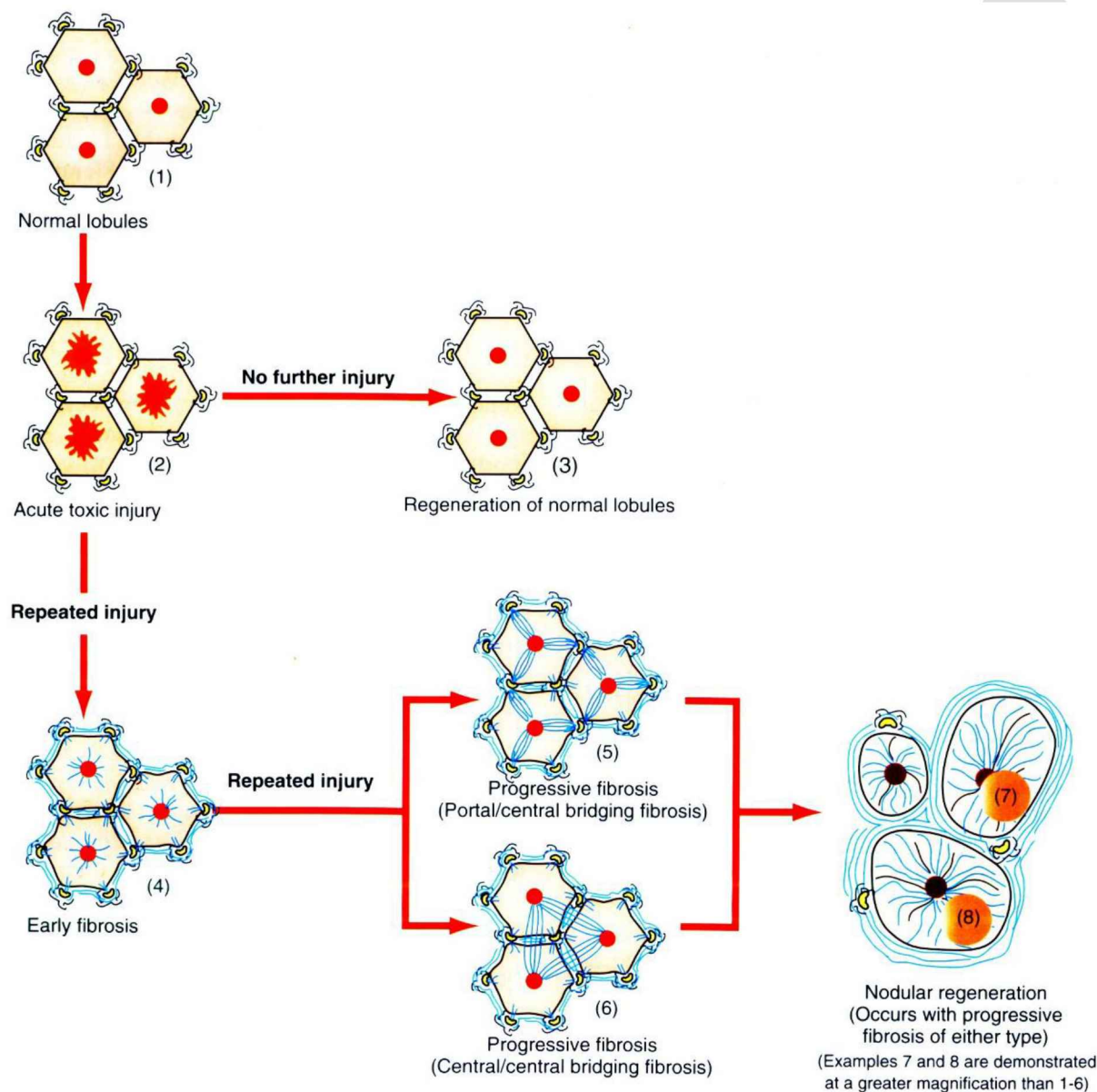


Schematic diagram of the mechanism how intestinal bacterial overgrowth causes malabsorption and diarrhea.

- decrease in total protein:fibrinogen ratio
 - serosanguineous peritoneal fluid with large numbers of neutrophils
- Peritonitis
 - same hemogram as in reticuloperitonitis with leukopenia as the disease progresses
 - total protein is greatly increased
 - if peritonitis is due to rupture of the digestive tract, plant material is present
 - if peritonitis is due to rupture of the urinary bladder, peritoneal fluid contains urine (warming will give characteristic urine odor)
 - Abomasal Disorders
 - hypochloremia, hypokalemia, and metabolic alkalosis
 - hemoconcentration as a consequence of dehydration in late stages
 - Vagus Indigestion
 - hemoconcentration
 - azotemia due to reduced renal perfusion
 - metabolic alkalosis and hypochloremia may develop if there is functional pyloric stenosis
 - Hemorrhage in the GIT – positive for fecal occult blood; Hematest tablet or Hemoccult Test, or a dilute solution of Guaiac Test (most sensitive test for occult blood)



Schematic illustration of the types of stenosis and atresia. A, Stenosis. B, Stenosis with partial membrane. C, Membrane atresia. D, Cord atresia. E, Blind end atresia. F, Christmas tree atresia (1, jejunum; 2, ileum; 3, colon; 4, ileocolic artery).



Schematic diagram of the effects of hepatic injury on the development of fibrosis. Acute hepatic centrilobular injury (2) that occurs only once usually resolves, and normal liver architecture returns (1, 3). Repeated bouts of injury or severe injury can initiate hepatic fibrosis (4). In the earliest stages, fibrosis may be reversible, but as fibrosis progresses it reaches a point at which repair is not likely. Fibrosis starts as fine branches of collagen deposition between portal areas or central areas or dissecting into the hepatic parenchyma (5, 6). Over time, greater amounts of collagen and other extracellular matrix are deposited and the lobular architecture becomes progressively distorted. In the end-stage liver, nodular regeneration (7, 8) and extensive, circumferential fibrosis are typical. The regenerative nodules shown here (7, 8) are at an early stage of regeneration. These nodules will often compress (7) the central vein(s) of hepatic lobules within and adjacent to those from which they arose.

Intestinal Diseases in Pigs

- ✓ Pigs of all ages are susceptible to intestinal diseases, and diarrhea is the sign common to nearly all such disorders.

Edema Disease (*Escherichia coli* enterotoxemia)

- ✓ Edema disease is an acute, highly fatal, neurologic disorder that usually is seen 5 days to 2 wk after weaning and may be accompanied by diarrhea

Enteric Colibacillosis

- ✓ Enteric colibacillosis is a common disease of nursing and weanling pigs caused by colonization of the small intestine by enterotoxigenic strains of *Escherichia coli*.

Etiology and Pathogenesis:

- ✓ Certain strains of *E. coli* possess fimbria or pili that allow them to adhere to or colonize the

absorptive epithelial cells of the jejunum and ileum.

- ✓ The common antigenic types of pili associated with pathogenicity are K88, K99, 987P, and F41.
- ✓ Pathogenic strains produce enterotoxins that cause fluid and electrolytes to be secreted into the intestinal lumen, which results in diarrhea, dehydration, and acidosis.
- ✓ Infection in neonates is commonly caused by K88 and 987P strains, whereas postweaning colibacillosis is nearly always due to the K88 strain

Lesions:

- ✓ Dehydration and distention of the small intestine with yellowish, slightly mucoid fluid is characteristic.

- ✓ The fundic portion of the gastric mucosa is often reddened.
- ✓ Pigs dying suddenly may have patchy cutaneous erythema.
- ✓ Histologically, the villi are usually of normal length and have many small bacterial rods adhered to the absorptive enterocytes.

Hemorrhagic Bowel Syndrome (Mesenteric torsion of the small intestine)

- ✓ Hemorrhagic bowel syndrome affects rapidly growing swine 4-6 mo of age.
- ✓ Pigs die suddenly without evidence of diarrhea, but the small intestine is thin walled on necropsy and filled with either clotted or unclotted blood.
- ✓ The large intestine usually contains tarry fecal material but no lesions suggestive of swine dysentery, salmonellosis, proliferative enteritis, or intestinal spirochetosis.
- ✓ The condition can be prevented by the administration of either bacitracin or chlortetracycline in the feed.
- ✓ When performing a necropsy, the mesenteric root should be palpated prior to opening the abdomen.
- ✓ A peracute form of proliferative enteritis may have similar clinical and gross lesions; however, histology and culture of the intestine will discern the presence or absence of epithelial proliferation and *Lawsonia intracellularis*.

Intestinal Spirochetosis

- ✓ Intestinal spirochetosis is a disease of the large intestine seen in the absence of *Brachyspira hyodysenteriae*
- ✓ This disease syndrome is being recognized more frequently worldwide.

Etiology and Pathogenesis:

- ✓ The primary cause of intestinal spirochetosis is *B. pilosicoli*.
- ✓ The pathogenesis is not well studied, but apparently the end-on attachment of the spirochete to the mucosal surface interferes with the absorptive capacity of the colon, resulting in diarrhea.

Lesions:

- ✓ The lesions in the large intestine are milder than those caused by *B. hyodysenteriae* in swine dysentery.
- ✓ The volume of the large intestine may be increased and distended with thickening of the mucosa.
- ✓ In some pigs, mucohemorrhagic colitis develops in association with enlarged mesenteric lymph nodes.
- ✓ Microscopically, spirochetes may be seen attached end-on to the mucosal surface and give the appearance of a false brush border.
- ✓ The mucosal surface has focal erosions with mild catarrhal exudate.
- ✓ Colonic crypts are often dilated containing numerous spirochetes.

Intestinal Salmonellosis

- ✓ Enteropathogenic salmonellae cause inflammation and necrosis of the small and large intestines, resulting in diarrhea that may be accompanied by generalized sepsis.
- ✓ All ages are susceptible, but the disease is most common in weaned and growing-finishing pigs.

Etiology and Pathogenesis:

- ✓ *Salmonella choleraesuis kuzendorf* (*S. choleraesuis*) is one of the most common salmonella species affecting pigs.
- ✓ It sometimes produces necrotizing enterocolitis but far more common is a septicemic disease characterized by hepatitis, pneumonia, and cerebral vasculitis.
- ✓ *S. typhimurium* infection of the intestine results in necrotizing, nonsuppurative inflammation of the mucosa and submucosa of the ileum, cecum, and colon; frequently, the mucosa is ulcerative.
- ✓ Usually, there is extension to regional lymph nodes and, occasionally, generalized septicemia.
- ✓ Sources of infection for *S. choleraesuis* and *S. typhimurium* are primarily asymptomatic carrier pigs but also may include rodents and contaminated feed and premises.
- ✓ Numerous other serotypes of salmonellae are seen in pigs, some of which have been associated with human foodborne illness.
- ✓ Common serotypes seen in pigs are *S. typhimurium*, *S. Heidelberg*, *S. Worthington*, and *S. infantis*. These serotypes may cause mild to moderate diarrhea in swine and may be resistant to multiple drugs.

Lesions:

- ✓ Pigs infected with *S. choleraesuis* have an inflamed, slightly thickened ileum and colon, usually with necrotic debris on the mucosal surface.
- ✓ Mesenteric lymph nodes are enlarged, edematous, and sometimes red.
- ✓ Mucosal ulceration may or may not be evident. A small amount of hemorrhage may be seen in acute cases.
- ✓ Occasionally, rectal strictures may develop.
- ✓ Other enteropathogenic salmonellae, except for *S. typhimurium*, produce lesions similar to but less severe than those of *S. choleraesuis*.
- ✓ Lesions of *S. typhimurium* enteritis are distinctive, typically yellow, round (button) ulcers in the colon, cecum, and less commonly the ileum.

Parasitism

- ✓ *Ascaris suum* is the most common intestinal nematode of pigs.
- ✓ Adults in the intestine reduce feed efficiency, and heavy infections cause emaciation.
- ✓ Larval migration incites inflammation in the liver and lungs.
- ✓ *Cryptosporidium* sp is a coccidium that attaches to the mucosal epithelium of the intestine of pigs ≥10 days old.

- ✓ It causes villous atrophy in the lower small intestine. Malabsorption and diarrhea may result.
 - ✓ *Eimeria* spp are common in pigs, but overt disease is seldom seen.
 - ✓ Heavy infections may cause significant enterocolitis in young growing pigs.
 - ✓ *Hyostrogylus rubidus* is the common stomach worm found in pasture-raised pigs. It usually causes little harm.
 - ✓ *Isospora suis* is a common and important cause of coccidiosis in pigs 6 days to 3 wk old.
 - ✓ Infection causes necrosis and villous atrophy of the ileum and jejunum.
 - ✓ Secondary bacterial infection of the injured intestinal mucosa is common.
 - ✓ Mortality often is 20-25%, and many pigs are stunted.
 - ✓ Diagnosis can be based on identification of immature coccidial forms in the intestinal mucosa by direct mucosal smear stained with Giemsa stain or by histologic examination of the affected intestine.
 - ✓ Successful prevention most commonly depends on thorough cleaning of farrowing facilities to minimize the number of oocysts. After cleaning, thorough disinfection with 50% bleach has been useful.
 - ✓ Coccidiostats are sometimes fed to sows 2 wk before farrowing or administered PO to pigs from birth to 3 wk of age.
 - ✓ Adult nodular worms of *Oesophagostomum* spp in the large intestine cause little harm, but heavy infection by larvae encysted in the intestinal wall may lead to emaciation.
 - ✓ *Strongyloides ransomi* (intestinal threadworm) larvae can be transmitted via colostrum or acquired from contaminated skin of the dam.
 - ✓ Heavily infected piglets develop severe diarrhea when 10-14 days old, with high mortality.
 - ✓ Diagnosis is based on direct microscopical observation of mucosal scrapings.
 - ✓ *Trichuris suis* (whipworms) penetrate the mucosa of the cecum and colon and cause multifocal inflammation.
 - ✓ Heavy infections cause diarrhea and emaciation.
 - ✓ The feces are hemorrhagic; therefore, heavy whipworm infections may be confused clinically with swine dysentery or proliferative enteritis.
 - ✓ Diagnosis is based on direct observation of whipworms in the large intestine or on fecal flotation.
- Porcine Epidemic Diarrhea**
- ✓ This coronaviral diarrhea (not yet recognized in the western hemisphere) affects pigs of all ages and clinically resembles transmissible gastroenteritis in several respects.
- Etiology and Epidemiology:**
- ✓ The porcine epidemic diarrhea (PED) virus is not related to any other member of the Coronaviridae.
 - ✓ Pigs are the only known host.
- ✓ Antibodies to the virus have not been found in wild pigs or in other animal species.
 - ✓ On large breeding farms, the virus persists in consecutive litters of pigs after weaning and after they lose their immunity from antibody in the milk.
 - ✓ On these farms, the virus may be associated with weaning diarrhea.
 - ✓ In Belgium, the virus is most frequently associated with diarrhea in feeder pigs, which develops shortly after they are gathered from different breeding farms and assembled in large fattening units.
 - ✓ The virus was demonstrated in fecal material in 80% of these groups.
 - ✓ Epidemiologic data from other countries are scarce.
 - ✓ Spread of the virus mainly occurs directly through infected pigs and indirectly through virus-contaminated fomites and via transport trucks.
- Pathogenesis:**
- ✓ The pathogenesis and immune mechanisms are similar to those reported for TGE.
 - ✓ Oral infection results in viral replication in the epithelial cells of the small intestinal villi.
 - ✓ Cells on colonic villi also become infected. No other tissue tropisms have been shown. Virus is excreted in the feces.
- Lesions:**
- ✓ Macroscopic lesions are confined to the small intestine with villous shortening as the main characteristic.
 - ✓ These lesions closely resemble those seen with TGE.
 - ✓ No lesions have been described in the colon. A consistent finding is acute necrosis of back muscle.
- Porcine Proliferative Enteritis (Porcine intestinal adenomatosis, Proliferative hemorrhagic enteropathy, Ileitis)**
- ✓ Porcine proliferative enteritis is a common diarrheal disease of growing-finishing and young breeding pigs characterized by hyperplasia and inflammation of the ileum and colon.
 - ✓ It often is mild and self-limiting but sometimes causes persistent diarrhea, severe necrotic enteritis, or hemorrhagic enteritis with high mortality.
- Etiology and Pathogenesis:**
- ✓ The etiology is an intracellular gram-negative small rod-shaped bacterium called *Lawsonia intracellularis*.
 - ✓ The organism has been cultivated only in cell cultures, and attempts to propagate it in cell-free medium have failed.
 - ✓ Koch's postulates have been fulfilled by inoculation of pure cultures of *L. intracellularis* into conventionally reared pigs; typical lesions of the disease were produced, and *L. intracellularis* was reisolated from the lesions.

- ✓ Inoculation of *L. intracellularis* into gnotobiotic pigs does not cause the disease; therefore, other factors in the conventionally reared pig may contribute to development of lesions.

Lesions:

- ✓ Lesions may be seen anywhere in the lower half of the small intestine, cecum, or colon but are most frequent and obvious in the ileum.
- ✓ The wall of the intestine is thickened, and the mesentery may be edematous.
- ✓ The mesenteric lymph nodes are enlarged. The intestinal mucosa appears thickened and rugose, may be covered with a brownish or yellow fibrinonecrotic membrane, and sometimes has petechial hemorrhages.
- ✓ Yellow necrotic casts may be found in the ileum or passing through the colon.
- ✓ Diffuse, complete mucosal necrosis in chronic cases causes the intestine to be rigid, resembling a garden hose.
- ✓ Proliferative mucosal lesions often are in the colon but are detected only by careful inspection at necropsy.
- ✓ In the profusely hemorrhagic form, there are red or black, tarry feces in the colon and clotted blood in the ileum.

Rotaviral Enteritis

- ✓ Rotaviral enteritis is a common disease of the small intestine of pigs.
- ✓ All ages are susceptible, but significant diarrheal disease usually is seen in nursing or postweaning pigs.

Etiology and Pathogenesis:

- ✓ The causal rotavirus infects and destroys villous enterocytes throughout the small intestine, but lesions are most severe in the middle third of the intestine.
- ✓ Loss of villous epithelium results in partial villous atrophy, malabsorption, and osmotic diarrhea.
- ✓ Multiple antigenic types of rotavirus affect pigs. They are easily spread by direct contact.
- ✓ Healthy carrier sows may be fecal shedders during the periparturient period, thereby exposing their litters to infection.

Lesions:

- ✓ The small intestine appears thin walled, and the cecum and colon contain liquid feces.

***Streptococcus dispar* Enteritis**

- ✓ This diarrheal disease of nursing piglets usually 5-10 days old has been associated with colonization of the small intestine with *S. dispar*.
- ✓ Diagnosis may be aided by observation of gram-positive cocci adhered to the villous epithelial cells.
- ✓ Antibacterials such as penicillin should be useful in treatment.

Swine Dysentery (Bloody scours)

- ✓ Swine dysentery is a common, mucohemorrhagic diarrheal disease of pigs that affects the large intestine.

Etiology and Pathogenesis:

- ✓ The essential causal agent is *Brachyspira* (*Serpulina*) *hyodysenteriae*, an anaerobic spirochete that produces a hemolysin, although other organisms may contribute to the severity of lesions.

- ✓ It proliferates in the large intestine and causes degeneration and inflammation of the superficial mucosa, hypersecretion of mucus by mucosal epithelium, and multifocal bleeding points on the mucosal surface.
- ✓ The organism does not penetrate beyond the intestinal mucosa.
- ✓ Decreased ability of the mucosa to reabsorb endogenous secretions from the unaffected small intestine results in diarrhea.

Lesions:

- ✓ The diffuse lesions are confined to the cecum, spiral colon, and rectum.
- ✓ The affected mucosa is covered with a layer of transparent or gray mucus, often with suspended flecks of blood in early stages; a mixture of blood, fibrin, and necrotic debris in more advanced cases; and a yellow, necrotic debris late in the course.

Transmissible Gastroenteritis

- ✓ Transmissible gastroenteritis (TGE) is a common viral disease of the small intestine that causes vomiting and profuse diarrhea in pigs of all ages.

Etiology and Pathogenesis:

- ✓ The causal coronavirus infects and destroys villous epithelial cells of the jejunum and ileum, which results in severe villous atrophy, malabsorption, osmotic diarrhea, and dehydration.
- ✓ The incubation period is ~18 hr.
- ✓ The infection spreads rapidly by aerosol or contact exposure. Severe epidemics are more common during winter due to survival of the virus in colder temperatures.

Lesions:

- ✓ Piglets dying of TGE are severely dehydrated, and the skin is soiled with liquid feces.
- ✓ The stomach usually contains milk curd but may be empty.
- ✓ The small intestine is thin walled, and the entire intestine contains greenish or yellow watery fluid and clumps of undigested milk.
- ✓ Older pigs have few remarkable lesions except that the colon contains liquid rather than formed feces.
- ✓ Villous atrophy can be observed by examining the mucosa of the small intestine with a hand lens.

a. Respiratory System

Defense Mechanisms Provided by
Some Cells and Secretory Products
Present in the Respiratory System

Cell/Secretory Product	Action
Alveolar macrophage	Phagocytosis, main line of defense against inhaled particles and microbial pathogens in the alveoli
Intravascular macrophage	Phagocytosis, removal of particles, endotoxin, and microbial pathogens in the circulation
Ciliated cells	Expel mucus and inhaled particles and microbial pathogens by ciliary action
Clara cells	Detoxification of xenobiotics (mixed function oxidases) and protective secretions against oxidative stress and inflammation
Mucus	Traps inhaled particles and microbial pathogens and neutralizes soluble gases
Surfactant	Protects alveolar walls and enhances phagocytosis
Lysozyme	Antimicrobial enzyme
Transferrin and lactoferrin	Inhibition and suppression of bacterial growth
α_1 -Antitrypsin	Protects against the noxious effects of proteolytic enzymes release by phagocytic cells; also inhibits inflammation
Interferon	Antiviral agent and modulator of the immune and inflammatory responses
Interleukins	Chemotaxis, up-regulation of adhesion molecules
Antibodies	Prevent microbe attachment to cell membranes, opsonization
Complement	Chemotaxis; enhances phagocytosis
Antioxidants*	Prevent injury caused by superoxide anion, hydrogen peroxide, and free radicals generated during phagocytosis, inflammation, or by inhalation of oxidant gases (ozone, NO_2 , SO_2)

*Superoxide dismutase, catalase, glutathione peroxidase, oxidant free radical scavengers (tocopherol, ascorbic acid).

Main Defense Mechanisms of the Respiratory System

Conducting system (nose, trachea and bronchi)	Mucociliary clearance, antibodies, lysozyme, mucus
Transitional system (bronchioles)	Clara cells, antioxidants, lysozyme, antibodies
Exchange system (alveoli)	Alveolar macrophages (inhaled pathogens), intravascular macrophages (circulating pathogens), opsonizing antibodies, surfactant, antioxidants

Rhinitis and sinusitis

Rhinitis – inflammation of the nasal mucosa.

Sinusitis- inflammation of the sinus(es).

- usually occur together.

Based on the nature of exudate, rhinitis can be classified into serous, catarrhal, purulent, fibrinous, or granulomatous.

Nasal cavity and sinuses

Epistaxis

- clinical term for presence of blood from the nose regardless whether blood originates from the nasal cavity or from the lungs.

Common Pathogens, Allergens, and Toxic Substances Present in Inhaled Air

Microbes	Viruses, <i>Chlamydomphila</i> , bacteria, fungi, protozoa
Plant dust	Grain, flour, cotton, wood
Animal products	Dander, feathers, mites, insect chitin
Toxic gases	Ammonia (NH_3), hydrogen sulfide (H_2S), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), chlorine
Chemicals	Organic and inorganic solvents, herbicides, asbestos, nickel, lead

EQUINE DISEASES

Equine viral rhinopneumonitis - caused by equine herpes virus.

Equine influenza -caused by type A influenza virus.

Strangles

lesions: - Mucopurulent rhinitis with localizations in the regional lymph nodes (usually retropharyngeal and submandibular

-caused by *Streptococcus equi subsp. equi* (common in young horses)

Glanders

Lesions: Nodular, confluent suppurative lesions in the upper respiratory tract, also affect lungs and skin.

- caused by *Pseudomonas mallei*

Melioidosis (Pseudoglanders)

- Involvement of the res. system or part of septicemia in pigs. Caused by *Ps. pseudomallei*

Equine Rhinopneumonitis

- Caused by EHV4 (equine herpes virus); affects young horses

CATTLE DISEASES

Infectious bovine rhinotracheitis

- Serous rhinitis with hyperemia and edema of the mucosa.

FELINE DISEASES

Feline viral rhinotracheitis

- caused by feline herpesvirus, char. by oculonasal discharges, severe rhinitis, and conjunctivitis.

- Bronchopneumonia (susceptible: kittens)

- Initially serous then catarrhal (complicated)

Feline Caliciviral Disease

- may cause erosion of the nasal philtrum and multifocal interstitial pneumonia.

Miscellaneous Types:

allergic type - Affects dogs, sheep and cattle including bovine nasal granuloma (bovine atrophic rhinitis)

- There is hypertrophy and hyperplasia of glandular epithelium and squamous metaplasia of the ducts. Edema, eosinophilia, plasma cell and mononuclear cell infiltration are the features. Seen in type I and II hypersensitivity; seen more frequently in Jersey cattle.

PARASITES

- *Oestrus ovis* larvae causes sinusitis in sheep
- *Habronema sp.* and *Capillaria sp.*

NEOPLASIA

Sarcoma (fibrosarcoma)

most common - adenocarcinoma

PHARYNX, LARYNX, TRACHEA, AND BRONCHI**Brachycephalic airway syndrome**

- respiratory impairment caused by stenotic external nostrils and excessive length of the soft palate.
- present in bulldogs, boxers, Boston terriers, pugs, Pekingese (brachycephalic breeds).

Laryngeal Paralysis in Horses

- "roaring" - most common in the left side due to degeneration of the left recurrent laryngeal nerve and resultant atrophy of the cricoarytenoideus muscle.
- Cause: unknown

Edema - can result from trauma

- also seen in edema disease of swine,
- ICH and acute interstitial pneumonia of cattle.

Tracheal Collapse

- in toy and miniature breeds of dogs
- dorsoventral flattening: hypocellularity of the cartilage with fibrous replacement
- in horse: scabbard trachea (lateral flattening)

INFLAMMATIONS

- frequently the upper respiratory tract
- caused by bacteria, viruses, parasites, foreign agents and fungi.
- obstructive lesions
- putrid bronchitis and gangrene following aspiration pneumonia.

Chronic Pulmonary Disease

- in horse; diffuse bronchitis, with epithelial hyperplasia

Heaves- In horses, having difficulty in breathing and show a marked abdominal muscle movement.

Canine tracheobronchitis (kennel cough) - chronic bronchitis with thick mucopurulent exudates and polyp-like lesions.

THE LUNGS**Lung types in Domestic Animals**

- 1) Type I lung
 - well developed secondary lobules, interlobular septa and thick pleura. Alveoli between lobules lack interalveolar pores of Kohn.
 - (cattle, sheep, goats and pigs)
- 2) Type II lung
 - absence of secondary lobules, ill-defined intra-parenchymal supportive tissue strands, and with thin membranous pleura.
 - (dog, cat and monkey)

3) Type III lung

- incompletely developed secondary lobules, well defined but haphazardly arranged interlobular septa, and with thick vascular pleura
- Horse

Some Responses of the Lung to Injury

Atelectasis - incomplete distention (congenital or neonatal), or collapse of previously distended lung (acquired).

- a) neonatal atelectasis or hyaline membrane disease occur in human infants where a lack of surfactant is the primary factor (failure of type II cell development) - condition has been reported in foals, and less frequently in lambs, pigs, pups, and kittens.
- b) hypostatic atelectasis - postural forces on lungs prevent adequate ventilation. May be seen in large animals kept in abnormal postures (e.g. surgery) for prolonged periods.
- c) compression atelectasis - due to space occupying lesions, fluids, air (pneumothorax).
- d) obstructive atelectasis - collapse of lungs due to obstruction of airways; more pronounced in animals with Type I lung; the surrounding lung tissue show emphysema.

EMPHYSEMA

- abnormal enlargement of air spaces (alveoli) distal to the terminal bronchioles due either to dilation or destruction of their walls.
- over-inflation in the lungs. Ruptured alveolar septae do not repair.

Chronic bronchiolitis

- emphysema (heaves in horses; Chronic Pulmonary Disease [CPD]; Broken wind).
- narrowing of bronchioles due to exudation and eventual peri-bronchiolar fibrosis.

EDEMA AND CONGESTION

Congestion and edema are terminal events and are seen commonly seen in death.

- "mulberry heart" disease in pigs as well as alpha naphthyl thiourea (ANTU) poisoning are examples of occurrence.

HEMORRHAGE, EMBOLI AND THROMBOSIS

Hemorrhage can occur as a result of trauma, blood clotting defects, or any inflammatory cause where rupture of a blood vessel occurs. Blood is often aspirated at slaughter; and blood in this case has a lobular distribution.

Emboli from valvular endocarditis are rare. Most likely to occur in cattle. Parasitic emboli in *Dirofilaria immitis* infection.

The bronchial arteries provide a collateral supply to lungs.

PIGMENTS

Carbon particles (anthracosis) - appear as black pigment in the lung as fine particulate matter and is

common in older animals that live in an urban environment.

Hemosiderin - a brown pigment derived from hemoglobin occurs in lung tissue as a result of old hemorrhage. *Dirofilaria immitis* infection in dogs usually has associated hemosiderin pigmentation of lung tissue.

INFLAMMATION

Pneumonia is a term used to describe lung inflammation involving alveolar parenchyma.

pneumonia - for more acute and exudative inflammations

pneumonitis - for more chronic, proliferative lesions

4 morphologic distinct types of pneumonia

1. bronchopneumonia
2. interstitial pneumonia
3. embolic pneumonia
4. granulomatous pneumonia

According to distribution of inflammatory lesion in the lungs:

1. cranioventral - bronchopneumonia
2. focal - embolic pneumonia
3. diffuse - interstitial pneumonia
4. locally extensive - granulomatous pneumonia

3 main categories:

1. Bronchopneumonia - the most common form of pneumonia characterized by inflammation in the bronchio-alveolar junction.
2. Lobar pneumonia - one which involves the entire pulmonary lobes or major portion of lobes
3. Interstitial pneumonia - diffuse reaction to blood borne agents centered on the alveolar septa. Characterized by collapsed alveolar walls.

BRONCHOPNEUMONIA

- a distinctive pattern which involve the cranio-ventral parts in either a lobar or lobular distribution.
- most common form of lung inflammation. The common causes are bacteria and mycoplasma and in some instances viruses play a role.

Organisms associated with bronchopneumonia include:

Actinobacillus actinoides, *Salmonella* sp., *Pseudomonas*

LOBAR (FIBRINOUS) PNEUMONIA

- a rapidly confluent, fulminating form of bronchopneumonia which is usually lobar but may sometimes be diffusely spread.

Organisms causing the fibrinous form of bronchopneumonia include *P. hemolytica* and *P. multocida* (mainly cattle but also sheep). *Mycoplasma pleuropneumonia* in cattle (Contagious Bovine Pleuro-pneumonia [CBPP]) and goats; *Hemophilus* (nov. *Actinobacillus*) *pleuropneumonia*; *Streptococci* sp. in horses.

INTERSTITIAL PNEUMONIA (DIFFUSE FIBROSING ALVEOLITIS/PNEUMONITIS)

An inflammatory process resulting from diffuse or patchy alveolar septal damage without obvious orientation of the lesion around small airways, i.e. it has a diffuse distribution. This process can not be diagnosed grossly, and may be focal or diffuse.

Causes of Interstitial Pneumonia

Infectious causes - Herpes, adeno- and calici viruses project an interstitial pneumonia, but initially the change may be oriented around the airways (broncho-interstitial). This bronchopneumonic (lobular, lobar) appearance may be reinforced by secondary bacterial infection. Other viral infections include canine distemper (paramyxovirus) where large multinucleate cell containing intracytoplasmic and intranuclear inclusions may be found, and parainfluenza-3-virus in cattle.

SPECIAL FORMS OF PNEUMONIA

- 1) Gangrenous pneumonia
- 2) Aspiration pneumonia - can cause severe necrotizing and suppurative reaction. May lead to gangrene. Usually lobular but can be focal in distribution.
- 3) Lipid/lipoid pneumonia - special for of aspiration pneumonia in which droplets of oils are inhaled.
- 4) Uremic pneumonopathy - severe uremia causes increased permeability of the alveolar air-blood barrier and is therefore a cause of pulmonary edema. In dogs: degeneration and calcification of smooth muscle and connective tissue.

NEOPLASIA

The adenocarcinoma of either alveolar cell or bronchiolar cell origin is perhaps the most common primary tumor.

THE PLEURA AND THE THORACIC CAVITY

The thoracic wall, diaphragm and the mediastinum are lined by the parietal pleura, which reflects at the hilum and continues as the visceral pleura, covering the entire surfaces of the lungs.

NON-INFLAMMATORY CONDITIONS - this include:

- Pneumothorax (air in the pleural cavity),
- Hydrothorax (excess serous fluid - edema),
- Chylothorax (chylous fluid in the thorax; leaky lymphatics),
- Hemothorax (blood in the pleural cavity).

PLEURITIS or PLEURISY - inflammation of the parietal pleura is usually secondary to pneumonia. Clinically, pleuritis causes severe pain. Usually occurs as part of pneumonia.

Causes:

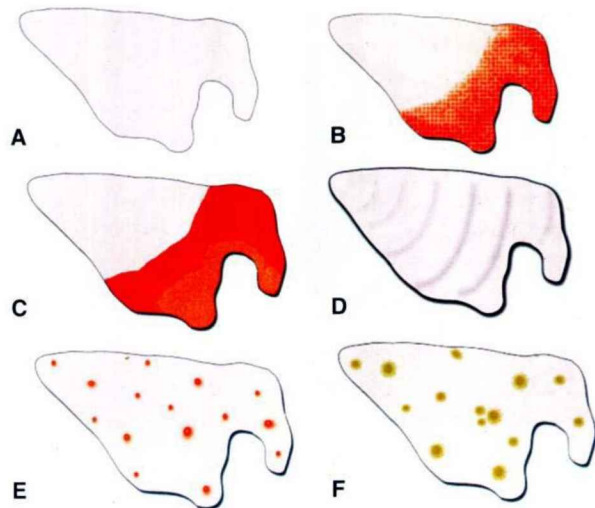
Hemophilus suis infection in pigs (Glasser's Disease) and Feline Infectious Peritonitis (FIP), pleurisy is part of the infectious process.

NOCARDIOSIS, ACTINOMYCES AND

BACTEROIDES - chronic suppurative granulomatous process which can involve the pleural and peritoneal cavities. It affects dogs and

cats, Causative organism is *Nocardia asteroides*, an actinomycete (fungus-like bacteria).

PLEURAL CALCIFICATION / MINERALIZATION- focal thickening on the parietal pleura in the intercostal spaces may be seen in renal failure (uremia) or in Vitamin D toxicity.



Schematic diagram of the patterns of pneumonia. A, Normal lung. B, Suppurative bronchopneumonia showing cranioventral consolidation and accentuated lobular pattern. C, Fibrinous bronchopneumonia showing cranioventral consolidation and fibrin on pleura. D, Interstitial pneumonia showing diffuse distribution and rib imprints in all pulmonary lobes. E, Embolic pneumonia showing multifocal distribution involving all pulmonary lobes. F, Granulomatous pneumonia showing multifocal nodules in all pulmonary lobes.

Portals of Entry into the Respiratory System

Aerogenous (air)	Virus, bacteria, <i>Chlamydomphila</i> , fungi, toxic gases, and pneumotoxins
Hematogenous (blood)	Virus, bacteria, fungi, parasites, toxins, and pneumotoxins
Direct extension	Penetrating wounds, migrating awns, bites, and ruptured esophagus or perforated diaphragm (hardware)

Classification of Pulmonary Neoplasms

PRIMARY EPITHELIAL ORIGIN

Benign

Papillary adenoma
Bronchiolar-alveolar adenoma

Malignant

Adenocarcinoma (acinar or papillar)
Squamous cell carcinoma
Adenosquamous carcinoma
Bronchiolar-alveolar carcinoma
Small cell and large cell carcinomas
Anaplastic (undifferentiated) carcinoma
Carcinoid tumor (neuroendocrine)
Ovine (retroviral) pulmonary carcinoma

PRIMARY MESENCHYMAL ORIGIN

Benign

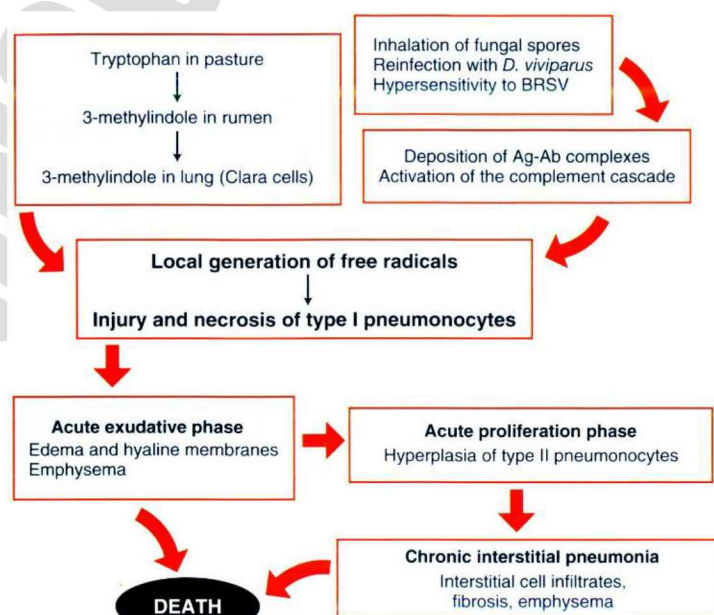
Hemangioma

Malignant

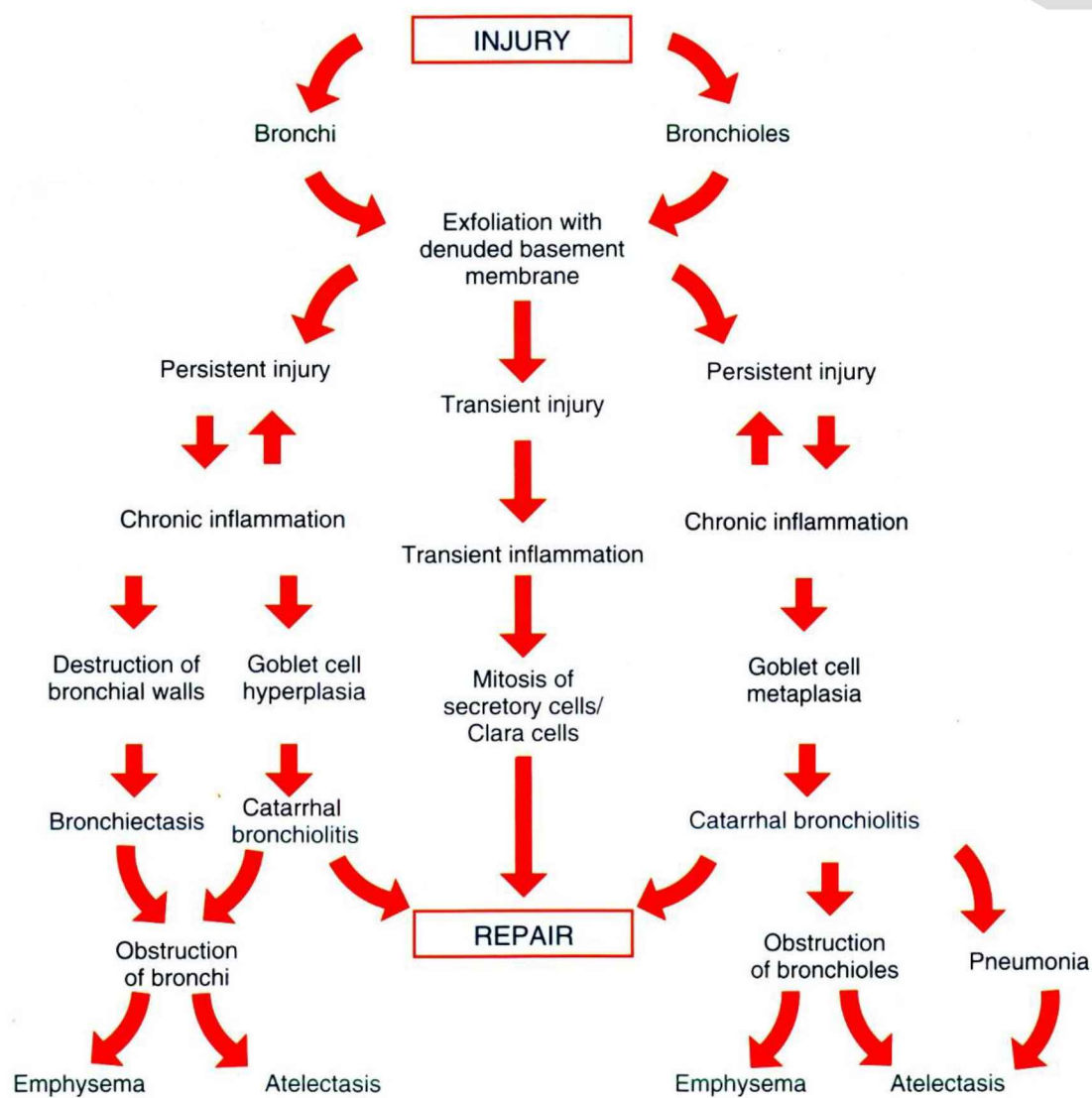
Osteosarcoma, chondrosarcoma
Hemangiosarcoma
Malignant histiocytosis
Lymphomatoid granulomatosis
Granular cell tumor
Mesothelioma

SECONDARY (METASTATIC) LUNG TUMORS

Any malignant tumor metastatic from another body location (e.g., osteosarcoma in dogs, uterine carcinoma in cows, malignant melanoma in horses)



Schematic diagram of the pathogenesis of toxic and allergic pneumonias ("atypical interstitial pneumonia") in cattle.



Schematic diagram of the patterns of host response and possible sequelae to bronchial and bronchiolar injury.

Morphologic Types of Pneumonias in Domestic Animals

Type of Pneumonia	Port of Entry (e.g., Pathogens)	Distribution of Lesions	Texture of Lung	Grossly Visible Exudate	Disease Example	Common Pulmonary Sequelae
Bronchopneumonia: Suppurative (lobular)	Aerogenous (bacteria and mycoplasmas)	Cranioventral consolidation	Firm	Purulent exudate in bronchi	Enzootic pneumonia	Cranioventral abscesses, adhesions, bronchiectasis
Fibrinous (lobar)	Aerogenous (bacteria and mycoplasmas)	Cranioventral consolidation*	Hard	Fibrin in lung and pleura	Pneumonic manheimiosis	BALT hyperplasia, "sequestra," pleural adhesions, abscesses
Interstitial pneumonia	Aerogenous or hematogenous (virus, toxin, allergen, sepsis)	Diffuse	Elastic with rib imprints	Not visible, trapped in alveolar septa	Influenza, extrinsic allergic alveolitis, PRRS, ARDS	Edema, emphysema, type II alveolar hyperplasia, alveolar fibrosis
Granulomatous pneumonia	Aerogenous or hematogenous (Mycobacteria, systemic mycoses)	Multifocal	Nodular	Pyogranulomatous, caseous necrosis, calcified nodules	Tuberculosis, blastomycosis, cryptococcosis	Dissemination of infection to lymph nodes and distant organs
Embolic pneumonia	Hematogenous (septic emboli)	Multifocal	Nodular	Purulent foci surrounded by hyperemia	Vegetative endocarditis, ruptured liver abscess	Abscesses randomly distributed in all pulmonary lobes

ARDS, Adult respiratory distress syndrome; BALT, bronchial associated lymphoid tissue; PRRS, Porcine reproductive and respiratory syndrome.
*Porcine pleuropneumonia is an exception because it often involves the caudal lobes.

c. Cardiovascular System

Etiologies of congenital cardiovascular anomalies:

1. Failure of closure of fetal cardiovascular shunts
 - a) patent ductus arteriosus
 - b) atrial septal defect
 - c) ventricular septal defect
 - d) tetrad of Fallot
2. Failure of Normal Valvular Development
 - a) pulmonic stenosis
 - b) subaortic stenosis
 - c) endocardial cushion defects
 - d) mitral and tricuspid malformations in cats
3. Malpositioning of Great Vessels
 - a) persistent right aortic arch
 - b) transposition of aorta and pulmonary artery

Specific Congenital Anomalies:

1. Patent ductus arteriosus. If PA - aorta shunt remains open, shunting usually occurs from left to right with resultant pulmonary hypertension. Inherited among poodles. Poodles, Collies, Pomeranians (most common)
 - Failure of the ductus arteriosus to close by 3 weeks - normally forms ligamentum arteriosum
2. Persistent Right Aortic Arch
 - A right aorta, instead of the normal left arches over the origin of the right bronchus.
3. Septal Defects:
 - Atrial septal defects (persistent foramen ovale)
 - Left to right shunting of blood (Of clinical significance)
 - Ventricular Septal Defect
 - Blood squirting produce valvular incompetence ("jet lesions") and right atrial dilatation. May occur singly

or in association with other defects such as transposition defects.

Pathology:

- 1) Right ventricular hypertrophy
- 2) Pulmonary hypertension and edema

Tetralogy of Fallot (Tetrad of Fallot)

(mnemonic acronym: ITPR)

Component Defects

- 1) Interventricular septal defect
- 2) Transposition of the aorta
- 3) Pulmonic stenosis
- 4) Right ventricular hypertrophy

Pathologic Physiology:

- 1) Right to left shunting of blood aggravated by pulmonic stenosis
- 2) Right ventricular hypertrophy due to pressure and volume overload
- 3) Shunting of blood result to mixing of oxygenated and nonoxygenated blood in the circulation. Since there is pulmonic stenosis, blood flow to the lungs is hampered with resultant congestion of the visceral organs (Right sided congestive heart failure may result)

Eisenmenger's Complex (similar with Tetrad of Fallot except no pulmonic stenosis).

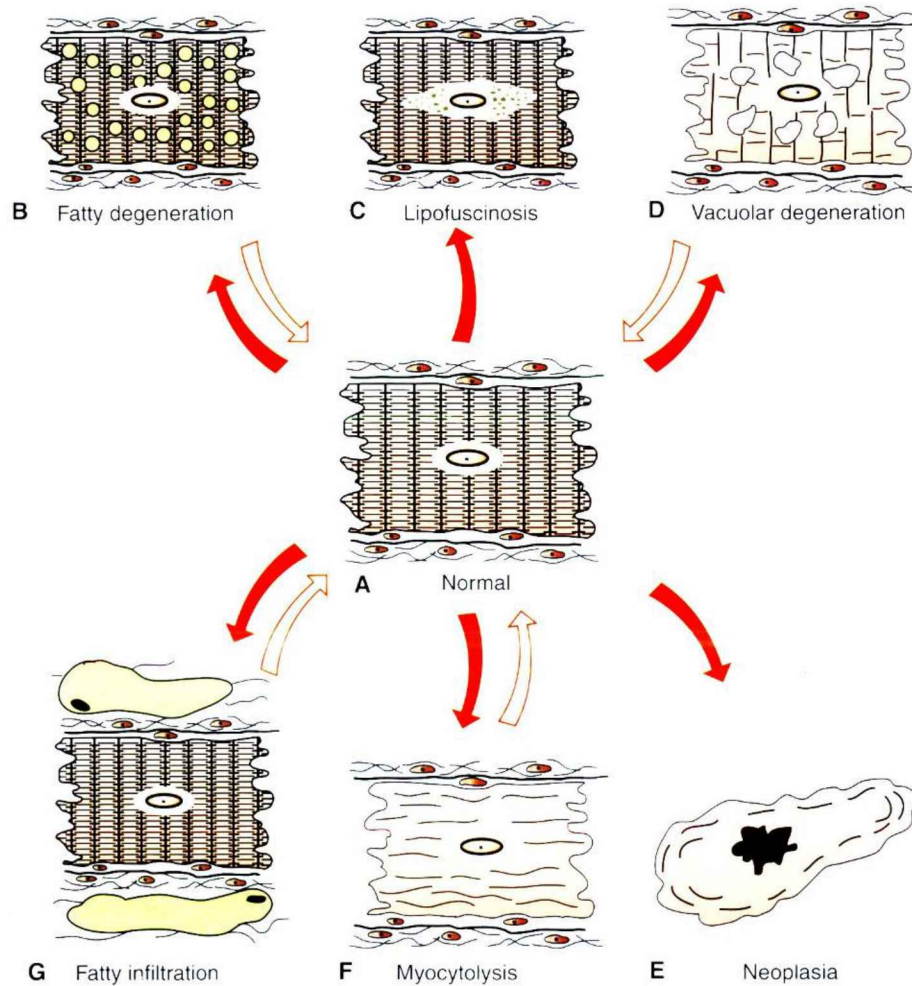
Component Defects:

- 1) Interventricular septal defect
- 2) Transposition of aorta
- 3) Right ventricular hypertrophy

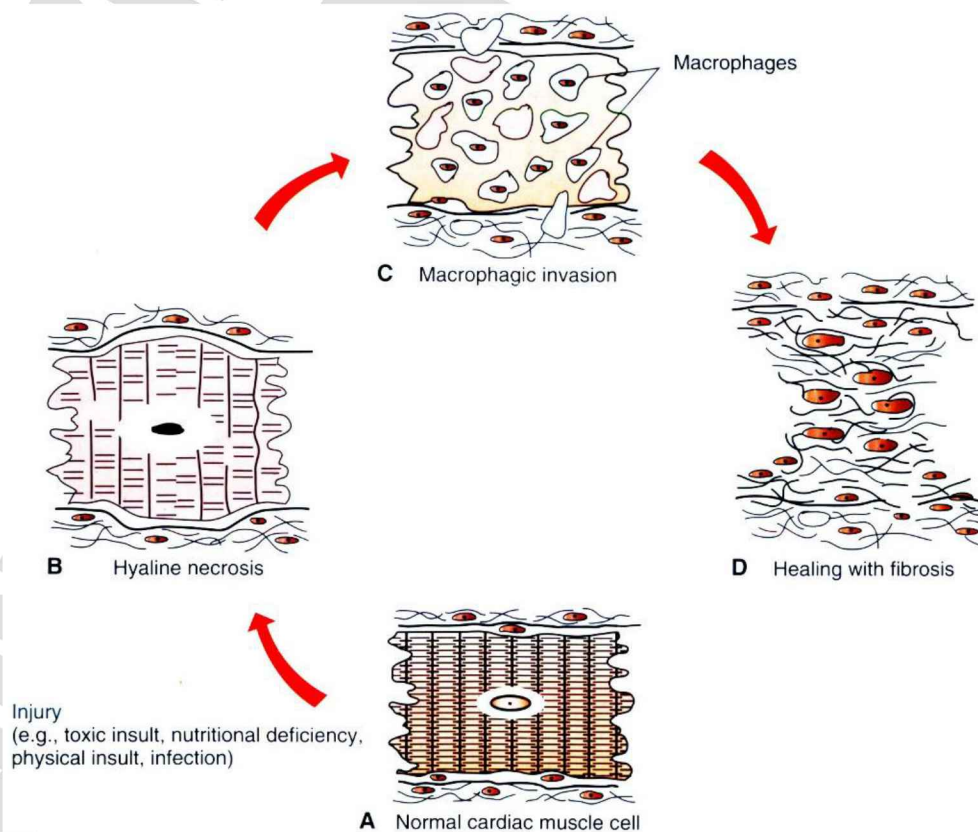
Aortic and Subaortic Stenosis

Subvalvular lesions are often more common. Irregular bands or ridge of fibrous tissue stretch across the subaortic endocardium.

- frequently in dogs and Danish pigs.



Schematic diagram of various sublethal cardiac muscle cell injuries. A, Normal muscle cell. B., Fatty degeneration. C. Lipofuscinosis. D, Vacuolar degeneration. F, Myocytolysis. Also illustrated is fatty infiltration of interstitium (G) and neoplastic transformation of myocytes (E).



Schematic diagram of the sequential events in myocardial necrosis. A, Various injuries lead to (B) hyaline necrosis or apoptosis of myocyte. C, Healing with phagocytosis of cellular debris by macrophages, and (D) subsequent healing with fibrosis, rather than by regeneration.

Pulmonary Stenosis

May occur at the valve site with or without supra or subvalvular constriction. Leads to right ventricular hypertrophy. Most common in dogs: Bulldogs, Chihuahua, Terrier types.

Transposition Defects

- a) aorta and pulmonary artery leaving the right ventricle(rare)
- b) Aorta may straddle a septal defect(VSD) and receive blood from both ventricles.
- c) Eisenmenger's Complex - whereby the aorta is dextroposed; there is a VSD, right ventricular hypertrophy.
- d) Tetralogy of Fallot - this has the same defects as Eisenmenger's complex except with the additional pulmonary stenosis.

Ectopia Cordis - preternally or intrabdominally located heart. Common in cattle and pigs.

Endocardial Fibroelastosis –

- Diffuse fibroelastic thickening of the left ventricular endocardium; necrosis and calcification of the adjacent myocardium.
 - AV valves and chordae tendinae may be thickened.
 - congenital form usually regarded as primary. (inherited in Burmese kittens?). Secondary endocardial fibrosis may occur in mature animals.
- Congenital hematomas - Hematocysts on the margins of the AV valves may be seen in calves.

Defense Mechanisms in the Cardiovascular System**PERICARDIUM**

Immunologic responses–humoral and innate

ENDOCARDIUM

Constant blood flow through cardiac chambers
Immunologic responses–humoral and innate

MYOCARDIUM

Immunologic responses–humoral and innate

ARTERIES

Constant blood flow through arteries
Immunologic responses–humoral and innate

VEINS

Constant blood flow through veins
Immunologic responses–humoral and innate

LYMPH VESSELS

Constant lymph flow through lymph vessels
Immunologic responses–humoral and innate

Portals of Entry for the Cardiovascular System**PERICARDIUM**

Hematogenous dissemination
Foreign body penetration from reticulum (cattle)

ENDOCARDIUM

Hematogenous dissemination
Parasitic migration
Intravenous and intracardiac catheters (long-term placement)
Uremia-induced vascular damage and secondary endocardial ulceration (dog, left atrium)

MYOCARDIUM

Hematogenous dissemination
Embolic dissemination of infective material fragments from vegetative endocarditis lesions into coronary arterial tree

ARTERIES

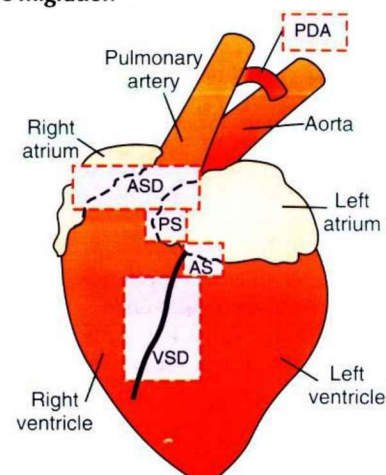
Hematogenous dissemination
Local extension of suppurative and necrotizing inflammatory processes
Immune-mediated arterial injury
Parasitic migration

VEINS

Hematogenous dissemination
Local extension of severe inflammatory processes
Intravenous injections and indwelling catheters
Parasitic migration
Immune-mediated venous injury

LYMPH VESSELS

Hematogenous dissemination
Local extension of severe inflammatory processes
Parasitic migration



Schematic diagram of the sites of the major cardiovascular anomalies of the dog. AS, aortic stenosis; ASD, atrial septal defect; PDA, patent ductus arteriosus; PS, pulmonic stenosis; VSD, ventricular septal defect.

Most Common Cardiovascular Anomalies in Several Domestic Animal Species

DOG

Patent ductus arteriosus
Pulmonic stenosis
Subaortic stenosis
Persistent right aortic arch

CAT

Endocardial cushion defects
Mitral malformation
Ventricular septal defect
Endocardial fibroelastosis
Patent ductus arteriosus

COW

Atrial septal defect
Ventricular septal defect
Transposition of aorta and pulmonary artery
Valvular hematomas

PIG

Subaortic stenosis
Endocardial cushion defect

CONGESTIVE HEART FAILURE

Right Sided Heart Failure

Causes:

1. Myocardial degeneration
2. Myocarditis
3. Cardiomyopathies
4. Congenital abnormalities
 - a) Pulmonic valve stenosis
 - b) Tricuspid valve insufficiency
 - c) Interventricular septal defect
5. Cor pulmonale
6. Hydropericardium
7. Pericarditis
8. Failure of left side of the heart

Principal Manifestation:

Increased hydrostatic pressure in systemic and hepato-portal venous system (portal hypertension); Reduction of flow of blood from lungs to the left ventricle.

Associated Pathology:

- 1) Congestion of viscera with hypoxic injury
- 2) Portal hypertension leading to periarterial necrosis/atrophy of liver
- 3) Splenomegaly with fibrotic metaplasia of reticulum and hemosiderosis
- 4) Congestion of stomach and intestines interfering with normal function leading to diarrhea.
- 5) Cyanosis due to blood stagnation
- 6) Edema due to increased venous pressure as:
 - a) dependent edema in horse
 - b) ascites in dog
 - c) hydrothorax in cat

7) May lead to disseminated intravascular coagulation due to stagnation of blood; also thrombosis and embolization.

Left Congestive Cardiac Failure

Causes:

- 1) myocardial degeneration
- 2) myocarditis
- 3) cardiomyopathies
- 4) congenital abnormalities
 - a) aortic valve stenosis
 - b) bicuspid valve insufficiency
 - c) patent ductus arteriosus

Principal Manifestation:

Damming back of blood in the lungs (pulmonary hypertension);

Diminution of cardiac output.

Associated Pathology:

- 1) Pulmonary hypertension leading to:
 - a) alveolar edema
 - b) interstitial edema
 - c) hemosiderosis of lungs
 - d) right sided heart failure due to back pressure on pulmonary arterial circulation
- 2) Cyanosis due to impaired gaseous exchange and diminished cardiac output
- 3) Coughing and dyspnea due to:
 - a) hypoxic stimulation of carotid sinus and medullary respiration associated centers in the brain
 - b) irritation of respiratory mucosa by the edema fluid
- 4) May lead to peripheral circulatory failure (hypovolemic shock) due to diminished cardiac output.

DISEASES OF THE ENDOCARDIUM

Endocardial mineralization and endocardial fibrosis

- maybe be single or multiple lesion

Mineralization will occur with Vit. D toxicosis

Fibrosis with or without mineralization will occur in heart chronically dilated, with John's disease, "jet lesions"

Vit. D toxicosis and carcinogenic plants containing Vit. D analogs (*Cestrum diurnum*, *Trisetum flavescens*, *Solanum torvum*)

Valvular Endocardiosis

- an important age-related cardiac disease of dogs.

other name: valvular fibrosis and myxomatous or mucoid degeneration

- most common cause of congestive heart failure in old dogs

- more frequent on the mitral than the tricuspid valves.

INFLAMMATORY LESIONS:**Endocarditis**

- usually a bacterial infection (*Actinomyces pyogenes*, *Streptococcus spp.*, *Erysipelothrix rhusiopathiae*). Also, parasites such as *Strongylus vulgaris* larvae in horses.
- lesions are large and generally present on valves.
- grossly, affected valves have large, adhering, friable, yellow to gray masses termed "vegetations" occluding valvular orifices. Chronic: Irregular nodular masses termed "verrucae" (wartlike lesions).

Ulcerative Endocarditis

- a distinctive lesion common affecting left atrium associated with acute renal insufficiency in dogs.

Causes of Myocardial Necrosis in Animals**NUTRITIONAL DEFICIENCIES**

Selenium-vitamin E, potassium, copper, thiamine, magnesium

TOXICITIES

Cobalt, catecholamines, vasodilator antihypertensives, methylxanthines (theobromine, theophylline, caffeine), ionophores (monensin, lasalocid, salinomycin, narasin), vitamin D and calcinogenic plants (*Cestrum diurnum*, *Trisetum flavescens*, *Solanum malacoxylon*, *Solanum torvum*), other poisonous plants (*Acacia georginae*, *Gastrolobium spp.*, *Oxylobium spp.*, *Dichapetalum cymosum*, *Persea americana*, *Cassia occidentalis*, *Cassia obtusifolia*, *Karwinskia humboldtiana*, *Ateleia glazioviana*), blister beetles (*Epicauta*), high-erucic-acid rapeseed oil, brominated vegetable oils, gossypol, T-2 mycotoxin, uremia

PHYSICAL INJURIES AND SHOCK

Central nervous system lesions and trauma ("heart-brain syndrome"), gastric dilation and volvulus, stress, overexertion, electrical defibrillation, hemorrhagic shock

MYOCARDIAL DISEASES:**Myocardial hypertrophy****2 Anatomic Forms:****1. Eccentric Hypertrophy**

- enlarged cardiac chambers with normal to decreased wall thickness. Produced by lesions with increased blood volume (i.e. valvular insufficiency and septal defects).

2. Concentric Hypertrophy

- Char. by small cardiac chambers with thick walls. Results from lesions with increased pressure load such as valvular stenosis, systemic hypertension and pulmonary disease.

Three stages of myocardial hypertrophy

- 1) initiation
- 2) stable hyperfunction
- 3) deterioration of function associated with degeneration of hypertrophied muscle.

Diseases resulting to right ventricular hypertrophy:

1. Dirofilariasis
2. Congenital pulmonic stenosis in dogs
3. "brisket disease" (high altitude disease) in cattle
4. "heaves" (chronic alveolar emphysema) in horses

Left Ventricular Hypertrophy occurs

- 1) in dogs with congenital subaortic stenosis

Biventricular hypertrophy with:

- 1) hypertrophic cardiomyopathy
- 2) various congenital cardiac anomalies

Fatty Infiltration

- affects myocardial cells associated with obesity and abundant epicardial fat deposits

Fatty Degeneration

- fatty change; accumulation of abundant lipid droplets in muscle sarcoplasm.
- lipofuscinosis (brown atrophy) of myocardium of aged animals occurs with cachexia; a hereditary lesion in Ayshire cattle.

CARDIOMYOPATHY

- term for progressive weakening of cardiac muscle.

2 forms:

- 1) Primary (idiopathic cardiomyopathy)
 - a) hypertrophic
 - b) dilated
 - c) restrictive
- 2) Secondary (specific cardiac muscle diseases)
 - a) heritable
 - b) nutritional deficiencies
 - c) toxic
 - d) physical injuries, shock
 - e) endocrine disorders (hypo, hyperthyroidism; excess glucocorticoid; diabetes mellitus)

MYOCARDIAL INFARCTION

- thrombosis or embolism of the coronary arteries; leads to cardiac failure
- entities: arteriosclerosis, atherosclerosis or periarteritis

MYOCARDITIS

- often hematogenous; types include:

- 1) suppurative myocarditis
- 2) necrotizing myocarditis
- 3) hemorrhagic myocarditis
- 4) lymphocytic myocarditis
- 5) eosinophilic myocarditis

NEOPLASTIC DISEASES

- 1) rhabdomyoma and rhabdomyosarcoma (primary neoplasms)
- 2) Schwannoma (cardiac nerve involved, cattle)
- 3) cardiac hemangiosarcoma
- 4) chemodectoma (heart base tumors or aortic body tumor)

Diseases That Cause Myocarditis in Animals

VIRAL

Canine parvovirus, encephalomyocarditis, foot-and-mouth disease, pseudorabies, canine distemper, cytomegalovirus, Newcastle disease, avian encephalomyelitis, Eastern and Western equine encephalomyelitis

BACTERIAL

Blackleg (*Clostridium chauvoei*), listeriosis (*Listeria monocytogenes*), Tyzzer's disease (*Bacillus piliformis*), necrobacillosis (*Fusobacterium necrophorum*), tuberculosis (*Mycobacterium* spp.), caseous lymphadenitis (*Corynebacterium pseudotuberculosis*), disseminated infections by *Actinobacillus equuli*, *Staphylococcus* sp., *Corynebacterium kutscheri*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*

PROTOZOAN

Toxoplasmosis (*Toxoplasma gondii*), sarcocystosis (*Sarcocystis* sp.), neosporosis (*Neospora caninum*), encephalitozoonosis (*Encephalitozoon cuniculi*), trypanosomiasis (Chagas' disease [*Trypanosoma cruzi*])

PARASITIC

Cysticercosis (*Cysticercus cellulosae*), trichinosis (*Trichinella* spp.)

IDIOPATHIC

Eosinophilic myocarditis

- concurrently occurring with hydrothorax and ascites
- may occur with "mulberry heart disease" and septicemia in pigs; heartwater (*Cowdria ruminantium*) in small ruminants; African horse sickness and bovine ephemeral fever.
- rapid onset may lead to cardiac tamponade or compression.

Hemopericardium - accumulation of whole blood in the pericardial sac. Death suddenly follows - cardiac tamponade.

Inflammatory Lesions:

Fibrinous pericarditis - the most common; often hematogenous; the "bread and butter" heart; with fibrous adhesions

- 1) in cattle: pasteurellosis, blackleg, coliform septicemia
- 2) in pigs: Glasser's disease, streptococcal disease,
- 3) in birds: psittacosis

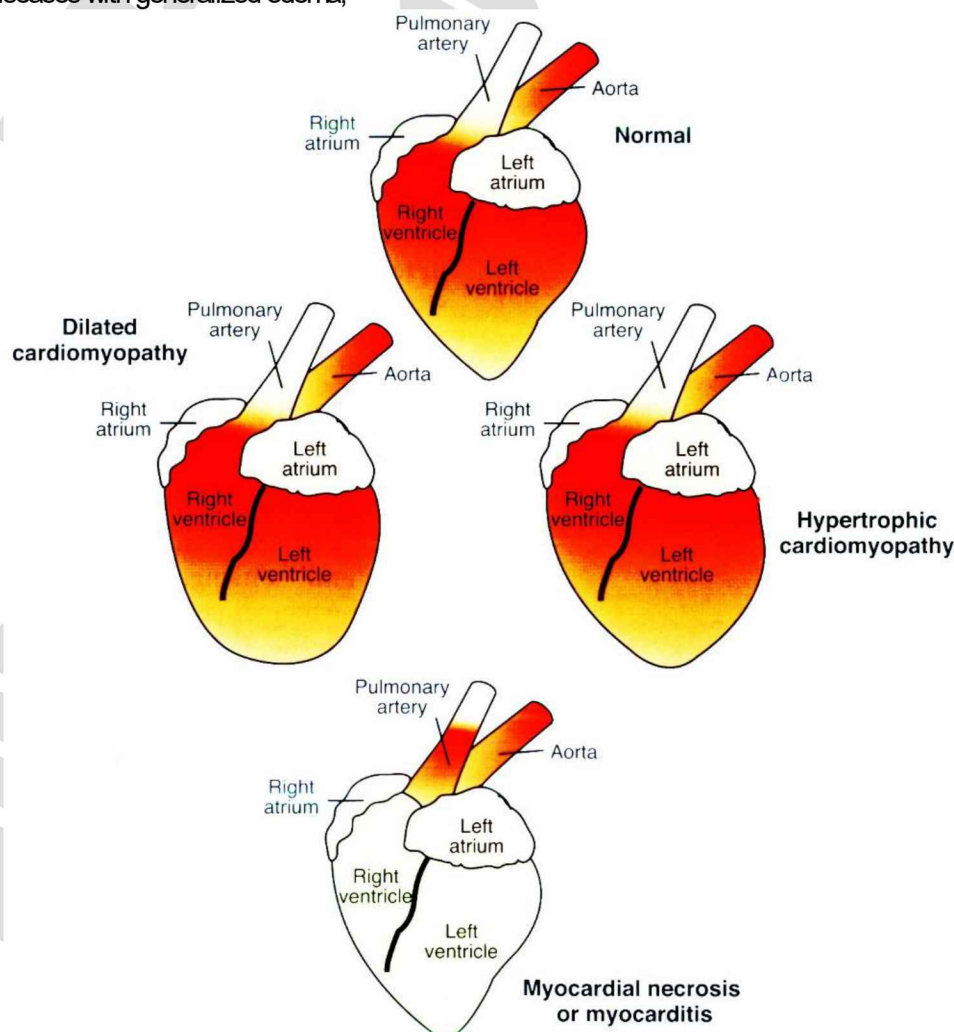
Suppurative pericarditis - common in cattle; due to traumatic reticuloperitonitis (Hardware disease)

Constrictive pericarditis - extensive fibrous proliferation and formation of fibrous adhesions across the pericardial space.

PERICARDIAL DISEASES

Hydropericardium - accumulation of clear to light yellow, watery, serous fluid in the pericardial sac which become distended.

- occurs in diseases with generalized edema;



Schematic diagram of the major myocardial diseases.

Diseases of the blood, vascular and lymphatic vessels

The vascular system is subdivided into:

a) arterial b) capillary c) venous d) lymphatic

Postmortem changes:

1. Imbibition with hemoglobin - will turn white intimal surface red.
2. Postmortem Clots - found in veins and large elastic arteries
 - a) red "currant-jelly" clots
 - b) pale "chicken-fat" clots

Arterial Diseases

Aneurysms- a localized dilatation or outpouching of a thinned and weakened portion of a blood vessel.

Causes:

- copper deficiency in pigs (copper essential in elastic artery formation)
- *Spirocerca lupi* infection
- some idiopathic origins

Dissecting aneurysm

- rare; seen in birds with and result from intimal disruption

Arterial Rupture - following trauma

Arterial hypertrophy - result from sustained increase in pressure or volume overload. Generally affects muscular arteries.

Arteriosclerosis - "hardening of the arteries"; age-related frequent in animal species

- hyperplasia of medial tunics and fibrous tissue infiltration in the intima.

Atherosclerosis - the accumulation of extensive deposits (atheroma) of lipid, fibrous tissue and calcium in vessel walls.

- a vascular disease of greatest importance in humans. Observed in aged swine, birds, dogs with hypothyroidism

Thrombosis and Embolism

Arteritis/Vasculitis – inflammation of arteries/blood vessels

Neoplastic lesions:

- Hemangiomas
 - Hemangiosarcomas
 - Hemangiopericytoma (common in canine skin)
- Inflammatory conditions:
- Arteritis, Phlebitis,

Venous diseases:

- Portocaval shunts
- Dilatation:

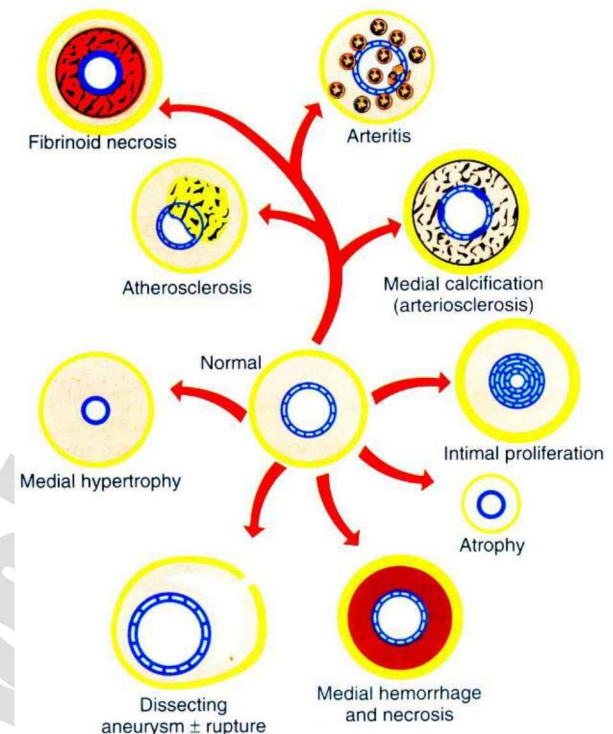
Varicosity - localized venous dilatation of a weakened vascular walls.

Phlebectasia - generalized venous dilatation.

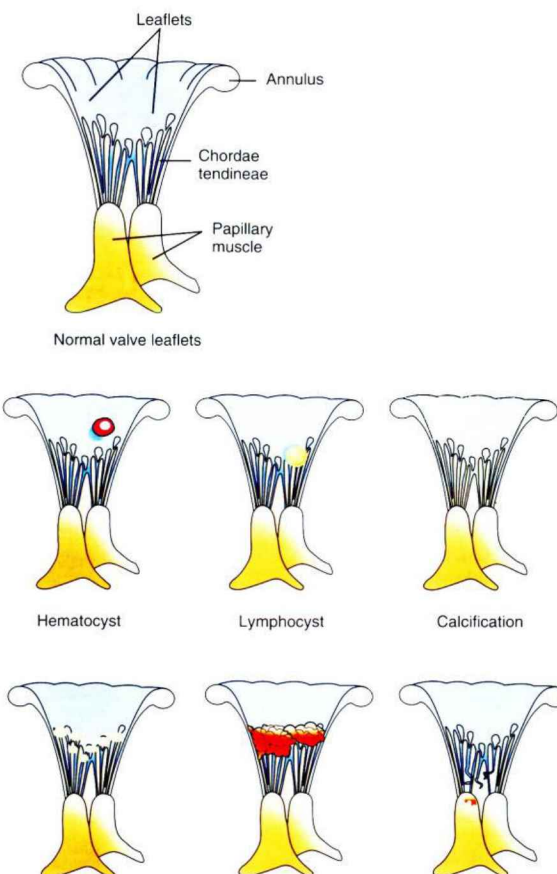
Inflammation:

Phlebitis

Omphalophlebitis ("navel ill")



Schematic diagram of the major arterial diseases.



Schematic diagram of the major types of cardiac atrioventricular valvular disease.

Highlights on Cardiovascular System

Etiologies

The following mechanisms can result in abnormalities of the cardiovascular system:

- 1) the cardiac valves fail to close or open properly (valvular disease);
- 2) the heart muscle pumps too feebly or relaxes inadequately (myocardial disease);
- 3) the heart beats too slowly, too rapidly, or too irregularly (arrhythmia);
- 4) the systemic vessels offer too great an interference to blood flow (vascular disease);
- 5) there may be holes between chambers of the left side and right side of the heart (cardiac shunts);
- 6) there is too little or too much blood compared with the ability of the blood vessels to store that blood; and
- 7) there is parasitism of the cardiovascular system (eg, heartworm disease).

The diseases of greatest importance, due to their prevalence, are

1. mitral regurgitation in dogs,
2. hypertrophic cardiomyopathy in cats,
3. dilated cardiomyopathy in dogs,
4. arrhythmic cardiomyopathy in Boxers, and
5. heartworm disease.

Valvular Disease:

- ✓ Inadequate closure of valves leads to regurgitation, which occurs most commonly as mitral regurgitation, tricuspid regurgitation, and least commonly as aortic regurgitation.
- ✓ As blood regurgitates through either set of AV valves, it often does so at a velocity great enough to produce turbulence, and a typical systolic murmur is heard between the first and second heart sounds.
- ✓ The valve orifices may be assessed by color Doppler echocardiography; regurgitant blood produces a clear, colored signal.
- ✓ With mitral regurgitation, it is common to see enlargement of the left atrium, pulmonary veins, and left ventricle. T
- ✓ Mitral or tricuspid regurgitation is most common in small-breed dogs and old horses that have valve leaflets thickened and gnarled by infiltration with glycosaminoglycans
- ✓ Aortic regurgitation occurs most often in large-breed dogs and in older horses after developing infections of the aortic valves.
- ✓ The murmur produced by blood regurgitating from the aorta into the left ventricle is always a diastolic murmur, heard immediately after the second heart sound.

Stenosis

- ✓ Inadequate opening of valves is termed stenosis.
- ✓ Pulmonic and aortic stenoses are equally prevalent; mitral stenosis is rare.

- ✓ Subaortic stenosis, produced by a fibrous band of tissue just beneath the aortic valves, is prevalent in certain breeds (eg, Golden Retrievers, Boxers, Newfoundlands, and German Shepherds).

- ✓ Pulmonic stenosis is most common in small-breed dogs; aortic stenosis develops most commonly because of a partially constricting band of fibrous tissue beneath the aortic valve in large-breed dogs.

Myocardial Disease

- ✓ Impaired force of contraction is termed reduced systolic function, which occurs most commonly in dilated cardiomyopathy
- ✓ Impaired ventricular relaxation is termed reduced diastolic function
- ✓ Ventricular muscles relax poorly in hypertrophic cardiomyopathy (ie, when the muscle is too thick), or with pericardial disease when either the thickened pericardium or fluid contained within the pericardial sac interfere with relaxation. Hypertrophic cardiomyopathy is most common in cats.

Arrhythmias

- ✓ A heart beating too fast, too slowly, or too irregularly to sustain an acceptable cardiac output is termed arrhythmia.
- ✓ The most common arrhythmias are:
 1. atrial fibrillation (seen commonly in horses and in large-breed dogs with an enlarged left atrium)
 2. ventricular premature depolarizations
 3. sick sinus syndrome (seen mainly in aged Miniature Schnauzers), and
 4. third-degree AV block.
- ✓ In atrial fibrillation, depolarization of the atria is not coordinated, stimulation of the AV node is frequent but random, and the heart rate is rapid and irregular.
- ✓ Ventricular premature depolarizations (also called ventricular premature beats or complexes) arise from irritated regions of the ventricles.
- ✓ A single premature beat causes no trouble, but premature beats may evolve into short or long bursts that lead to hemodynamic impairment and syncope, or even to a complicated ventricular spasm (ventricular fibrillation) leading to sudden death.
- ✓ With either sick sinus syndrome (ie, transient arrest of discharge of the SA node) or complete heart block (in which no atrial depolarization enters the ventricles), the ventricular rate is exceptionally slow and may lead to hemodynamic impairment and syncope.

Vascular Disease:

- ✓ Interference to blood flow through arterioles often leads to hypertension, which is most common in aging animals with impaired renal function.

Cardiac Shunts:

- ✓ Abnormal communications between chambers of the left and right side of the heart are termed intracardiac shunts.
- ✓ These take the form of (in decreasing prevalence)
 1. patent ductus arteriosus (between the aorta and pulmonary trunk),
 2. ventricular septal defect (between the left and right ventricles), or
 3. atrial septal defect (between the left and right atria).
- ✓ 4. Tetralogy of Fallot (*Tetralogy of Fallot*)
- ✓ Tetralogy of Fallot is the most common form of a right-to-left shunt.

Patent Ductus Arteriosus

- ✓ results in significant shunting of blood from left to right, ie, systemic to pulmonary.
- ✓ The result is volume overload of the pulmonary arteries and veins, left atrium, and left ventricle.
- ✓ Chronic volume overload and dilatation of the left-sided cardiac chambers usually result in signs of left-sided CHF.
- ✓ most untreated cases develop refractory CHF.

Atrial Septal Defects

- ✓ A communication between the atria may be the result of a patent foramen ovale or a true atrial septal defect.
 1. foramen ovale
 - a flapped oval opening of the interatrial septum, allows shunting of blood from the right atrium to the left atrium, in order to bypass the nonfunctional lungs.
 - At birth, the drop in right atrial pressure causes the foramen ovale to close and shunting to cease.
 - Increased right atrial pressure may reopen the foramen ovale where the septa have not sealed and allow shunting to resume.
 2. true atrial septal defect is a consistent opening of the interatrial septum, which allows blood to shunt from the atrium with the greater pressure.

Ventricular septal defects

- ✓ are most commonly located in the perimembranous portion of the septum, high in the ventricular septum immediately beneath the right and noncoronary aortic valve cusps on the left and just below the cranioseptal tricuspid valve commissure on the right.
- ✓ Ventricular septal defects may occur with other congenital cardiac anomalies. This defect is heritable in miniature swine.

Tetralogy of Fallot

- ✓ Tetralogy of Fallot is the most common defect that produces cyanosis.

- ✓ It results from a combination of pulmonic stenosis, a typically high and large ventricular septal defect, right ventricular hypertrophy, and varying degrees of dextropositioning of the aorta.
- ✓ A single conotruncal malformation (cranially displaced formation of the upper portion of the interventricular septum) is believed to result in narrowing of the right ventricular outflow tract (pulmonic stenosis), overriding of the aorta, and the ventricular septal defect. The right ventricular hypertrophy is simply a consequence of these abnormalities.

Persistent Right Aortic Arch

- ✓ In this vascular ring anomaly, the right aortic arch persists, which causes obstruction of the esophagus at the level of the heart base.
- ✓ Other vascular ring anomalies have been reported and result in findings similar to PRAA.
- ✓ These congenital defects do not cause clinical signs referable to the cardiovascular system—signs of regurgitation and aspiration pneumonia predominate.

Outflow Tract Obstructions

- ✓ This group of congenital cardiac defects includes aortic stenosis, pulmonic stenosis, and coarctation of the aorta.
- ✓ All involve obstruction to either right or left ventricular outflow.

Aortic Stenosis

- ✓ Aortic stenosis induces left ventricular hypertrophy, the degree of which depends on the severity of the stenosis.
- ✓ The major ramification of left ventricular hypertrophy is the creation of areas of myocardium with poor perfusion.
- ✓ Myocardial ischemia is a major factor in the development of serious life-threatening ventricular arrhythmias.

Pulmonic Stenosis

- ✓ The right ventricle must generate increased pressure during systole to overcome the stenosis, which in moderate to severe cases can lead to dramatic right ventricular hypertrophy and dilatation.
- ✓ The increased flow velocity deforms the wall of the main pulmonary artery, resulting in a poststenotic dilatation.
- ✓ In severe cases, right-sided congestive failure may be noted.

Coarctation of the Aorta

This rare condition of dogs and cats involves narrowing of the aorta distal to the subclavian artery, typically in the area of the ductus arteriosus. Other uncommon congenital abnormalities of the aorta include tubular hypoplasia of the ascending aorta and aortic interruption. Surgical correction has been reported.

d. Lymphatic System

Response of the Thymus to Injury

Lymphoid atrophy
Neoplasia
Hemorrhage and hematomas
Inflammation—very rare
Lymphoid hyperplasia—very rare

LYMPH VESSEL Diseases**Hereditary lymphedema**

- affected animals have prominent subcutaneous edema.
- due to lymph drainage interference.

Lymphangiectasis - dilatation of lymph vessels;
one cause is obstruction of tumor mass

Trauma may cause rupture of thoracic duct.

Lymphangitis - inflammation of lymph vessels;
often located in vessels of distal limbs

Lymphangioma - a rare benign neoplasm of lymph channels.

Causes of Lymphoid Atrophy

Infectious agents
 Viruses
 Bacteria
Toxins
Chemotherapeutic agents
Ionizing radiation
Malnutrition
Cachexia
Aging
Neoplasia

Response of the Lymph Node to Injury**HYPERPLASTIC CHANGES**

Cells of the monocyte macrophage system—sinus histiocytosis
Lymphoid tissue—hyperplasia with the production of antibody, immediate cell-mediated immunity

ATROPHIC CHANGES

Lymphoid atrophy

INFLAMMATION

Acute—microabscess and abscess formation
Chronic—abscesses and granulomas

Response of Lymphoid Nodule to Injury**LYMPHOID ATROPHY**

Viral Infections
Malnutrition
Cachexia
Aging
Antineoplastic chemotherapeutic drugs
Toxins
Irradiation

LYMPHOID HYPERPLASIA

Antigenic stimulus

Response of the Spleen to Injury

Acute inflammation—hyperemia, microabscesses, acute abscesses
Monocyte macrophage system hyperplasia—granulomatous diseases
Lymphoid hyperplasia—production of plasma cells and antibody, cell-mediated immunity
Lymphoid atrophy
Storage of blood or contraction to expel reserve blood
Neoplasia

Portals of Entry into Bone Marrow and Lymphatic Organs**BONE MARROW**

Hematogenously
Direct penetration (trauma)

THYMUS

Hematogenously

SPLEEN

Hematogenously
Direct penetration—rare

LYMPH NODE

Via afferent lymphatics
Hematogenously

LYMPHOID NODULE

Hematogenously
In the intestine, via M cells and dendritic cells to Peyer's patches

e. Urinary System

Major systemic effects affecting renal functions following injury or obstruction

- 1) azotemia
- 2) uremia
- 3) plasma protein loss
- 4) water/electrolyte and acid/base imbalance
- 5) hyperparathyroidism and osteodystrophy
- 6) retention of drugs

Cortex: medulla ratio is 1:2 to 1:3 in domestic animals.

Five basic components of renal function

- 1) Urine formation for elimination of metabolic wastes.

- 2) Acid- base regulation through reclamation of bicarbonate from the glomerular filtrate.
- 3) Water conservation through reabsorption by the proximal convoluted tubules.
- 4) Maintenance of normal extracellular potassium ion concentration through passive reabsorption in the proximal tubules and tubular secretion in the distal tubules under the influence of aldosterone.
- 5) Endocrine function through three hormonal axes (erythropoietin, renin-angiotensin, and vitaminD).

Erythropoietin produced in the kidneys in response to reduced oxygen tension stimulates bone marrow to produce erythrocyte.

Renin, produced by cells in the juxtaglomerular apparatus, stimulates the production of angiotensin that constricts afferent arterioles, maintain renal blood pressure, and stimulate aldosterone secretion from the adrenal glands, thus increasing sodium reabsorption.

Vitamin D is converted in the kidneys to its most active form [1,25 dihydroxycholecalciferol (calcitriol)].

- this facilitates calcium absorption by the intestine.

Renal failure

Azotemia - intravascular elevation of nitrogenous wastes.

Uremia - presence of excess accumulation in the blood of constituents normally eliminated in the urine that produces a severe toxic condition and usually occurs in severe kidney disease.

- a syndrome: renal failure –toxemia

(Literally, “urine in the blood”, but must not be thought in this way please).

Cause of death due to renal failure:

- Results from cardiotoxicity of increased serum potassium, metabolic acidosis and pulmonary edema.

Developmental Anomalies:

Renal aplasia (or renal agenesis) - failure of development of one or both kidneys

- seen in Doberman and beagle dogs

Renal Hypoplasia - incomplete development of kidneys

- inherited in purebred and cross-bred large white pigs

Renal dysplasia - abnormality of differentiation

Ectopic and fused kidneys -misplaced from normal sub-lumbar location

Renal cysts - not clinically significant

Cystinuria - excretion of large quantities of cystine in the urine

Glucosuria - inherited in Norwegian elkhound

- capacity to reabsorb glucose is reduced

Renal infarcts - are areas of coagulative necrosis that result from ischemia of vascular occlusion usually due to thrombosis and aseptic emboli.

Maybe pale or red.

- often wedge-shaped conforming to distribution of obstructed vessel.

Renal cortical necrosis -results from widespread thrombosis that occur in glomerular capillaries, interlobular arteries, afferent arterioles in DIC.

Hemorrhage

Renal cortical hemorrhages occur in association with many septicemic diseases and result from vasculitis or vascular necrosis.

Petechiae are common in the surface/cortex in:

1. hog cholera
2. African swine fever
3. erysipelas
4. streptococcal infections
5. salmonella infections.

Tubular Necrosis

Nephrosis - a result of ischemic or toxic insult to renal tubular cells

- acute tubular necrosis often termed nephrosis

Oliguria - decreased urine production

Anuria - absence of urine

Causes of acute tubular necrosis

- 1) severe hypotension associated with shock
- 2) complete ischemia for longer than 2 hours
- 3) prolonged ischemia
- 4) hemoglobin/RBC stromal component toxicity
- 5) heavy metals(mercury, lead)
- 6) antibacterial/antifungal agents
- 7) excessive/prolonged Vit. D supplementation
(Vitamin D nephropathy)

Incidental lesions

Lipofuscin - streaks of brown discoloration

Glomerular necrosis

Glomeruli are complex capillary tufts where main function is to form a filtrate of plasma excreted in the lower urinary tract as urine.

Components: glomerular capillaries, mesangium, mesangial cells, fenestrated capillaries, endothelium, basement membrane and slit-pores
Damage to glomerular filtration barrier can result in renal disease.

- leakage of various low molecular weight(small molecule) proteins into glomerular filtrate/urine
- proteinuria = protein-losing nephropathy

Viral glomerulitis

Suppurative glomerulitis (embolic nephritis)

Immune-mediated glomerulonephritis

Immune-complex glomerulonephritis

glomerular lesions:(immune-complex glomerulitis)

- 1)proliferative
- 2)membranous
- 3)membranoproliferative

Glomerulosclerosis -seen in diabetes mellitus

Amyloidosis - deposits in renal glomeruli

Tubulointerstitial nephritis - interstitial inflammation (infection)

Granulomatous nephritis - chronic systemic disease.

Pyelonephritis

pyelitis - renal pelvis inflammation

pyelonephritis - inflammation of both renal pelvis and renal parenchyma.

- occurs more commonly in females than males

Causes: alpha-hemolytic *E. coli*, *Proteus*, *Klebsiella*, *Staph*, *Strep*.

Hydronephrosis - refers to dilatation of renal pelvis due to obstruction of urine output.

Renal fibrosis (scarring) - a chronic/healing phase

Fibrotic kidneys - chronic interstitial nephritis,

- End-stage kidneys or nephrosclerosis

Tumors

Nephroblastomas - common renal neoplasm of

pigs: chickens

Fibromas, hemangiosarcoma

Renal lymphosarcoma

The Lower Urinary Tract

Ureter, urinary bladder: urethra

Urethral aplasia (agenesis) - rare

Patent urachus - or pervious urachus

- the most common urinary bladder malfunction.

- failure of the urachal remnant-umbilical arteries and veins to involute.

Urolithiasis (uroliths)

Urinary calculi - concretions found in urinary tract

cystine or xanthine, struvite, carbamate, silica, urate, cystine, xanthine.

urolith - obstructive- /dysuria

Cystitis - inflammation of the urinary bladder

Ureteritis - ureter

Urethritis-urethra

Enzootic hematuria -prolonged ingestion of bracken fern

Neoplasm

Epithelial neoplasm is common.

Portals of Entry to the Kidney**ASCENSION**

- Extension from lower urinary tract secondary to gastrointestinal content contamination (diarrhea) (females primarily)
- Extension from lower urinary tract secondary to genital tract contamination (pyometra) (females exclusively)
- Extension from lower urinary tract secondary to dermal contamination (perivulvar dermatitis)

HEMATOGENOUS

- Localization within corticomedullary vessels
 - Septic-embolic nephritis
 - Nonseptic necrosis with infarction
- Localization within large renal vasculature
 - Massive infarction
- Localization within glomerular tufts
- Localization within interstitial vessels

METABOLIC PROCESSING IN RENAL TUBULES

- Activation of products in proximal tubules-necrosis
- Presence of heavy metal-mercury, cadmium
- Crystalline oversaturation
- Direct toxic action-cisplatin

Renal Responses to Injury**GLOMERULI**

Necrosis

Glomerular cell proliferation

Glomerular basement membrane proliferation

Mesangial cell proliferation

Infiltration of leukocytes

Reduced vascular perfusion

Increased vascular permeability

Atrophy of the glomerular tuft

Fibrosis of the glomerular tuft

TUBULES

Cell degeneration

Cell necrosis

Cell apoptosis

Cell atrophy

Basement membrane rupture

Basement membrane thickening

Cell regeneration

Compensatory hypertrophy

INTERSTITIUM

Edema

Hemorrhage

Inflammation

Fibrosis

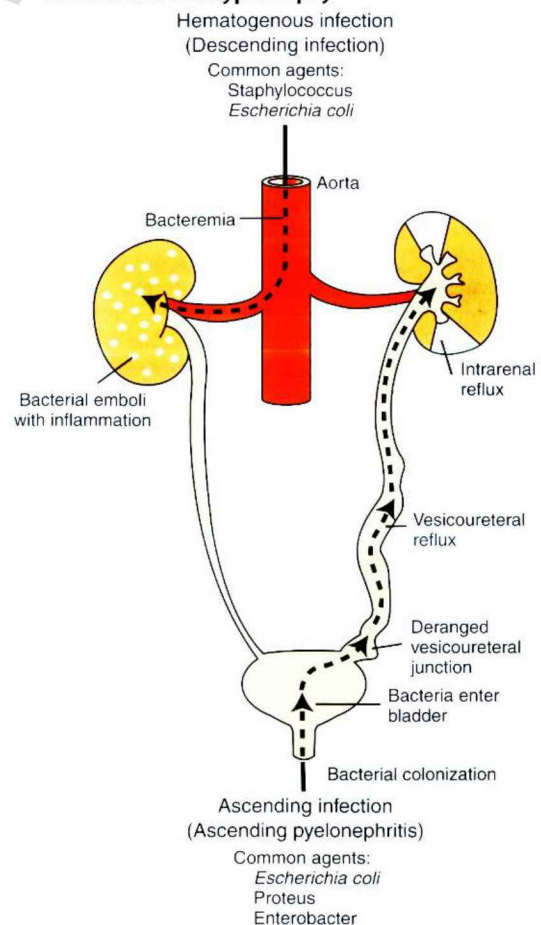
VASCULATURE

Thrombosis

Sclerosis

Basement membrane thickening

Endothelial cell hypertrophy



Schematic diagram of the pathways of renal infection. Hematogenous infection results from bacteremia. More common is ascending infection, which results from a combination of urinary bladder infection, vesicoureteral reflux, and intrarenal reflux.

Diseases with Immune-Complex Glomerulonephritis

HORSES

Equine infectious anemia
Streptococcus sp.

CATTLE

Bovine viral diarrhea
Trypanosomiasis

SHEEP

Hereditary hypocomplementemia in Finnish Landrace lambs

PIGS

Hog cholera
African swine fever

DOGS

Infectious canine hepatitis
Chronic hepatitis
Chronic bacterial diseases
Endometritis (pyometra)
Pyoderma
Prostatitis
Dirofilariasis
Borreliosis (Lyme disease)
Systemic lupus erythematosus
Polyarteritis
Autoimmune hemolytic anemia
Immune-mediated polyarthritis
Neoplasia—mastocytoma
Hereditary C3 deficiency

CATS

Feline leukemia virus infection
Feline infectious peritonitis
Feline immunodeficiency virus
Progressive polyarteritis
Neoplasia
Progressive membranous glomerulonephritis

Nonrenal Lesions of Uremia

Lesion	Mechanism
Pulmonary edema	Increased vascular permeability
Fibrinous pericarditis	Increased vascular permeability
Ulcerative and hemorrhagic gastritis	Ammonia secretion and vascular necrosis
Ulcerative and necrotic stomatitis	Ammonia secretion in saliva and vascular necrosis
Atrial and aortic thrombosis	Endothelial and subendothelial damage
Hypoplastic anemia	Increased erythrocyte fragility and lack of erythropoietin production in the kidney
Soft-tissue mineralization	Altered calcium-phosphorus metabolism (stomach, lungs, pleura, kidneys)
Fibrous osteodystrophy	Altered calcium-phosphorus metabolism
Parathyroid hyperplasia	Altered calcium-phosphorus metabolism

Common Nephrotoxins of Domestic Animals

HEAVY METALS

Mercury
Lead
Arsenic
Cadmium
Thallium

ANTIBACTERIAL AND ANTIFUNGAL AGENTS

Aminoglycosides:
 Gentamicin
 Neomycin
 Kanamycin
 Streptomycin
 Tobramycin
Tetracyclines
Amphotericin B

GROWTH-PROMOTING AGENTS

Monensin

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Aspirin
Phenylbutazone
Carprofen
Flunixin meglumine
Ibuprofen
Naproxen

MYCOTOXINS

Ochratoxin A
Citrinin

PLANTS

Pigweed (*Amaranthus retroflexus*)
Oaks (*Quercus* sp.)
Isotropis sp.
Yellow wood tree (*Terminalia oblongata*)

OXALATES

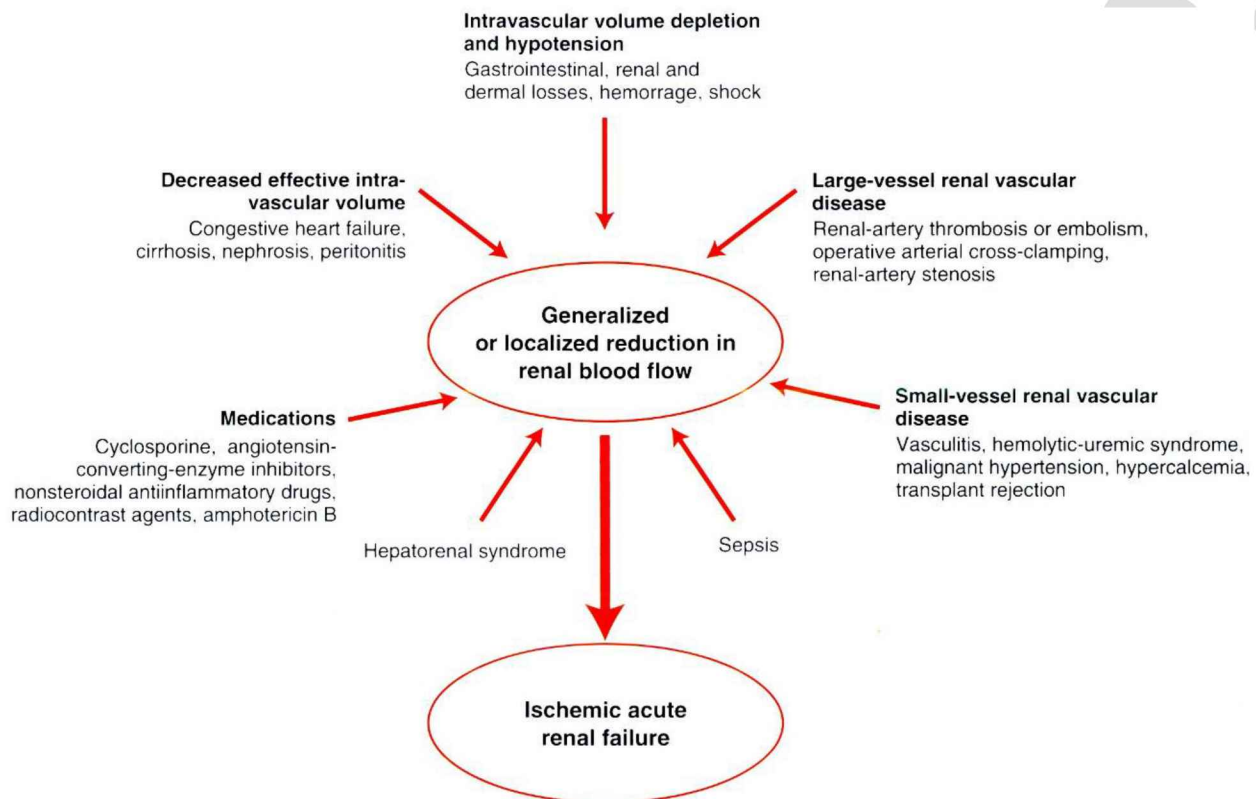
Ethylene glycol (antifreeze)
Halogeton (*Halogeton glomeratus*)
Greasewood (*Sarcobatus vermiculatus*)
Rhubarb (*Rheum rhaponticum*)
Sorrel, dock (*Rumex* sp.)

VITAMIN D

Vitamin D supplements
Calciferol-containing rodenticides
Cestrum diurnum
Solanum sp.
Trisetum sp.

ANTINEOPLASTIC COMPOUNDS

Cisplatin



Schematic diagram of ischemic renal failure. A wide spectrum of clinical conditions can result in a generalized or localized reduction in renal blood flow, thus increasing the likelihood of ischemic acute renal failure. The most common condition leading to ischemic acute renal failure is severe and sustained prerenal azotemia. Kidney ischemia and acute renal failure are often the result of a combination of factors.

Highlights on the urinary system

I. Congenital and Inherited Anomalies of the Urinary System

- group of anatomic defects that may have functional consequences

1. Renal Anomalies

A. Renal Dysplasia and Hypoplasia

- ✓ most common in dogs
- ✓ reported in Alaskan Malamutes, Bedlington Terriers, Chow Chows, Cocker Spaniels, Doberman Pinschers, Keeshonden, Lhasa Apsos, Miniature Schnauzers, Norwegian Elkhounds, Samoyeds, Shih Tzus, Soft-coated Wheaten Terriers, and Standard Poodles
- ✓ Lesions:
 - ✓ unilateral or bilateral
 - ✓ small, firm, and pale kidneys with have a uniformly diminished renal cortex.
 - ✓ immature glomeruli, primitive tubules, and secondary inflammatory lesions, especially interstitial fibrous connective tissue

B. Renal Agenesis

- ✓ accompanied by ureteral aplasia
- ✓ may be associated with aplastic reproductive tissues on the same side.
- ✓ typically an incidental finding so long as the other kidney is functioning normally
- ✓ bilateral agenesis results in early perinatal death.

C. Polycystic Kidneys

- ✓ condition may be associated with hepatic biliary cysts

- ✓ familial in Beagles, Cairn Terriers, Persian cats, and domestic long-haired cats
- ✓ seen concurrently and precipitate renal insufficiency
- ✓ Lesions:
 - ✓ Multiple cysts form within the renal parenchyma,
 - ✓ grossly enlarged kidneys

D. Simple Renal Cysts

- ✓ solitary, unilocular cysts generally do not communicate with the renal collecting system
- ✓ origin is uncertain
- ✓ usually an incidental finding

E. Perirenal Pseudocysts

- ✓ accumulations of fluid that develop external to the renal parenchyma
- ✓ unknown origin
- ✓ accumulated fluid or transudate may be located between the renal parenchyma and the renal capsule or between the renal capsule and a thin-walled fibrous sac attached to the capsule
- ✓ not lined by epithelium.
- ✓ Lesion:
 - ✓ large, firm, nonpainful mass located in the area of the kidneys.

F. Miscellaneous Renal Anomalies

- ✓ Double or multiple renal arteries
 - are seen in ~5% of dogs.
- ✓ renal malpositioning
- ✓ renal fusion
- ✓ nephroblastoma
 - an embryonal tumor and is rare in domestic animals except pigs.

- may cause no problems but may be very large and cause abdominal distention

2. Ureteral Anomalies

A. Ectopic Ureter

- ✓ most commonly reported in 3- to 6-mo-old dogs, with females affected 8 times more frequently than males
- ✓ anomalies frequently associated with ectopic ureter include hydroureter, hydronephrosis, renal hypoplasia, bladder hypoplasia, and urethral sphincter incompetence
- ✓ generally result from disruption of development of the mesonephric and metanephric duct systems.
- ✓ identifying high-risk breeds (West Highland White Terriers, Fox Terriers, and Miniature and Toy Poodles)
- ✓ familial occurrence in Siberian Huskies and Labrador Retrievers
- ✓ Lesions
 - low-grade vaginitis or vulvitis due to urine scalding.
 - ureters may open into the urethra, the uterus, or the vagina.

B. Miscellaneous Ureteral Anomalies

Ureterocele

- characterized by dilation of the submucosal ureter segment within the bladder

3. Bladder Anomalies

A. Urachal Remnants

1. Patent urachus

- associated with continuous urinary incontinence, urine scalding of the ventral abdomen, and development of bacterial urinary tract infections

2. Urachal diverticulum

- predispose to urinary tract infection by serving as a nidus for bacteria

B. Miscellaneous Bladder Anomalies

- ✓ Bladder duplication
- ✓ Dysplasia
- ✓ Hypoplasia
- ✓ Agenesis
- ✓ exstrophy

4. Urethral Anomalies

Hypospadias

- ✓ developmental defect results from failure of the urethral grooves to fuse during phallus elongation
- ✓ penis or scrotum may be underdeveloped urine scalding and complications of increased susceptibility to urinary tract infection

Urethrectal fistula

- ✓ more prevalent in English Bulldogs, possibly as a congenital defect
- ✓ abnormal separation of the embryonic cloaca into the urethra and rectum

- ✓ hematuria and dysuria secondary to urinary tract infection.
- ✓ Simultaneous passage of urine from the anus and urethra during micturition may be noted.
- ✓ urethral stenosis.

II. Renal Dysfunction

A. Acute Kidney Disease

- ✓ seen when a sudden, major insult damages the kidneys
- ✓ principal causes are toxins (eg, ethylene glycol, aminoglycoside antibiotics, hypercalcaemia, hemoglobinuria) and ischemia (eg, embolic showers from disseminated intravascular coagulation or severe prolonged hypoperfusion).
- ✓ kidneys, which may be normal-sized to slightly enlarged

B. Obstructive Uropathy

- ✓ obstruction of urine flow at any point below the level of the kidneys leads to accumulation of metabolic wastes and postrenal azotemia/uremia.
- ✓ Obstruction of the urethra
 - uroliths in dogs
 - matrix-crystalline plugs in cats
 - uroliths, tumors, or blood clots may obstruct the ureters (or urethra) in either species.

Lesions:

- ✓ Hydronephrosis
 - dilatation of the renal pelvis as the result of partial or complete obstruction of outflow of urine from one or both kidneys.
 - obstruction is acute, complete, and bilateral, morphologic changes in the kidneys are less extensive because the period of survival is short.
- ✓ Hydroureter
 - develops when the obstruction is located lower in the tract.
 - Increased hydrostatic pressure results in atrophy of functional renal parenchyma.
 - kidneys eventually become grossly enlarged, functionless sacs, filled with urine or serous fluid that may harbor bacteria.

C. Glomerular Disease

- ✓ well-recognized cause of chronic (but not acute) kidney disease in dogs
- ✓ Damage to the glomerular basement membrane results in albuminuria, which may lead to hypoalbuminemia.

D. Immune-mediated glomerulonephropathy

- ✓ deposition or in situ formation of immune complexes in the glomerular capillary wall inciting inflammatory changes
- ✓ occurrence associated with neoplasia, rickettsial diseases, systemic lupus erythematosus (SLE), heartworm disease, pyometra, chronic septicemia, and adenovirus infection, but it is usually idiopathic.

E. Primary glomerular disease

- ✓ associated with chronic infection by feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), or feline

infectious peritonitis (FIP) virus also with neoplasia and systemic inflammatory diseases.

- ✓ Predilection in young animals and in males
- F. Familial glomerulopathies**
- ✓ primary cause of chronic kidney disease have been reported in several breeds of dogs, including Bernese Mountain Dogs, English Cocker Spaniels, Doberman Pinschers, Greyhounds, Lhasa Apsos, Poodles, Rottweilers, Samoyeds, Shih Tzus, and Soft-coated Wheaten Terriers

Amyloid

- any several chemically inert fibrillar protein subunits that can be deposited in tissue and interfere with normal organ function

G. Amyloidosis

- ✓ familial amyloidosis in Shar-Peis and Abyssinian cats, are reactive, or secondary amyloidosis.
- ✓ amyloid A protein is deposited in various tissues after serum levels increase as a result of chronic inflammation
- ✓ nonfamilial form of this disease, amyloid is found primarily in the medullary interstitium producing nonproteinuric chronic kidney disease than protein-losing glomerular amyloid deposition
- ✓ Beagles, Collies, and Walker Hounds are reported to be at increased risk
- ✓ nonspecific except that ascites, pleural effusion, and/or peripheral, pitting, nonpainful, subcutaneous edema, are evident in some animals (75% of cats and 15% of dogs).

H. Renal Tubular Acidosis

- ✓ uremic acidosis, is due to reduced urine-acidifying ability of diseased kidneys
- ✓ individual tubular cells= is generally far less total cell mass present
- ✓ Acid accumulates if the animal is under metabolic or dietary acid pressure
- ✓ Rare renal tubular defects in dogs and cats may result in hyperchloremic metabolic acidosis, referred to as renal tubular acidosis.
- ✓ In Type I (distal), the ability of the distal tubule to secrete hydrogen ions against a concentration gradient is defective; in Type II (proximal), the ability to reabsorb bicarbonate in the proximal tubule is reduced.
- ✓ Type I renal tubular acidosis has been associated with demineralization of the skeleton (due to buffering of excess hydrogen ions) and nephrolithiasis (due to hypercalciuria from bone resorption) in dogs.
- ✓ Type II renal tubular acidosis is diagnosed by demonstrating increased urinary fractional excretion of bicarbonate when

plasma bicarbonate levels are normal or decreased;

I. Fanconi Syndrome

- ✓ generalized proximal tubular reabsorptive defect resulting in excessive loss of many solutes in the urine
- ✓ acquired condition in dogs (gentamicin nephrotoxicosis and an idiopathic form) and in a heritable form in a variety of breeds (most notably Basenjis), in which it develops gradually in adults of both sexes.
- ✓ There is excessive urinary loss of glucose, sodium, potassium, phosphorus, uric acid, bicarbonate, and amino acids.
- ✓ Blood glucose concentrations are normal.
- ✓ Serum electrolytes are normal early in the disease, but hypophosphatemia, hypokalemia, and metabolic acidosis are seen in the later stages.

J. Renal Glucosuria

- ✓ congenital defect in proximal tubular handling of glucose that results in glucosuria despite normal blood glucose concentration.
- ✓ demonstrating persistent glucosuria despite a normal blood glucose concentration and by identifying no other renal reabsorptive abnormalities

III. Infectious diseases of Large Animals

A. Bovine Cystitis and Pyelonephritis (Contagious bovine pyelonephritis)

- Bovine cystitis is an inflammation of the urinary bladder of cattle that may ascend the ureters to cause infection of the kidneys (pyelonephritis).
- Causative agents: *C. renale*, *C. cystitidis*, and *C. pilosum*, as well as *Escherichia coli*

Lesions:

1. enlarged left kidney
2. loss of lobulation, and pain
3. thickened and dilated ureters with a purulent exudate.
4. involved kidneys develop multiple small abscesses on the surface that may extend into the cortex and medulla.

B. Porcine Cystitis-pyelonephritis Complex

- causative agents: *Escherichia coli*, *Arcanobacterium (Actinomyces) pyogenes*, *Streptococcus* spp, and *Staphylococcus* spp, *Actinobaculum suis*

Lesions:

- catarrhal, hemorrhagic, purulent, or necrotic inflammation on the mucosal surface of the bladder
- thickened bladder wall
- struvites in the lumen
- enlarged ureters with exudates unilateral or bilateral: primary lesion
- pelvic region of the kidney with blood, pus and foul-smelling urine, often shows irregular ulceration and necrosis of the papillae.
- Chronic cases: fibrosis replaces inflammation.

IV. Infectious Diseases of the Urinary System in Small Animals

A. Bacterial Cystitis

- infection and inflammation of the urinary bladder
- pollakiuria, hematuria, dysuria, and urinating in inappropriate places
- pain on palpation of the caudal abdomen, and the bladder may feel thickened or irregular

B. Pyelonephritis

- Kidney infection usually due to ascending bacteria (hematogenous spread is possible)

Lesions:

- dilation of one or both renal pelvises secondary to inflammation and partial obstruction.
- asymmetric renal size and architectural changes with renal pelvic dilatation

C. Interstitial Nephritis

- causative agents: *Leptospira interrogans* (Leptospirosis in dogs), *Leishmania donovani* and *Borrelia burgdorferi*

D. *Capillaria plica* Infection

- urinary bladder (occasionally the ureters and renal pelvises) of dogs and cats
- parasite may be self-limiting in the absence of reinfection.

Most dogs and cats are asymptomatic

- Some show signs of pollakiuria, urinary incontinence, and urinating in abnormal places.
- hematuria and increased numbers of epithelial cells may also be present

E. Giant Kidney Worm Infection in Mink and Dogs

- causative agent: *Dioctophyma renale*

Lesions:

- obstruction, hydronephrosis, and destruction of the renal parenchyma
- right kidney is most commonly affected

V. Urethral Obstruction

- ✓ Some mineral solutes precipitate to form crystals in urine; these crystals may aggregate and grow to macroscopic size, at which time they are known as uroliths (calculi or stones)
- ✓ Urolithiasis is a general term referring to stones located anywhere within the urinary tract.
- ✓ Uroliths can develop in the kidney, ureter, bladder, or urethra and are referred to as nephroliths, ureteroliths, urocystoliths, and urethroliths, respectively.
- ✓ three main contributing factors in stone formation are:
 - 1) matrix—the inorganic protein core may facilitate initial urolith formation,
 - 2) crystallization inhibitors—organic and inorganic crystallization inhibitors may be lacking or dysfunctional in animals with uroliths, and
 - 3) precipitation crystallization factors—a complex relationship among urine solutes and other chemical factors in the urine can lead to conditions favoring crystallization.

- ✓ For selected stones (eg, struvite, cystine, urate), other favorable conditions (eg, proper pH) for crystallization must also exist.
- ✓ These criteria can be affected by urinary tract infection, diet, intestinal absorption, urine volume, frequency of urination, therapeutic agents, and genetics.
- ✓ clinical signs of renal dysfunction are generally not apparent until two-thirds or more of total functional renal parenchyma is lost, clinical signs may not be observed unless both ureters are obstructed, there is contralateral chronic kidney disease, or a renal infection develops.

Urolithiasis in Ruminants

- ✓ Uroliths in cattle, sheep, and goats are common.
- ✓ Urolithiasis is seen most often during winter in steers and wethers on full feed, or on range during severe weather conditions with limited water intake, especially when the water has a high mineral content.
- ✓ obstructive urolithiasis develops primarily in males because of anatomic differences.
- ✓ Ruminant urolithiasis is considered primarily a nutritional disease.
- ✓ The mineral composition of water, in concert with dietary mineral imbalances, probably contributes more to initiating urolith formation than does the lack of water itself.
- ✓ A definitive diagnosis of urolithiasis in a single animal suggests that all males in the population are at risk for the disease.

Urolithiasis in Horses

- ✓ Urolithiasis is a less common condition in horses than in small ruminants or steers. The disease can affect immature horses but is seen most frequently in adults.
- ✓ Urolithiasis is seen more frequently in males than females, which has been attributed to anatomic differences between the male and female urethra.
- ✓ Most equine uroliths are composed of calcium carbonate, in various hydrated forms, with struvite uroliths occasionally noted.
- ✓ The mechanism of urolith formation in horses is unknown, although the alkaline pH and high mineral content of normal equine urine may favor crystal formation and precipitation.
- ✓ Normal equine urine also contains large amounts of mucoproteins, which may serve as a cementing substance to adhere crystals.
- ✓ Multiple nephroliths may develop in horses with renal papillary necrosis (associated with NSAID administration while dehydrated) and mineralization of the papillae.

Uroperitoneum in Foals

- ✓ Uroperitoneum is defined as urine leakage into the peritoneal space.
- ✓ In foals, this most commonly results from tearing of the bladder during parturition or rupture of the urachus secondary to umbilical abscessation.
- ✓ Ureteral or urethral tears are rare.
- ✓ Some studies indicate a higher incidence of bladder rupture in males than in females, possibly because the narrower pelvis and the longer, narrower urethra of colts is a predisposing factor.
- ✓ Urachal rupture occurs in both males and females.
- ✓ Traumatic bladder rupture is thought to be caused by uterine contractions on a full bladder as the foal passes through the birth canal.
- ✓ Most bladder tears are located on the dorsum of the bladder.
- ✓ Prematurity, cystitis, ascending infection, abdominal trauma, failure of passive transfer, and sepsis may predispose the foal to bladder rupture.
- ✓ Neoplasms of the kidney are uncommon and represent ~0.5-1.7% of all neoplasms in dogs.

VI. Primary Malignant Renal Neoplasms (except nephroblastomas)

- ✓ are most common in middle-aged to older animals.
- ✓ The most common primary malignant renal neoplasm is carcinoma, which originates from the renal tubular epithelium.

1. Nephroblastomas (embryonal nephroma, Wilms' tumor)

- ✓ arise from vestigial embryonic tissue.
- ✓ They are seen in young animals and, in dogs, are most commonly diagnosed at <1 yr of age.
- ✓ Males are affected twice as commonly as females.

2. Transitional cell carcinomas

- ✓ arise from transitional epithelium of the renal pelvis, ureter, bladder, or urethra (see neoplasms of the lower urinary tract,
- ✓ Other primary malignant renal neoplasms are uncommon and include hemangiosarcomas, fibrosarcomas, leiomyosarcomas, and squamous cell carcinomas.

3. Lymphosarcoma

- ✓ the most common multicentric tumor involving the kidneys.
- ✓ Renal involvement is usually multifocal or diffuse, interstitial, and bilateral, and results in large, irregular kidneys.

- ✓ Lymphosarcoma in cats frequently is associated with infection by feline leukemia virus.

VII. Neoplasms of the Lower Urinary Tract

- ✓ Neoplasms of the ureters, bladder, and urethra are uncommon in dogs and rare in cats.
- ✓ The low incidence in cats may be due to a difference in tryptophan metabolism that results in low urinary concentrations of carcinogenic tryptophan metabolites.
- ✓ In the lower urinary tract, primary neoplasms are more likely to be malignant than benign.
- ✓ Among primary malignant neoplasms of the lower urinary tract, transitional cell carcinomas are diagnosed most frequently in both species.

VIII. Disorders of Micturition

- ✓ Disorders of micturition result from a dysfunction in the storage or voiding of urine and may be neurogenic or non-neurogenic in origin.
- ✓ Urinary incontinence is the failure of voluntarily control micturition, with constant or intermittent unconscious passage of urine.
- ✓ The coat around the vulva or prepuce may be wet, and perivulvar or peripreputal dermatitis can result from urine scalding.
- ✓ Failure of urine storage is characterized by inappropriate leakage of urine due to failure of bladder relaxation, urethral incompetence, anatomic defects, or overflow of stored urine.
- ✓ The most common non-neurogenic incontinence is attributed to deficiency of sex hormones in neutered animals, particularly female dogs, and is referred to as hormonal-responsive urethral incompetence. Idiopathic urethral sphincter incompetence also is seen.

f. Nervous System

I. Features of the central and peripheral nervous system for consideration in neuropathology

1. CNS has no regenerative capacity. PNS has limited to regenerative power. (neurons are permanent cells).
2. Complexity and relative great sizes of the cells concerned (neurons and glial cells). Axonal cytoplasmic transport system is vulnerable.
3. High rate of aerobic metabolism. Requires adequate blood and oxygen.
4. Limited collateral blood supply in CNS.
5. Brain is encased in rigid skull (bone). While protective, it compresses during swelling.
6. Its complexities predispose to structural and biochemical anomalies during development.

7. Age (neurons must last a lifetime)

II. Basic response to injuries

1. Increased or decreased excitability (e.g. hypoxia)
2. Neuronal degeneration (chromatolysis, inclusions, storage products, nuclear eccentricity, vacuolation, shrinkage, satellitosis and neuronophagia, and axonopathies)
3. Wallerian degeneration (the events that follow disruption of axons in the CNS and PNS by various insults). Spheroid formation.
4. Glial degeneration and necrosis (malacia)
5. Glial reactions and proliferation (gliosis)
6. Demyelination

Primary demyelination

- pathological process whereby the myelin sheath is removed from an axon in the CNS or PNS, leaving the axon more or less intact.
- may be due to immunological attack aimed specifically at the myelin sheath.
- may be due to virus infection damaging the myelin-producing cells

Oligodendrocytes - in CNS

Schwann cells - in PNS

Primary demyelination in both CNS and PNS may be very rapid

- may be reversible if cause is removed and if the axon survives.

Secondary demyelination:

- the removal of myelin that occurs automatically once a myelinated axon degenerates and dies.
- "Gitter cells"-lipid-laden macrophages or microglial cells with fatty myelin debris.
- may accumulate in both primary and secondary demyelination.

Wallerian degeneration - process of degeneration of nerve fibers in CNS and PNS following detachment of axons, or following death of the entire neuron.

- secondary demyelination – seen as part of the wallerian degeneration in myelinated nerve fiber tracts in CNS and PNS.

- a. Partial demyelination and its causes
- b. (pressure, senility, etc.)
- c. Demyelination and its causes
- d. (congenital, toxic, infections and deficiencies)
- e. Remyelination
- f. Edema of CNS.
- g. CNS hemorrhage
- h. Inflammation

Ependymal cells- cuboidal or columnar cells lining the ventricles, choroid plexus and spinal canal
 Virchow-Robin (V-R) space- zone that surrounds the blood vessels within the central nervous parenchyma in which cells and fibers are

Perivascular lymphocytic infiltrations ("cuffing")

- accumulation of lymphocytes in V-R space in infectious inflammations.

TISSUE CHANGES

- postmortem autolysis occurs fast in the CNS leading to liquefaction necrosis
- ranges from slow death of an occasional neuron to softening and liquefaction of considerable volumes of CNS tissues.

- usual causes:

1. anoxia
2. chemical and plant poisons
3. mycotoxins
4. metabolic disorder
5. infectious diseases

cyanides
Hg
Pb
Mn

Anoxia

- frequent cause of death of nerve cells in a limited area
- results from interference of blood supply

Necrosis of neurons (Nerve Cell Bodies)

Acute injury:

1. characterized by cellular swelling
 2. dendritic process tend to disappear - outline of cell
 3. Nissl granules degranulate- smooth and rounded.
 - central chromatolysis and blackening of cytoplasm (pyknosis)
 4. Nucleus swells and nucleolus also enlarges
 - nucleus displaced into an eccentric position
 - karyorrhexis or karyolysis- disappears
 5. Whole neuron then shrinks into an angular and unrecognizable form – disappears
 6. Axon swells and loses Nissl substance, and is distorted into a twisted form.
- All (1-6 item) happens in disease except in scrapie.

Satellitosis- clustering of satellite cells or microglia cells around a dying neuron (a reversible change)

- as neuron dies satellite cells engulf bits of its cytoplasm (neuronophages, neuronophagia)

Glial nodule- small collection of microglia

Astrocytosis- increase in number of astrocytes in response to nerve cell injury.

Necrosis of nerve fibers

- degeneration of the myelin sheaths of the affected fibers and swelling of the axons.
- demyelination
- axons or nerve fibers eventually disappear, as well as the neuroglia
- Gitter cells - microglia again engulf axonal fragments and myelin sheaths, converting myelin to neutral fat.

Wallerian degeneration

- part of neuron distal to injury point dies, undergoes wallerian degeneration throughout its length, and is associated with an influx of macrophages and proliferation of Schwann cells.

-unless injury is very close to the nerve cell body, the cell body does not die.

Nissl's degeneration

- a rounding of the cells, displacement of the nucleus, and fading of Nissl granules.
- recovery usually occurs

Demyelination of nerve fibers results from:

1. mechanical pressure
2. thiamine and vit. B complex deficiency

CONCUSSION & COMPRESSION

Concussion- results from a nonfatal blow on the head.

- produces instant unconsciousness
- causes a sudden, violent displacement of the subarachnoid and other brain fluid
- certain amount of blood is moved
- prematurely from capillaries into large vessels.

Coup contusion- impact site location of lesion.

Contrecoup - lesions are often on opposite side of the blow

But when two lesions occur together:

- severe impact site must be mentioned first.
- Coup-contrecoup
- Contrecoup-coup

Diffuse compression

- from pressure of extensive hemorrhage, tumors, abscesses, or edema.

Symptoms:

1. hyperirritability
2. convulsions
3. mental depression
4. somnolence
5. coma
6. paralysis- compression of motor centers
7. headaches
8. vomiting without any digestive order

Pressure upon the cord lead to paralysis of parts supplied from segments below the point of compression

- Flaccid paralysis involves parts that happen to be innervated directly from the injured segment.
- Sensation ceases from the parts below the lesion.
- Softening and liquefaction necrosis result from local pressure.

III. ENCEPHALITIS and ENCEPHALOMALACIA

Inflammation and inflammatory disease

- same laws of inflammation apply but manifestations of inflammatory process are restricted according to the kind of cells and tissues present and anatomic limitations:

1. Catarrhal inflammation does not occur because there are no mucous membranes

2. Serous inflammatory reactions most likely do not occur, but if present, are not differentiated from edema.

3. Hemorrhagic exudates seldom seen.

4. Fibrinous inflammation is limited to meninges and to penetrating wounds

5. Purulent, lymphocytic, and proliferative are the types regularly encountered in the CNS.

Malacia – (softening) an important feature of a number of inflammatory diseases and likewise, in conditions characterized by malacia, there is an inflammatory reaction.

Purulent inflammation occurs as the result of infection by pyogenic microorganisms.

- Listeriosis is the most frequent cause of purulent inflammations in brains of farm animals.

The primary lesion in most types of viral encephalitis is necrosis of neurons.

Toxoplasmosis and cryptosporidiosis also result in lymphocytic infiltrations when they involve the NS.

Lymphocytic infiltrations- may be considered indicative of an infectious disease, usually a viral disease.

MALACIA- necrosis of CNS

Encephalomalacia- necrosis in brain

Myelomalacia- necrosis in spinal cord

Poliomalacia- gray matter is affected

Leukomalacia- white matter is affected

Diseases of uncertain etiology

Causes of anomalies to the NS:

1. hereditary
2. nutritional deficiency
3. in-utero viral infection

Congenital Anomalies:

- 1) Anencephaly – agenesis of most of the brain -usually associated with failure of closure of the skull
- 2) Microencephaly- abnormally small brain
- 3) Cranioschisis – failure of cranial fusion
- 4) Meningocele – herniation of the meninges
- 5) Meningoencephalocele – herniation of brain and meninges
- 6) Spina bifida – failure of closure of vertebral arches
- 7) Hydromyelia – term describing dilation of central spinal canal.
- 8) Syringomyelia – condition characterized by cavitation of spinal cord. Common in Weimaraner dogs.
- 9) Porencephaly – characterized by cystic cavities within the brain.

- 10) Hydranencephaly – results from destruction of most cerebral hemispheres, leaving a thin-walled membranous sac composed of meninges and a thin rim of cortex lacking an ependymal lining.
- 11) Hydrocephalus – slow accumulation of cerebrospinal fluid in the lateral and other ventricles.

Dysmyelinating and Demyelinating Diseases

Dysmyelinating when there is defect in myelin formation (hypomyelogenesis)

Demyelinating when there is destruction of myelin.

LEUKODYSTROPHIES AND LIPIDODYSTROPHIES of the Central Nervous System (Neuronal Storage Disease)

NEOPLASMS OF THE NERVOUS TISSUES

Most are coming from neuroglia

– glioma

subdivided to:

1. astrocytoma
2. glioblastoma multiforme
3. medulloblastoma
 - Ependymoma
 - Oligodendroglioma
 - Cholesteatoma
 - Neuroblastoma
 - Ganglioneuroma
 - Schwannoma
 - Neurofibroma
 - Meningioma

Some important neurological diseases.

Dogs (and other canidae):

- a) Viral infections
 - Distemper
 - Acute and chronic effects on CNS, role of immune system and persistent virus
 - Rabies
 - Infectious canine hepatitis (adenovirus)
- b) Bacterial and fungal infections
 - often a miscellaneous infection extending from inner ears or upper respiratory tract, or embolic during septicemias
- c) Protozoal infections
 - encephalitis and polyradiculoneuritis caused by *Toxoplasma* and similar unnamed sporozoan
- d) Aberrant helminth infections
 - *Angiostrongylus*; *Toxocara*, etc.
- e) Intoxications
 - Lead poisoning; organophosphate; organochlorines; hexachlorophene; strychnine; fluoroacetate; hepatic encephalopathy; tick paralysis, etc.
- f) Deficiencies
 - Thiamine or Vit. B1
- g) Trauma

Includes disc protrusion, spinal instability ("wobblers"), radial paralysis, spinal infarcts due to cartilaginous emboli

h) Congenital and developmental anomalies

Storage diseases:

Examples: ceroid-lipofuscinosis, α -fucosidosis, Abiotrophies, e.g. leukomyelopathy of Afghan hounds, various idiopathic axonal degenerations, myelinolysis of Rottweilers Heritable spinal dysraphism in Weimaraners; hydrocephalus

i) Diseases of unknown cause

Granulomatous meningoencephalomyelitis

Idiopathic epilepsy

Coonhound paralysis

Neoplasms

Common in brachycephalic breeds

Cats

- a) Viruses, e.g., rabies; FEV, FIP
- b) Bacterial and fungal infections
- c) Cryptococcosis - more common in cats
- d) Protozoan infections - toxoplasmosis
- e) Intoxications
 - Organochlorines; organophosphates; thallium. Hepatic encephalopathy.
- f) Ixodes (ticks); snakebite;
- g) puffer fish (tetrodotoxin)
- h) Congenital anomalies:
 - Prenatal FEV; spinal dysraphism; ceroid lipofuscinosis and other storage diseases
- i) Unknown cause
- j) Reversible inflammatory disease of vestibular apparatus

Cattle

- a. Viral and chlamydial infections
 - Sporadic bovine encephalomyelitis
 - Herpesviruses (IBR, MCF, Aujeszky's)
 - Rabies
- b. Bacterial infections
 - Infectious thromboembolic meningoencephalitis (ITEME) due to *Haemophilus somnus*
 - Listeriosis
 - Coliforms and other miscellaneous infections
 - Streptococci in calves
- c. Protozoal infections
 - Babesia bovis*; leishmaniasis
 - Intestinal coccidiosis and CNS signs in calves
- d. Toxins
 - Lead; chronic organophosphate poisoning; Cycads, tremorgenic fungi; cyanide and nitrite; mercury; tetanus, botulism.
- e. Metabolic diseases
 - Ketosis; hypocalcemia and hypomagnesemia, hepatic encephalopathy
- f. Deficiency diseases
 - Thiamine (polioencephalomalacia)
 - Vitamin A deficiency in calves
- g. Congenital anomalies

α -mannosidosis in Angus
glycogenosis in Brahms and Beef Shorthorns;
progressive ataxia in Charolais inherited
myodonus and hydrocephalus in Herefords;
cerebellar hypoplasia in Shorthorns (all
heritable); citrullinemia in Holstein-Friesians
Hydranencephaly and cerebellar hypoplasia due
to prenatal virus infections, also spinal
dysraphism and arthrogryposis
h. Neoplasms
Neurofibromatosis

Sheep

- a. Virus infections
Scrapie and Maedi-visna, rabies; louping ill
- b. Bacterial infections
Listeriosis; pasteurellosis in lambs; spinal
abscesses
- c. Protozoal infections
- toxoplasmosis
- d. Parasites
Coenurus cerebralis; *Oestrus ovis*
(occasionally);
Elaphostrongylus; *Setaria*
- e. Toxins
Ryegrass; *Phalaris*; *Swainsona*; *Clostridium*
perfringens; enterotoxaemia and focal
symmetrical encephalomalacia; chronic
organophosphates; cyanide and nitrite; botulism
and tetanus
- f. Metabolic disease
Ketosis; hypocalcaemia and magnesemia;
hepatic encephalopathy
- g. Deficiency disease
Thiamine (polioencephalomalacia); copper
- h. Congenital anomalies
Copper deficiency (congenital and delayed)
Hypomyelinogenesis due to prenatal mucosal
disease virus infection; hydranencephaly;
microencephaly; cerebellar hypoplasia and
spinal dysraphism all due to prenatal infection
by various Arboviruses

Goats (similar with sheep conditions)

- Retrovirus causing encephalomyelitis, arthritis and
interstitial pneumonia
- a. α -mannosidosis in Anglo-Nubians
- b. burnt brain from dehorning kids

Horses

- a. Virus infections
 - Arthropod-borne equine encephalomyelitides
(eastern, western, Venezuelan)
 - Rabies
 - Borna
 - Equine herpesvirus 1
- b. Bacterial infections (very rare)
- c. Protozoal infections
Trypanosomiasis
Toxoplasma-like organism causing myelitis
- d. Parasitic
Aberrant strongyle migration
Micronema deletrix
- e. Intoxications:

Swainsona; *Indigofera*; nigropallidal
encephalomalacia due to starthistle (*Centaurea*)
poisoning; mercury; hepatic encephalopathy;
tetanus; chronic organophosphates; bracken
(thiamine deficiency); *Fusarium*
(leukoencephalomalacia)

f. Neoplasia

Cholesteatoma (rare)

g. Trauma

Susceptibility of brain and cervical spine due to
size and speed movement (as in race horses)

h. Developmental disease

Cerebellar abiotrophy in Arabs

Cervical stenosing myelopathy

Equine degenerative myeloencephalopathy
(EDM); occasional hydrocephalus

Perinatal cerebral ischemia in relation to the birth
process

i. Diseases of unknown cause

Neuritis of the cauda equina (cauda equina is the
root of the upper sacral nerve that extends beyond
the termination of the spinal cord at the first
lumbar vertebra in the form of a bundle of
filaments within the vertebral canal resembling a
horse's tail).

Stringhalt

Laryngeal hemiplegia ("roaring")

Poultry/Fowls

- a. Virus infections
Avian encephalomyelitis
Marek's disease
Newcastle disease
- b. Deficiencies
Riboflavin; thiamine
Vit E and Se (nutritional encephalomalacia)
Pantothenic acid
- c. Intoxications
Organophosphates; botulism (especially ducks);
lead or Pb (also in ducks)
- d. Developmental
Spondylolisthesis
(means forward displacement of a lumbar
vertebra on the one below it and especially of
the fifth lumbar vertebra on the sacrum
producing pain by compression of nerve roots
("kinky back"))

Pigs

- a. Virus
Polioencephalomyelitis of swine
(Teschen disease)
Aujeszky's disease
Swine fever
- b. Bacterial
Streptococcal meningoencephalitis
Hemophilus suis meningitis (Glasser's disease)
Spinal abscesses
- c. Toxicities
"Salt" poisoning
Edema disease "mulberry heart" disease;
Organic arsenicals
- d. Congenital anomalies
Swine fever vaccine

- e. Deficiency
Vitamin A deficiency

Microscopic Changes That Can Occur in the Neuronal Cell Body

1. Central chromatolysis following axonal injury
2. Ischemic cell change
3. Enlargement of the cell body in lysosomal storage diseases
4. Accumulation of lipofuscin pigment in aging
5. Accumulation of neurofilaments in certain neuronal degenerative diseases
6. Inclusion body formation in certain viral diseases
7. Cytoplasmic vacuolation in spongiform encephalopathies

Portals of Entry into the Central Nervous System

DIRECT EXTENSION

- Penetrating trauma through the calvarium or vertebral bodies
Extension of middle and/or inner ear infection
Extension of a nasal cavity/sinus infection through the cribriform plate or calvarium
Extension from osteomyelitis

HEMATOGENOUS

- Localization within capillary beds of the meninges and parenchyma of the central nervous system (CNS)
Localization within capillary beds of the choroid plexuses and extension into the cerebrospinal fluid

LEUKOCYTIC TRAFFICKING

- Macrophages or lymphocytes (containing microbes) during their migration through the CNS

RETROGRADE AXONAL TRANSPORT

- Transported from the periphery into the CNS by neuronal retrograde axoplasmic flow

Defense Mechanisms against Injury and Infectious Agents in the Central Nervous System

SKIN

- Structural and functional (secretions) barrier

CALVARIUM, VERTEBRAE

- Structural barrier

MENINGES, CEREBROSPINAL FLUID

- Structural and functional (continuous flow of cerebrospinal fluid [CSF]) barrier

BARRIER SYSTEMS

Blood-brain barrier

- Structural and functional barrier formed by vascular endothelium, basement membrane, and astrocytic foot processes. This barrier regulates the movement of agents from the blood to the central nervous system (CNS).

Blood-CSF barrier

- Structural and functional barrier formed by choroid plexuses cells and the arachnoid membrane. This barrier regulates movement of agents from the blood to the CSF.

GLIA LIMITANS

- Formed by astrocytic foot processes immediately subjacent to the pia mater. This structure may have some barrier function in preventing movement of microbes from CSF into the CNS through the pia mater.

MICROGLIA, TRAFFICKING MACROPHAGES

- Resident and migrating cells that are part of the monocyte-macrophage system.

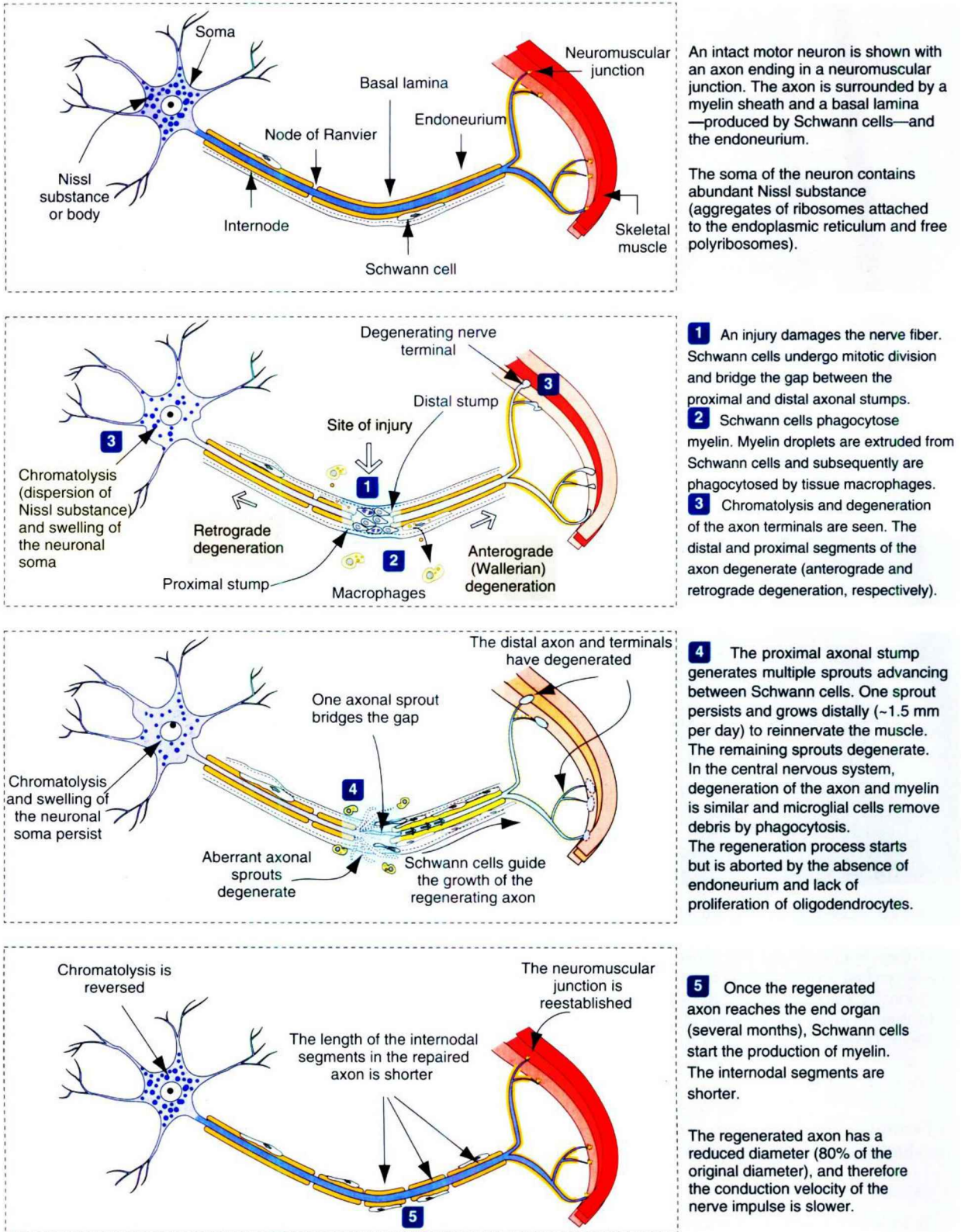
IMMUNOLOGIC RESPONSES

- Innate and adaptive immunologic responses that form the body's overall immune system.

Chronologic Sequence of Changes within Infarcted Tissue (in the Living Animal) following an Ischemic Event

TIME FOLLOWING	
Ischemic Event	Tissue Change
Immediate (seconds)	Cessation of blood flow (ischemia) and accumulation of waste products
Few minutes	Cellular injury and death; coagulation necrosis and edema; hemorrhage (especially in gray matter)
20 min	First microscopic evidence of neuronal injury (perfusion-fixation)
1-2 hr	First microscopic evidence of neuronal injury (immersion fixation)
2 hr	Pale staining of infarct microscopically (white matter); swelling of capillary endothelium; increase in size of astrocytic nuclei
3-5 hr	Ischemic cell change in most neurons; swelling of oligodendroglia and astroglia; beginning clasmotodendrosis of astrocytes
6-24 hr	Beginning neutrophilic infiltration; alteration of myelin (pale staining), 8-24 hours; degeneration and decrease of oligodendroglia, 8-24 hours; astrocytic swelling and retraction and fragmentation of processes (clasmotodendrosis), and degeneration*; cytoplasm of astrocytes visible, 8-24 hours*; vascular degeneration and fibrin deposition, 8-24 hours; thrombosis†, 6-24 hours; beginning endothelial proliferation at margin of infarct, 9 hours
8-24 (up to 48) hr	Initial gross detection of infarct unless hemorrhagic; infarct edematous (swollen), soft, pale, or hemorrhagic and demarcated
1-2 days	Swelling of axons and myelin sheaths; prominent neutrophilic infiltration
2 days	Prominent loss of neuroectodermal cells; continued proliferation of endothelial cells; reduced number of neutrophils; beginning increase in mononuclear cells (gitter cells)
3-5 days	Prominent number of mononuclear cells (gitter cells); disappearance of neutrophils; continued endothelial cell proliferation; number of capillaries appear increased; beginning of astrocytic proliferation (often at margin of infarct)
5-7 days	Grossly, swelling of infarct reaches maximum
8-10 days	Reduction in gross swelling of infarct; liquefaction necrosis; prominent number of mononuclear cells (gitter cells); continued endothelial cell proliferation; beginning fibroblastic activity with collagen formation, variable but most prominent in central nervous system tissue adjacent to the meninges; beginning increase of astroglial fiber production, 5-13 days
3 wk-6 mo	Mononuclear cells decreased; astroglial fiber density increased (especially at margin); astrocytic proliferation reduced; astrocytes return to original appearance; cystic stage of infarct, 2-4 months; vascular network may be present within cyst; endothelial cell proliferation reduced

*The degree of astrocytic injury will depend on location (e.g., central or peripheral) of the cells within the infarct.
†Obviously, thrombosis may occur earlier than 6 hours. This is the time when it may initially be prominent.



Peripheral nerve degeneration and regeneration (also applicable to neurons within the central nervous system).

Types of Edema in the Central Nervous System

Type of Edema	Cause	Outcome
Cytotoxic	Altered cellular metabolism (often due to ischemia)	Intracellular accumulation of fluid (neurons, glial cells, endothelial cells)
Vasogenic	Vascular injury with breakdown of the blood-brain barrier	Extracellular accumulation of fluid (cerebrocortical white matter)
Hydrostatic (interstitial)	Elevated ventricular hydrostatic pressure (hydrocephalus)	Extracellular accumulation of fluid (periventricular white matter)
Hypo-osmotic	Osmotic imbalances (blood plasma vs. extracellular and intracellular microenvironments of the central nervous system)	Extracellular and intracellular accumulation of fluid (cerebrocortical gray and white matter)

Primary Tumors of the Nervous System

CENTRAL NERVOUS SYSTEM				
Cell of Origin	Tumor Type	Location	Species Affected	Gross Appearance
Neuron	Medulloblastoma	Cerebellum (WM&GM)	Dog, cow, cat, pig (young animals)	Well-circumscribed, soft, gray to pink expansile mass (usually does not have hemorrhage, cysts, or necrosis)
Oligodendroglia	Oligodendroglioma	Cerebrum, brain stem, interventricular septum (WM&GM)	Dog, cat, cow	Well-demarcated, gray to pink-red, soft or gelatinous expansile mass, usually with areas of hemorrhage
Astroglia	Astrocytoma	Pyriform lobe, cerebral hemispheres, thalamus-hypothalamus, midbrain, cerebellum, spinal cord (WM&GM)	Dog, cat, cow	Poorly demarcated, firm, gray-white when well differentiated; anaplastic neoplasms are moderately to well demarcated, soft and friable, (usually with areas of necrosis, hemorrhage, edema, and cavitation)
Ependyma	Ependymoma	Ventricular system (lateral; less commonly, third and fourth), central canal of the spinal cord	Dog, cat, cow, horse	Poorly, to moderately, to well-demarcated, soft and gray-white, invasive, destructive gelatinous expansile mass (usually with areas of hemorrhage and cavitation)
Choroid plexus epithelium	Choroid plexus tumor	Ventricular system (fourth; less commonly, third and lateral)	Dog, horse, cow	Well-demarcated, granular to papillary, gray-white to red, expansile mass
Microglia	Microgliomatosis (reticulosis)	Cerebrum, brain stem	Dog	Poorly demarcated, gray-white, infiltrative mass (may have perivascular pattern)
Endothelium	Hemangiosarcoma	Cerebrum, brain stem	Dog	Well-demarcated, invasive red to dark red, expansile mass
Mesothelium (fibroblasts)	Meningioma	Meningeal surface of the CNS (basal cow, sheep areas, convexity and lateral surfaces of cerebral hemispheres, cerebellum-tentorium, falx cerebri, surface of the spinal cord)	Cat, dog, horse, cow, sheep	Well-demarcated, variable shapes, firm, encapsulated, and gray-white to soft, red-brown or gray, expansile masses (usually with areas of hemorrhage and necrosis)
PERIPHERAL NERVOUS SYSTEM				
Cell of Origin	Tumor Type	Location	Species Affected	Gross Appearance
Schwann cells (other supportive cells)	Peripheral nerve sheath tumor*	Cranial nerves, spinal nerves (brachial plexus)	Dog, cow, cat	Firm or soft (gelatinous), white or gray, nodular masses

WM&GM, White matter and gray matter.
*Other names for this tumor type include: schwannoma, neurofibroma, and neurilemmoma.

Transmissible Spongiform Encephalopathies (i.e., Prion Diseases)

Disease	Natural Host(s)	Prion	Pathogenic PrP Isoform
ANIMALS			
Ovine spongiform encephalopathy (scrapie)	Sheep, goats	Scrapie prion	OvPrP ^{Sc}
Bovine spongiform encephalopathy (BSE)	Cows	BSE prion	BoPrP ^{Sc}
Feline spongiform encephalopathy (FSE)	Cats	FSE prion	FePrP ^{Sc}
Chronic wasting disease (CWD)	Mule deer, elk, black	CWD prion	MdePrP ^{Sc}
Transmissible mink encephalopathy (TME)	tailed deer, white tailed deer mink	TME prion	MkPrP ^{Sc}
Exotic ungulate encephalopathy (EUE)	Nyala, greater kudu, oryx	EUE prion	UngPrP ^{Sc}
HUMAN BEINGS			
Kuru	Human beings	Kuru prion	HuPrP ^{Sc}
Creutzfeldt-Jakob disease (CJD)	Human beings	CJD prion	HuPrP ^{Sc}
Variant Creutzfeldt-Jakob disease (VCJD)	Human beings	VCJD prion	HuPrP ^{Sc}
Gerstmann-Sträussler-Scheinker syndrome (GSS)	Human beings	GSS prion	HuPrP ^{Sc}
Fatal familial insomnia (FFI)	Human beings	FFI prion	HuPrP ^{Sc}

Viruses Causing Central Nervous System Disease in Domestic Animals

Virus Group	Disease	Type of Injury
Arboviruses	Equine encephalomyelitis	Encephalitis/myelitis/meningitis/vasculitis
	Japanese encephalitis	Encephalitis/myelitis/meningitis
	Louping ill	Encephalitis/myelitis/meningitis
	West Nile viral encephalomyelitis	Encephalitis/myelitis
	Wesselbron virus	Malformations
Bunyaviruses	Akabane disease	Malformations/encephalitis
	Arthrogryposis hydranencephaly complex (Cache Valley fever)	Malformations/encephalitis
	Rift Valley fever	Malformations/encephalitis
Coronaviruses	Feline infectious peritonitis	Vasculitis/encephalitis/myelitis/meningitis
Enteroviruses	Hemagglutinating encephalomyelitis	Encephalitis/myelitis/meningitis/ganglioneuritis
	Enterovirus-induced porcine polioencephalomyelitis	Encephalitis/myelitis
Herpesviruses	Equine herpesvirus 1 myeloencephalopathy	Encephalitis/myelitis/meningitis/vasculitis
	Bovine malignant catarrhal fever	Encephalitis/myelitis/meningitis/vasculitis
	Infectious bovine rhinotracheitis	Encephalitis
	Pseudorabies	Encephalitis/myelitis/meningitis
Lentiviruses	Visna	Encephalitis/myelitis/demyelination
	Caprine leukoencephalomyelitis-arthritis	Encephalitis/myelitis/demyelination
Orbiviruses	Blue tongue	Malformations/encephalitis
Paramyxoviruses	Canine distemper	Demyelination/encephalitis/myelitis
	Old-dog encephalitis	Encephalitis/demyelination/meningitis/vasculitis
Parvovirus	Feline panleukopenia virus	Malformations/meningitis
Pestiviruses	Classical swine fever	Malformations/hypomyelination/encephalitis/meningitis/vasculitis
	Bovine viral diarrhea	Malformations/meningitis/dysmyelination
	Border disease	Malformations/hypomyelination
	Progressive multifocal leukoencephalopathy	Demyelination
Polyomaviruses	Rabies	Encephalitis/myelitis/meningitis/vasculitis/ganglioneuritis
Rhabdoviruses		
Unassigned viruses	Borna disease	Encephalitis/myelitis

g. Musculoskeletal System

Clinical Signs of Muscle Disease

- Muscle atrophy
- Muscle hypertrophy
- Muscle swelling
- Weakness
- Muscle spasm
- Abnormal gait
- Esophageal dysfunction (dogs, camelids)

Staining requirement of skeletal muscle:
Fiber-type staining

Pathologic Changes in Muscles

Changes in Fiber Size

- Work hypertrophy - increased in muscle size as a result of exercise.
- Disuse atrophy - decreased size of muscles due to inactivity.

Major types atrophy

- denervation
- disuse
- malnutrition, cachexia, senility

Abnormalities of Distribution of Fibers:

- small group atrophy - a small collection of atrophied fibers- characteristic of denervation.
- large group atrophy - involves large unit of muscle (fasciculi).
- perifascicular atrophy
- type grouping - seen in reinnervated muscle
- fiber type predominance - used to describe extreme form of type grouping.
- fiber type deficiency - when less than 10% of the fibers may be of one type.

Steatosis - the result of replacement of muscle fibers by adipose tissue.

Myasthenia gravis

- (uncommon) disease manifested by muscular weakness, increased fatigue, reduced exercise tolerance.
- alleviated by rest or administration of anticholinesterase drugs.

Myotonia

- describes "a muscle that continues to contract actively even after stimulus has ceased".

Three types of glycogenoses

- Type II – Acid maltase deficiency e.g., Pompe's disease (Corriedale sheep, shorthorn cattle, Brahman cattle, Lapland dogs)

2. Type III – Debranching enzyme deficiency e.g., Cori-Forbe's disease (German shepherd dogs Japanese quail, cats)
3. Type VII – Muscle phosphofructokinase deficiency e.g., (dogs)

Histochemistry -several types of fibers differentiated on reaction to various histochemical stains (ATPase, NADH) cannot be identified with formalin fixation

- a. type I - red muscle, sustained action, weight bearing, slow-twitch, high oxidative enzymes, low ATPase, many mitochondria, abundant fat
- b. type II - white muscle, glycolytic fibers, sudden action, fast-twitch, Low oxidative enzyme, high ATPase, few mitochondria, little fat

Clinical evaluation

Gross exam - shape, color, texture, volume (atrophy or hypertrophy): palpation, careful multiple incision

type I-red,

type II-white

necrosis-pale, if necrotic areas calcify:

glistening, chalky-white foci

muscle infiltrated by fat (e.g. steatosis):

pale hemorrhage: myorrhexia

eosinophilic myositis: green discoloration

Enzyme histochemistry: NADH, succinic dehydrogenase (SDH) for mitochondria

Rigor mortis: contraction and in stiffening of muscles

- myosin heads remain attached to actin-binding sites owing to deficiency of the ATP

*Cachectic animal with no energy store

-rigor may be slight or may not occur.

Response of muscle to injury

1. Degeneration

- a. pigmentation: lipofuscin, melanin, myoglobin
- b. calcification
- c. ossification
- d. degeneration: cloudy swelling,
- e. vacuolar, fatty, hyaline, granular

2. Segmental necrosis

3. Myolysis

Necrosis: toxic, metabolic, nutritional myopathy cause segmental necrosis

**total necrosis of myofiber is rare, stage of necrosis quickly merges into stage of regeneration*

extensive necrosis: massive trauma, large burn

earliest: hyaline fiber (hypercontracted, rounded; normal: polygonal)

index of extent of myofiber damage:

- creatinine kinase (CK),
- serum glutamic-oxaloacetic transaminase (SGOT),
- myoglobin (not specific, present in hepatocyte) – if muscle damage is extensive, myoglobinuria

Regeneration sequelae

- a. in the necrotic segment, muscle nuclei disappear, sarcoplasm and myofibril become hyalinized (eosinophilic, amorphous, homogenous) necrotic portion may separate from adjacent viable myofiber
- b. monocyte, neutrophil emigrate from capillary
- c. satellite cells begin to swell, become vesicular with prominent nucleoli, and then undergo mitosis
- d. proliferated satellite cells move from peripheral location to center of muscle fiber, among the macrophage
- e. macrophage lyse and phagocytose necrotic debris and form a clear space in the sarcolemmal tube plasmalemma disappear and shape of sarcolemmal tube is maintained by the basal lamina

satellite cell form myoblast, these fuse with one another to form myotube (thin, elongated, closely spaced nuclei) basophilia, central nuclei, lack of striation, narrower than normal diameter

- f. fiber grows and differentiates, diameter increase, striation appears, indicating formation of sarcomere

Success of regeneration

- a. presence of intact sarcolemmal tube
- b. availability of viable satellite cell.

Atrophy (disuse, neurogenic: loss of 2/3 of muscle mass in 2 to 3 wks

- a. neurogenic atrophy
- b. disuse
- c. cachexia, malnutrition, senility: dystrophic
- d. corticosteroids cause a utilization of muscle protein for hepatic gluconeogenesis

Type II muscle fibers are small and angular

Hypertrophy

- a. physiological: workload
- b. compensatory: secondary to degeneration atrophy of adjacent myofibers

Muscular dystrophy: Congenital, both type I and type II is affected, myofiber undergoing degeneration, necrosis, deficient in dystrophin (plasmalemma-associated protein) scattered chronic inflammatory cells, fibrosis, and hypertrophy of remaining muscle fibers. Inability to produce the membrane skeletal protein dystrophin

Myositides:

Causes:

Bacteria, virus, parasite, immune mediated

a. Clostridial myositis - Gram (+) bacilli, anaerobic, germination and growth of spores requires precise local conditions

1) gas gangrene - *C. novyi*

seen in devitalized muscle, associated with shearing, castration, bacterial decomposition

ruminant, horse, swine most affected, carnivores rarely gross-edema, gas, discoloration of skin

2) malignant edema - *C. septicum*

associated with penetrating wound and, no putrefaction, production of an exotoxin with lecithinase activity - action on membrane of vascular endothelium - cellulitis - edema

3) blackleg - *C. chauvoei*

ingestion of spores that cross intestinal mucosa(via macrophage)
spread to tissue, toxin damage capillary - produce serohemorrhagic
exudation, necrosis of muscle in which proliferating clostridia produces gas - emphysema and crepitus
gross: in large muscle of pectoral and pelvic region
dark red, moist with gas bubble at periphery of lesion
center: dry, friable, red-black, odor- butyric acid (rancid butter)
LM: cellulitis, edema (serohemorrhagic), degeneration and necrosis of muscle fiber

b. granulomatous myositis

- 1) tuberculosis
- 2) actinobacillosis

c. bovine and ovine eosinophilic myositis

suggest immune mediated inflammation, etiology is unknown
gross: important in meat inspection - green discoloration of the muscle
LM: infiltrated mass eosinophil

d. parasitic myositis

1. *Trichinella spiralis* larvae migrate from gut to muscle, enter myofibers and grow, muscle of tongue, masseter, diaphragm

2. Cysticercosis: *Cysticercus bovis*

small, white or gray cyst in heart, masseter, tongue

LM: displacement of myofiber by cyst but little myositis

Tania saginata: cattle

Tania solium: pig

3. Protozoa

sarcocytosis: herbivore and swine

Toxic myopathy

a. gossypol: cotton seed, swine are most susceptible
cardiac and skeletal: segmental necrosis
b. monensin: sodium ionophore, produced by *Streptomyces cinnamonensis*
- antibiotic and growth promoter in ruminant, toxicosis-improper mixing
gross: plaque white or gray streaking

ionophore produces intracellular influx of Na^+ and Ca^{++} : calcium overloading

Endocrine myopathy

Corticosteroid: muscle weakness in hyperadrenocorticism: atrophy of type II muscle.

Nutritional myopathy

White muscle disease: economically important muscle disease in cattle and pig

a. etiology: deficiency of selenium, vitamin E, or both

Vitamin. E - scavenger for free radical

Selenium - essential component of glutathione peroxidase, intracellular enzyme in neutralizing free radical

* Free radical: a product of normal cell function, initiate cell injury by causing peroxidation of membrane lipids

b. gross : white or gray opaque streaking of muscle, calves: shoulder, thigh, intercostal, diaphragm

pig: striking lesion in liver (hepatosis dietetica: acute hepatic necrosis) and heart (mulberry heart disease: serous fluid in pericardial sac)

LM : hyaline or granular degeneration, necrosis, fragmentation, possible mineralization, interstitial inflammation, possibly, calcification and regeneration

Exertional myopathy

a. intensive or exhaustive activity of major muscle;

b. rapid glycogen use produces heat and lactic acid anaerobic glycolysis

equine rhabdomyolysis (Monday morning disease)

acute form(azoturia): muscles are salmon-pink, after, become dark, moist

less severe form(lying-up syndrome)

porcine stress syndrome(malignant hyperthermia)

cellular defect, a deficiency of inositol 1,4,5-triphosphate phosphatase, which result in a high intracellular concentration of calcium ion - activate myofibrillar ATPase - produce rapid intracellular glycolysis - increase body heat-denature protein of myofiber

gross: pale, soft, exudative - pork in shoulder, back, thigh mushy, loose - textured, floppy, pale, and unappealing

muscle become acidic - protein lose their ability to retain juice

appear to have little or no marbling

turn gray in color

lacks uniform cured color, separated individual muscle

frozen cut lose excessive amount of juice upon thawing

Test for PSS: gene-Phi, Pgd, Po-2

serum - creatine phosphokinase (CPK)

Preventive measures:

1. avoid crowding in holding pens and truck
 2. eliminate the opportunity for fighting
 3. avoid extremes in temperature and other environment
 4. use general precaution in all phases of the marketing process
 5. include 1 2-to 4 hr resting period in preslaughter handling
- Neoplasia
Rhabdomyoma - benign
Rhabdomyosarcoma – malignant

BONE TISSUE

A. in a dynamic state, it is continuously being renewed by anabolic (apposition) and catabolic (resorption) processes

B. cellular element

- a. osteoblast - produces and mineralizes a matrix osteoid- present on surface of lamellar bone
- b. osteocyte -formed by endocure of osteoblast within osteoid, which is then mineralized
- function in demineralization and remineralization of periacular bone to help maintain calcium homeostasis - osteocytic osteolysis
- regulated by parathyroid hormone and vitamin D
responsive to calcitonin-deposition of mineral
- c. osteoclast -derived from mononuclear phagocytes within the marrow
multinucleated, located in Howship's lacunae
osteoclasts-responsible for the bulk of bone removal – osteoclasts

Hormone control

1. parathyroid hormone (PTH)

- a. stimulated by low levels of ionic calcium
- b. function - maintain extracellular Ca^{++} concentration
 - 1) increased bone resorption by osteoclasts (osteoclast) and osteocytic osteolysis (osteocyte), reduces mineralization of osteoid
 - 2) decrease phosphorus reabsorption in renal tubules - increased renal excretion of phosphorus
 - 3) promote uptake of calcium from kidney
 - 4) increase intestinal absorption of calcium via increased synthesis of active vitamin D in kidney. Mediation of dihydroxylation of Vit D.

2. calcitonin - from C-cells of thyroid gland

- a. release stimulated by hypercalcemia
- b. function: decrease bone resorption, and stimulate new bone formation

3. vitamin D

- a. source
ergocalciferol (D2)-plant origin
cholecalciferol (D3)-animal origin
poultry utilize principally Vit. D3
Vit. D2 has approximately 10 % of the activity of D3 in preventing rickets on poultry

b. metabolism occurs in liver (25 OH D3) and to the active form in kidney (1,25(OH)2D3)

c. function

1) facilitate absorption of calcium from intestine at intestinal epithelium by inducing formation of specific proteins-calcium binding protein, found in mucocalyx on microvillus border

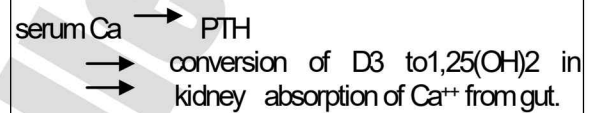
2) synergistic with PTH for resorption of bone-calcium mobilizing

d. regulation

1) 25 OH D3 levels are dependent on vitamin D content of diet and amount of exposure to sunlight (cholecalciferol, D3, produced in sebaceous gland)

2) dihydroxylation in kidney is the important site of regulation.

3) mediated by PTH in response to low dietary and serum calcium.



Estrogen - has an inhibitory effect on osteoclasts. removal of estrogen, as in postmenopausal women, increases internal remodeling. Resorption is increased, but formation remains the same.

Glucocorticoid- inhibitory effect on cellular component of osteonal remodeling unit; inhibition of osteoblast is greater than

osteoclast —→ bone loss. Inhibition of Ca^{++} absorption

parathyroid hormone(PTH) - increases osteoclasts.

calcitonin - decrease bone resorption and osteoclasts, formation

aging - remodeling decrease

Abnormalities of growth and development

Arrest line (or Harris line): growth plate become narrow and metaphyseal face of the plate can be sealed by a layer of bone, visible grossly and radiographically retarded longitudinal growth

- growth retardation lattice: impairment of osteoclastic activity within the primary trabeculae can result in the retention: fail to model into secondary and tertiary trabeculae dense band beneath the growth plate e.g., canine distemper, BVD, lead poisoning

osteopetrosis - osteosclerosis: osteosclerotic (increased bone mass), failure of osteoclast to resorb(remodel) the primary spongiosa-spicules of bone of calcified cartilage fill the medullary cavity: susceptible to fracture failure of normal osteoclastic bone resorption

Metabolic bone diseases - have a nutritional and/or endocrine basis

1. Osteopenia -too little bone

- a. osteoporosis-too little formation of matrix-osteoblast insufficiency - increased radiolucency and thin cortices-decreased amount of bone with normal ash content
- b. too little mineralized osteoid
rickets (immature), osteomalacia (mature)

2. Too much resorption - fibrous osteodystrophy (hyperparathyroidism-primary or secondary)

3. Osteonecrosis

4. Osteopetrosis - too much bone

- a. too little resorption - hypercalcitonism, vitamin A deficiency, lead (Pb) or fluoride (F) toxicosis
- b. too much bone formation - healing rickets, lymphoid leucosis
- c.

B. osteoporosis: decreased formation of osteoid

- a. etiology: protein deficiency, starvation, calcium deficiency
Vitamin C deficiency: important in synthetic activity of osteoblast, odontoblast, fibroblast
disuse - following casting,
paralysis: increased resorption with decreased formation
senile: normal progression of aging, faster rate in female,
corticosteroid: inhibition of protein synthesis and osteoblast, decreased calcium absorption

C. rickets: inadequate mineralization in young growing animals

Osteomalacia: adult form of the disease
- physis are closed

- a. etiology: lack of vitamin D2 or D3 in diet
lack of sunlight-vitamin D3 in sebaceous of skin
lack of Ca^{++} and phosphorus
- b. pathogenesis and lesion
irregular provisional mineralization of cartilage matrix-delayed osseous replacement-> widened growth plate
unmineralized spicules accumulate in metaphysis-resistant to osteoclast
osteoblast have produced matrix which dose not mineralize-> widened osteoid seams

D. fibrous osteodystrophy

- a. etiology - hyperparathyroidism
primary - parathyroid neoplasia or hyperplasia
secondary -due to lowed serum Ca^{++}
renal
nutritional
- b. pathogenesis
- increased PTH-increased bone resorption (osteocytic osteolysis and osteoclasts).
- c. primary hyperparathyroidism
- d. renal secondary
hyperparathyroidism(renal osteodystrophy)

Chronic renal failure-elevation of serum phosphate, depressed Ca^{++} → PTH release → decreased formation of $1,25(\text{OH})_2\text{D}_3$ → decreased intestinal Ca^{++} absorption

- e. Nutritional secondary hyperparathyroidism
dietary Ca^{++} deficiency and/or P excess

E. toxic osteodystrophy

- a. hypervitaminosis D: by supplement, ingestion of plant containing Vit. D, ingestion of Vit. D containing rodenticide (kill by inducing renal mineralization and subsequent renal failure)

acute: GI hemorrhage and crypt necrosis
myocardial necrosis
occasional soft tissue mineralization
chronic: soft tissue mineralization
renal tubular necrosis
early growth plate closure
osteosclerosis

- b. hypervitaminosis A: seen in cat fed diet high in beef liver
adult: exostotic growth and ankylosis
kitten: inhibition and destruction of physal cartilage and shortened leg
- seen in Hyena disease

c. fluorosis(F)

acute: rare, GI ulcer, renal tubular failure
chronic: F accumulates in bone, osteoblast produce abnormal matrix
fibrous osteodystrophy -woven bone and lack strength,

A.Cadmium: oestomalacia

B.ischemic bone disease

- a. etiology
thrombosis, toxin, trauma,
- b. lesion: dry, chalky, peritoneum can be easily removed
- c. LM: loss of osteocytes from lacunae; removal of dead bone by osteoclast; formation of new bone
- d. response to injury
 - 1) depend on: extent of necrosis
persistence of causative agent
extent to which marrow is involved
 - 2) type of response
sequestration: isolated fragment of non-viable bone

involucrum: reactive tissue that encapsulates a sequestrum

new bone formation
granulation tissue
osteopenia, resorption

F. fracture

traumatic
simple, compound, closed, open, complete, incomplete,
comminuted: shattered into several small fragment

avulsion :separation of bone fragment with its tendon or ligament
transverse, spiral

pathologic: structure of bone is altered and its strength reduced-metabolic, inflammatory or neoplastic

a. normal fracture repair

- formation of blood clot
- osteogenic cells and endothelial cell(capillaries) from periosteum and endosteum proliferate and infiltrate the fibrin clot, formation of granulation tissue, inflammatory cells also infiltrate mesenchymal cell, chondroblast, and cartilage formation-cartilaginous

callus- bone formation and replacement of cartilage by callous bone(bony callus)

bone remodeling by osteoclast occurs for months to years with eventual formation of compact bone

b. factor which frequently complicate fracture repair

- communication with large amount of dead bone which will require a long time to remove

- *. infection
- *. excess mobility
- *. malnutrition
- *. poor vascularity
- *. excessive distance
- *. loss of periosteum

Inflammatory bone disease

Osteitis -inflammation of bone

Osteomyelitis- inflammation of bone, bone marrow?

Periostitis-inflammation confined primarily to periosteum

A. pathologic factor

1. type of lesion

- a. lytic-lysis and resorption of bone
- b. proliferative-reactive bone formation

2. bone lysis in inflammation

- a. necrosis: ischemia, emboli, direct action of bacterial toxin
- b. bone resorption
 - increased osteoclast activity
 - bacterial product-dental plaque
- c. mediator from inflammation
 - prostaglandin-stimulate bone resorption-mediated by osteoclast
 - lymphokine-osteoclast activating factor, IL-1, IL-2

3. suppurative osteomyelitis

- a. agent - *Staphylococcus* sp., *Streptococcus*, *Corynebacterium*, *E. coli*, *Salmonella* sp., *Fusobacterium* sp., *Actinomyces bovis*.

Actinomyces bovis-actinomycosis

Lumpy jaw-involve mandible (occasionally maxilla)

4. Nonsuppurative osteomyelitis-granulomatous

a. brucellosis

Brucella suis-osteomyelitis of lumbar vertebral epiphysis and adjacent discs (diskospondylitis)

b. tuberculosis

c. fungi-*Coccidioides*, *Cryptococcus*, *Blastomyces*

Neoplasms:

Fibroma
Fibrosarcoma
Osteoma
Osteosarcoma
Chondroma
Osteochondroma
Chondrosarcoma

Diseases of Joint

1. Response to injury

- a. fluid exudation-fibrinous response
- b. neutrophil exudation
- c. bacteria cleared by phagocytic activity of Type A cell
- d. chronic response
 - synovial cell hyperplasia
 - fibrosis
 - lymphocyte-plasma cell infiltrate
- e. pannus- fibrovascular tissue arising from synovium and covering the articular surface, chronic infectious nonsuppurative synovitis, some immune-mediated
 - e.g. rheumatoid arthritis

2. Degenerative joint disease

a. etiology

aging
genetic-hip dysplasia:
excessive wear
trauma
disturbance in quality or quantity of synovial fluid

- b. pathogenesis - altered acid mucopolysaccharides produced by surface cells of articular cartilage-loss of elasticity articular cartilage-fibrillation(roughening of surface), fissure, erosion of articular cartilage subchondral bone- sclerosis, fissure, eburnation(L ebur=ivory)
joint capsule-synovial lining cell hyperplasia, capsular fibrosis, inflammatory cell. periarticular chondroblast proliferation
- c. joint mice: macroscopic particulate matter in synovial space-bone or cartilage fragment
- d. hip dysplasia: inherited
 - primarily an acetabular dysplasia
 - flat-shallow acetabulum
 - flattening and deformation of femoral head
 - laxity of joint-subluxation-pain, lameness
 - secondary degenerative arthropathy-due to subluxation
 - capsular fibrosis, fibrillation, periarticular osteophytes

e. cervicospinal arthropathy - Wobbler syndrome

- cervical instability
- static or functional compression of spinal cord-white matter degeneration
- clinical sign-ataxia

f. intervertebral disc disease

- a. pathogenic factor
 - nucleus pulposus losses semisolid nature and plasticity-become more cartilage-like with mineralization
 - nuclear change lead to increased stress and degeneration of annulus fibrosis rupture of annulus fibrosis and protrusion(usually dorsal) of nucleus pulposus
- b. common site-lower thoracic and lumbar portion
- c. spondylosis: formation and ultimate fusion of osteophytes(exostosis) on ventral aspect of adjacent vertebral bodies. eventual bony bridging of joint-ankylosis(arthrogryposis)

3. Infectious arthritis

- a. route-hematogenous(95%), direct, extension from adjacent soft tissue or bone
- b. etiology-often associated with systemic disease

Erysipelothrix sp.-swine, sheep

Streptococcus suis-swine

Hemophilus parasuis-swine

Mycoplasma sp. -swine, cattle, sheep, goat]

- viral arthritis-caprine arthritis encephalitis virus
- immune mediated

4. noninfectious arthritis

gout: deposition of crystals of uric acid or urate(tophi)
All of the clinical manifestations of gout are initiated by the crystallization of sodium urate or uric acid from supersaturated body fluids. Hyperuricemia and gout are both caused by either an overproduction of uric acid or renal underexcretion of uric acid, or rarely both.

- a. occurrence: human, bird-do not have enzyme uricase.
- b. bird-articular, visceral form
- c. cause: decomposition products of nucleic acid metabolism (purine or protein)
 - deficiency of Vit. A in bird (impair elimination of urates in kidney)
- d. gross: white and chalky
 - thin grayish layer on serous surface LM: macrophage and foreign body giant cell in conjunction with clusters of sharp crystal
 - *: deposition of calcium pyrophosphate in dog-chondrocalcinosis

Pseudogout: results from the abnormal formation of calcium pyrophosphate (CPP) crystals in the cartilage ("cushion" between the bones), which is later followed by the release of crystals into the joint fluid (synovial fluid). When CPP crystals are

released into the joint, they can cause a sudden attack of arthritis, similar to gout.

gross: chalky

LM: crystallic material(needle-shaped

Inflammatory LESIONS of joints:

arthritis – inflammation of the intra-articular structure of joints.

synovitis - inflammation of the synovium of joints.

Substances involved in joint injury

1. prostaglandin E2
2. Interleukin – 1
3. Neutral proteases
4. Superoxide radicals and H₂O₂

Degenerative Joint Disease (DJD)

- char. by focal erosion and fibrillation of articular cartilage.

Intervertebral disk disease – common in chondrodystrophic breeds such as DACSHUND.

Neoplasms:

CHONDROMA AND CHONDROSARCOMA
OSTEOMA AND OSTEOSARCOMAS

Terms:

Kyphosis-abnormal dorsal curvature of the spine

Scoliosis-lateral deviation or curvature of the spine

Lordosis- abnormal ventral curvature of spine

Kyphoscoliosis – abnormal dorsal and lateral curvature of the spine

Syndactyly – fusion of adjacent limbs

Synostosis- osseous union of bones that are normally distinct

Phocomelia – hypoplasia of limbs, hands and feet, attached directly to the body.

Amelia- absence of limb or limbs

Polymelia – excess in the number of limbs

Hemimelia – absence of longitudinal segment of a limb

osteoporosis –clinical disease of bone pain and fracture characterized microscopically by a reduction of bone mass (osteopenia) but with the remaining bone normally mineralized.

Osteopetrosis (increased bone mass) a very dense bone with no medullary cavity but are susceptible to fracture.

Exostosis (or osteophyte) – refers to a usually nodular, benign bony growth projecting outward from a surface of bone.

Enostosis – a bony growth within the medullary cavity.

Pannus – is a fibrovascular and histiocytic tissue that arises from the insertion of synovial membrane and spreads over adjacent cartilage as a velvety membrane.

Callus- refers to an unorganized meshwork of woven bone that forms following a fracture.

Defense Mechanisms of Skeletal Muscle

- SKIN, SUBCUTIS, AND FASCIA
- Form structural barriers to protect against external injury
- VASCULATURE
- Collateral circulation to protect against ischemia
- Recruitment of monocytes that become tissue macrophages
- Recruitment of neutrophils and other inflammatory cells
- Capillary endothelium resistant to tumor metastasis
- IMMUNOLOGIC RESPONSES
- Innate humoral and cellular immunologic responses
- OTHER
- Adequate tissue antioxidant concentrations
- Physiologic adaptation
- Regenerative capacity

Classification of Muscle Disease

Classification	Cause or Type of Disorder
Degenerative	Ischemia
	Nutritional
	Toxic
	Exertional
	Traumatic
Inflammatory	Bacterial
	Viral
	Parasitic
	Immune-mediated
Congenital and/or inherited	Anatomic defects
	Muscular dystrophy
	Congenital myopathy
	Myotonia
	Metabolic
	Malignant hyperthermia
	Hypothyroidism
	Hypercortisolism
	Hypokalemia
	Hypernatremia
Endocrine	Other electrolyte imbalances
	Peripheral neuropathy
	Motor neuronopathy
Electrolyte	Myasthenia gravis
	Botulism
	Tick paralysis
Neuropathic	Primary tumors (rhabdomyoma, rhabdomyosarcoma)
	Secondary tumors (hemangiosarcoma, fibrosarcoma, infiltrative lipoma, other tumor phenotypes)
	Metastatic tumors
Neuromuscular junction disorders	
Neoplasia	

Bacterial Myopathies

Infectious Agent	Species Affected
<i>Clostridium</i> spp. causing myositis	Horses, cattle, sheep, goats, pigs
<i>Clostridium botulinum</i>	Horses, cattle, sheep, goats, dogs
Pyogenic bacteria	Horses, cattle, sheep, goats, pigs, cats
Agents causing fibrosing and granulomatous lesions	Cattle, sheep, goats, pigs

Portals of Entry into the Muscular System

- DIRECT
- Penetrating wounds
- Intramuscular injections
- Bone fracture
- External pressure causing crush injury
- HEMATOGENOUS
- Blood-borne pathogens, toxins, autoantibodies, and immune complexes
- Cytotoxic lymphocytes causing immune-mediated damage
- Other inflammatory cells

Viral Myopathies

Disease	RNA VIRUSES	
	Family	Causal Agent
Porcine encephalomyelitis	Picornaviridae	Enterovirus
Foot-and-mouth disease	Picornaviridae	Aphthovirus
Bluetongue	Reoviridae	Orbivirus
Akabane disease	Bunyaviridae	Akabane virus

Parasitic Myopathies

Infectious Agent	Species Affected
<i>Sarcocystis</i> spp.	Horses, cattle, sheep, goats, camelids, pigs
<i>Trichinella spiralis</i>	Pigs
<i>Neospora caninum</i>	Dogs, fetal cattle
<i>Trypanosoma cruzi</i>	Dogs
<i>Cysticercus</i> spp.	Cattle, sheep, goats, pigs
Nematode larval migrans	Dogs
<i>Hepatozoon americanum</i>	Dogs

Immune-Mediated Muscle Disorders

Disorder	Species Affected
Purpura hemorrhagica	Horses
Viral-associated	Horses, cats
Polymyositis	Dogs
Masticatory myositis	Dogs
Extraocular muscle myositis	Dogs
Acquired myasthenia gravis	Dogs, cats

Myopathies Due to Endocrine and Electrolyte Abnormalities

Disorder	Species Affected
Hypothyroidism	Dogs
Hypercortisolism	Dogs
Hypokalemia	Cattle, cats
Hypophosphatemia	Cattle
Hypernatremia	Cats
Hypocalcemia	Cattle
Hypothalamic/pituitary dysfunction	Horses

Stable Fracture Repair

Time	Tissue at Repair Site	Stability
Immediate 24-48 hr	Hematoma	Unstable
	Undifferentiated mesenchymal cells and neovascularization	Unstable
36 hr 4-6 wk	Earliest woven bone	Unstable
	Primary callus of woven bone and possibly hyaline cartilage	Stable
Months to years	Modeling of woven bone into lamellar bone	Stable

Primary Skeletal Neoplasms of the Dog

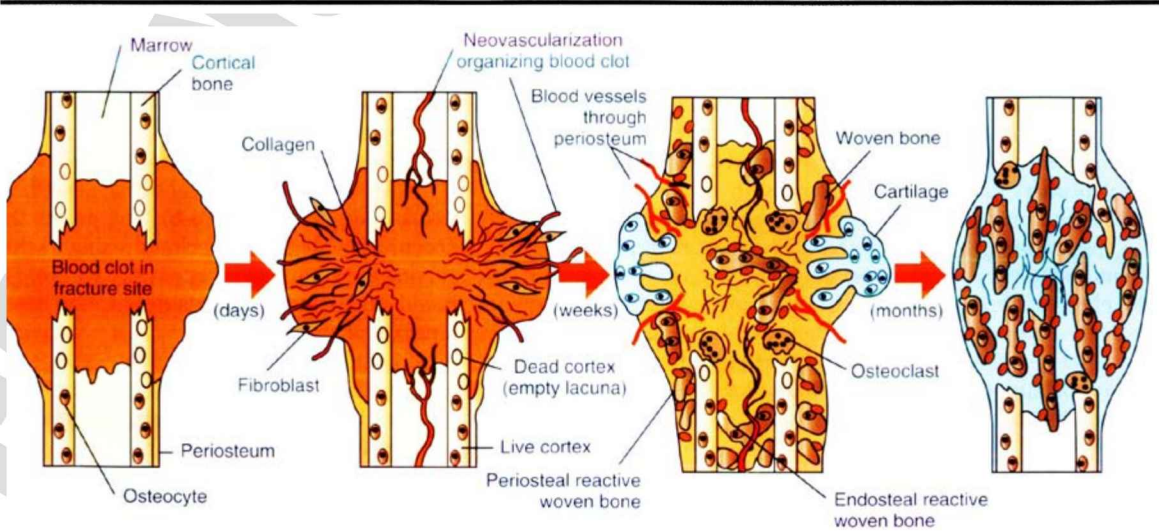
Name	Cell of Origin	Incidence	Primary Site	Biologic Behavior
Osteoma	Osteoblast	Rare	Flat bones	Benign
Osteosarcoma	Osteoblast	Common	Predominantly metaphyses of larger appendicular bones	Highly malignant with metastases early in clinical course
Chondroma	Chondroblast/chondrocyte	Rare	Flat bones	Benign
Chondrosarcoma	Chondroblast/chondrocyte	Relatively rare	Ribs, sternum, nasal cavity	Metastases not common and late in clinical course
Fibroma	Fibroblast			Not significantly recognized as a primary tumor of bone
Fibrosarcoma	Fibroblast	Relatively rare	Diaphysis of bones of appendicular skeleton	Metastases relatively late in clinical course

Toxic Osteodystrophies

Principal	Route/Source	Lesions	Mechanism
Vitamin D	Ingestion of plants (e.g., <i>Solanum malacoxylon</i>) that contain water-soluble glycosides of the vitamin; ingestion of excess vitamin D added to feed	Acute high-dose exposure: widespread soft tissue mineralization Chronic lower dose exposure: osteosclerosis with formation of abnormal woven bone matrix with increased basophilia	Acute high dose: increased absorption of calcium from intestines and increased release by osteoclasts from bone Chronic lower dose: suppression of bone resorption by hypercalcemia, which suppresses parathyroid hormone and increases calcitonin secretion Vitamin D also likely has direct stimulatory effect on osteoblasts
Vitamin A	Ingestion of excessive retinoids (not carotenoids) as found in certain plants (sweet potatoes) and meat (liver) or drug toxicity	Growing animals: multifocal premature closures of growth plates with subsequent growth deformity, osteoporosis, and pathologic fractures Adult animals: osteosclerosis, periosteal bone formation, and exostoses	Retinoids cause degeneration and necrosis of chondrocytes and osteoblasts in growing animals and paradoxically are stimulatory to osteoblasts in adult animals
Lead	Ingestion usually from licking lead-based paint	Characteristic lesion is a "lead line," an osteosclerotic band of bone parallel to the growth plate; osteoclasts can have acid-fast lead inclusions; osteoporosis also can be present, but likely secondary to systemic illness of lead toxicity	Lead is stored in bone mineral; part of the sclerosis seen radiographically is a result of the radiodensity of the lead; lead is toxic to osteoclasts; bone mineral with lead is somewhat resistant to osteoclasts
Fluoride	Ingestion of rock phosphates naturally high in fluoride; grazing on pastures with naturally high fluoride soil content or contaminated with fluoride as industrial by product; drinking water with naturally high fluoride content	Chronic low toxic levels cause osteosclerosis; chronic higher toxic levels cause osteopenia and periosteal bone formation	At lower toxic levels fluoride is stimulatory to osteoblasts and its incorporation in the hydroxyapatite make the crystal more resistant to resorption At higher toxic levels the mechanisms are uncertain, but direct toxic injury to osteoblasts is possible, resulting in osteopenia with the periosteal proliferation; begins a reaction to support the mechanically weakened skeleton

Metabolic Bone Disease		
Disease	Characteristics	Causes
Osteoporosis	Reduced bone mass—porous, thin, and brittle bones	Protein calorie malnutrition, immobilization, dietary calcium deficiency, glucocorticoid excess, menopause in human beings
Osteomalacia (adult animals)	Decreased bone mineralization (accumulation of osteoid)—soft bones	Vitamin D deficiency, phosphorus deficiency
Rickets (growing animals)	Decreased bone mineralization (accumulation of osteoid)—soft bones; thickened growth plates (failure of endochondral ossification)	Vitamin D deficiency, phosphorus deficiency
Fibrous osteodystrophy	Decreased bone mass because of resorption and replacement by fibrous tissue, rubbery bone	Hyperparathyroidism - Primary—functional chief cell adenoma of parathyroid gland - Paraneoplastic—parathyroid hormonelike-related protein from neoplasia-like adenocarcinoma of apocrine glands of anal sac - Secondary nutritional hyperparathyroidism from diets low in calcium and high in phosphorus - Secondary renal hyperparathyroidism from failure of the kidney to secrete phosphorus and reduced synthesis of 1,25-dihydroxyvitamin D

Necrosis of Bone		
Cause/Duration of Necrosis	Lesion	Clinical Significance
Acute aseptic (ischemic) necrosis	Death of bone cells and marrow; bone structure intact	Can be clinically silent
Chronic aseptic (ischemic) necrosis	- If no revascularization, dead bone can remain intact structurally for a long time but will accumulate microcracks - If revascularization takes place, dead bone can be resorbed slowly and replaced by new bone - If revascularization takes place, dead bone may be resorbed slowly and NOT be replaced by bone but by fibrous tissue	- Can remain clinically silent, but risk of microcrack progressing to complete clinical fracture increases with time and mechanical use - Can remain clinically silent from initiation of lesion to completion of repair - Can cause structural failure and collapse of the bone (e.g., chronic idiopathic necrosis of the femoral head)
Acute septic necrosis	Exudate, usually suppurative, will form at junction of dead bone and viable tissue with subsequent bone lysis and reactive bone formation	Pain due to cytokines from the inflammation and pressure in marrow cavity and periosteum
Chronic septic necrosis	- If the focus of dead bone is relatively small, it can be completely resorbed by the inflammatory process and osteoclastic bone lysis; there can be marked modeling of bone, usually with resorption predominating and replacement by fibrous tissue; in some cases excess formation can occur - If the focus of dead bone is relatively large, it can be sequestered (sequestrum) by a peripheral wall of reactive fibrous tissue or reactive bone (involucrum)	Pain due to cytokines and pressure in marrow cavity and periosteum; draining tracts can form; strength of the bone can be weakened because of resorption or its function can be affected by exuberant formation



Schematic diagram of the temporal course of callus formation and fracture repair.

Degenerative Joint Disease		
Name of Stage	Gross Appearance	Microscopic Lesion
Chondromalacia	Softened	Decreased proteoglycan content apparent with histochemical stains for mesenchymal mucins
Erosion	Ranges from matted appearance and normal thickness to grossly apparent thinning	Loss of cartilage layers—ranges from earliest loss only of the surface layer to later stages of loss extending to tangential, radial, and eventually deep (mineralized layer)
Fibrillation	Frayed appearance	Condensation of collagen fibers (because of loss of water at this stage) and splitting of the matrix along the vertical axis of the collagen fibers (perpendicular to the joint surface)
Ulceration/eburnation of subchondral bone	Exposure of the subchondral bone; the bone surface can be polished very smooth by wear	Loss of cartilage to the level of the subchondral bone; vascular and marrow spaces of the bone become smaller as they fill with bone (osteosclerosis) because of increased mechanical use; the surface of the exposed bone can be smooth; this combination of increased density (osteosclerosis) and surface smoothness is termed eburnation

Osteopathies in Small Animals

- ✓ Osteopathies can be developmental, infectious (osteomyelitis), idiopathic (eg, hypertrophic osteopathy), nutritional, or due to bone tumors or trauma.

Angular Deformity of the Forelimb (Radial and ulnar dysplasia)

- ✓ Abnormal development of the radius and ulna can occur secondary to distal physeal injury or hereditary breed characteristics (Bulldogs, Pugs, Boston Terriers, Basset Hounds, and Dachshunds).
- ✓ Asynchronous growth of the 2 bones leads to shortened limbs, cranial bowing of the bones, elbow joint subluxation, and valgus or varus deformities in the carpus.
- ✓ Clinical signs include lameness and reduced painful motion in the elbow or carpal joints.
- ✓ Radiography reveals the bone deformations and closed physes

Craniomandibular Osteopathy

- ✓ Craniomandibular osteopathy is a non-neoplastic, proliferative bone disorder of growing dogs that affects the mandible and tympanic bullae of Terrier breeds.
- ✓ The cause is unknown, but a genetic basis is suspected.
- ✓ The bone lesion is characterized by cyclical resorption of normal bone and replacement by immature bone along endosteal and periosteal surfaces.
- ✓ Clinical signs vary in severity and include oral discomfort, weight loss, fever, and painful palpable enlargement of the mandible.
- ✓ Radiography reveals bilateral bone proliferation in the mandibles and tympanic bullae.

Hypertrophic Osteodystrophy

- ✓ Hypertrophic osteodystrophy is a developmental disorder of the metaphyses in

long bones of young, growing dogs, usually of a large or giant breed.

- ✓ The exact etiology is unknown, although excessive dietary supplementation is suspected.
- ✓ The pathophysiology is based on metaphyseal vascular impairment leading to a failure in ossification and trabecular necrosis and inflammation.

Multiple Cartilaginous Exostoses

- ✓ (Osteochondromatosis)
- ✓ Multiple cartilaginous exostoses is a proliferative disease of young dogs and cats characterized by multiple ossified protuberances arising from metaphyseal cortical surfaces of the long bones, vertebrae, and ribs.
- ✓ Animals may be asymptomatic, and diagnosis is confirmed by palpation and radiography. Surgical excision of the masses is recommended if clinical signs such as lameness or pain develop.

Panosteitis

- ✓ Panosteitis is a spontaneous, self-limiting disease of young, rapidly growing, large and giant dogs that primarily affects the diaphyses and metaphyses of long bone.
- ✓ The exact etiology is unknown, although genetics (in German Shepherds), stress, infection, and metabolic or autoimmune causes have been suspected.
- ✓ The pathophysiology of the disease is characterized by intramedullary fat necrosis, excessive osteoid production, and vascular congestion.
- ✓ Endosteal and periosteal bone reactions occur.

Retained Ulnar Cartilage Cores

- ✓ Retained ulnar cartilage cores is a developmental disorder of the distal ulnar physis in young, large, and giant dogs

characterized by abnormal endochondral ossification.

- ✓ As a result, progressive physal calcification ceases, and forelimb bone growth is restrained. The exact etiology is uncertain, although dietary causes are suspected.

Scottish Fold Osteodystrophy

- ✓ This heritable condition of Scottish Fold cats is characterized by skeletal deformations of the vertebrae, metacarpal and metatarsal bones, and phalanges secondary to abnormal endochondral ossification.
- ✓ Affected cats are lame, and affected bones are deformed and swollen. Treatment is by removal of exostoses. Prognosis is guarded.

Osteomyelitis

- ✓ Inflammation and infection of the medullary cavity, cortex, and periosteum of bone are most frequently associated with bacteria such as *Staphylococcus* spp, *Streptococcus* spp, *Escherichia coli*, *Proteus* spp, *Pasteurella* spp, *Pseudomonas* spp, and *Brucella canis*.
- ✓ Anaerobic bacteria are less frequently isolated and may be part of a polymicrobial infection.

Hypertrophic Osteopathy

- ✓ Hypertrophic osteopathy is a diffuse periosteal proliferative condition of long bones in dogs secondary to neoplastic or infectious masses in the thoracic or abdominal cavity.
- ✓ The exact pathogenic mechanism is unknown, but periosteal vascularity is reduced.

Bone tumors

- ✓ Skeletal tumors can be benign or malignant and primary or secondary to metastases or adjacent soft-tissue structures.
- ✓ The most common primary bone tumor is osteosarcoma that affects the distal radius, proximal humerus, distal femur, or proximal tibia.
- ✓ Radiography reveals osteolysis, proliferation, and soft-tissue swelling; thoracic radiographs should be performed to delineate metastatic masses.
- ✓ Bone biopsy using a Michel bone trephine or Jamshidi biopsy needle is imperative in confirming the diagnosis.
- ✓ Less frequently identified tumors include chondrosarcoma, fibrosarcoma, and hemangiosarcoma.

Arthropathies in Large Animals

Arthritis

- ✓ Arthritis is a nonspecific term denoting inflammation of a joint.
- ✓ All joint diseases of large animals have an inflammatory component to varying degrees.
- ✓ Arthritic entities of importance include traumatic arthritis, osteochondritis dissecans,

subchondral cystic lesions, septic (or infective) arthritis, and osteoarthritis (also called degenerative joint disease).

Traumatic Arthritis

- ✓ Traumatic arthritis includes traumatic synovitis and capsulitis, intra-articular chip fractures, ligamentous tears (sprains) involving periarticular and intra-articular ligaments, meniscal tears, and osteoarthritis.
- ✓ Traumatic arthritis is seen in all breeds of horses worldwide.

Clinical Findings

- ✓ Traumatic synovitis and capsulitis is inflammation of the synovial membrane and fibrous joint capsule associated with trauma.
- ✓ Typically, the horse is an athlete and presents with synovial effusion in the acute stage, along with general thickening and fibrosis in the more chronic stage.
- ✓ Arthritis generally results in pain and altered function of the joint.
- ✓ If the process is active or acute, there is usually synovial effusion, and the surrounding tissues are swollen and warm.
- ✓ In more severe cases, manipulation of the joint causes pain.
- ✓ In more subtle cases, flexion tests are required to elicit lameness.
- ✓ As the disease process becomes chronic, the range of motion is reduced with fibrous thickening of the joint capsule.

Osteochondritis Dissecans

- ✓ In osteochondritis dissecans (OCD), a focal area of the immature articular cartilage is retained, and the matrix in the basal area of this region becomes chondromalacic and acellular.
- ✓ The immature articular cartilage separates from the underlying trabecular bone.
- ✓ The chondral fracture extends horizontally and vertically until a flap is formed.
- ✓ Synovial fluid gains entrance to the underlying medullary space, and subchondral cysts may form (usually only in larger animals).
- ✓ The flap of immature articular cartilage may break away completely ("joint mice") or may reattach by endochondral ossification to the underlying bone, especially in pigs, and result in a wrinkled articular surface.
- ✓ If the flap is torn free by joint motion, it may be ground into smaller pieces during locomotion and disappear, while the larger plaques may become attached to the synovial membrane, become vascularized, and ossify.
- ✓ The resultant articular defect, in time, fills with fibrocartilage.

Etiology:

- ✓ The exact cause is unknown but is assumed to be multifactorial.

- ✓ Factors include genetic predisposition, fast growth, high caloric intake, low copper and high zinc levels, and endocrine factors.

Subchondral Cystic Lesions

- ✓ Subchondral cystic lesions are seen in the femorotibial joint and in the fetlock, pastern, elbow, shoulder, and distal phalanx.
- ✓ Subchondral cystic lesions are most frequent in the femorotibial joint.

Septic Arthritis (Infective arthritis)

Etiology and Epidemiology:

- ✓ Septic or infective arthritis results from sequestration of bacterial infection in a joint.
- ✓ Infection of a joint develops in 3 main ways:
- ✓ 1) hematogenous infection, which is common in foals, calves, and lambs (commonly referred to as navel ill);
- ✓ 2) traumatic injury with local introduction of infection;
- ✓ 3) iatrogenic infection associated with joint injection or surgery (usually in horses)

Navel ill is only one example of a hematogenous route of infection, which can also be gained from GI or pulmonary sources.

Clinical Findings

- ✓ Septic arthritis is usually characterized by severe lameness and distention of the joint with cloudy, turbid synovial fluid that contains $>30,000$ WBC/mm³ and a total protein level of >4 g/dL.
- ✓ In foals, hematogenous osteomyelitis often accompanies septic arthritis.
- ✓ Septic arthritis in foals has been classified into type S (septic joint only), Type P (involving osteomyelitis of the adjacent growth plate as well), or type E (involving osteomyelitis of the epiphyseal and subchondral bone).
- ✓ Various organisms may be involved. In young lambs, *Actinobacillus seminis* causes polyarthritis, as do *Chlamydia psittaci* and *Erysipelothrix insidiosa*.

Bursitis

- ✓ Bursitis is an inflammatory reaction within a bursa that can range from mild inflammation to sepsis.
- ✓ It is more common and important in horses. It can be classified as true or acquired.
- ✓ True bursitis is inflammation in a congenital or natural bursa (deeper than the deep fascia), eg, trochanteric bursitis and supraspinous bursitis
- ✓ Acquired bursitis is development of a subcutaneous bursa where one was not previously present or inflammation of that bursa, eg, capped elbow over the olecranon process, shoe boil over the point of the elbow, and capped hock over the tuber calcaneus.
- ✓ Bursitis may manifest as an acute or chronic inflammation.

- ✓ Examples of acute bursitis include bicapital bursitis and trochanteric bursitis in the early stages.

- ✓ It is generally characterized by swelling, local heat, and pain.

- ✓ Chronic bursitis usually develops in association with repeated trauma, fibrosis, and other chronic changes (eg, capped elbow, capped hock, and carpal hygroma).

Capped Elbow and Hock

- ✓ Capped elbow and hock are inflammatory swellings of the subcutaneous bursae (acquired bursitis) located over the olecranon process and tuber calcaneus, respectively, of horses.
- ✓ Trauma from lying on poorly bedded hard floors, kicks, falls, riding the tailgate of trailers, iron shoes projecting beyond the heels, and prolonged recumbency are frequent causes.

Fistulous Withers and Poll Evil

- ✓ Fistulous withers and poll evil are rare, inflammatory conditions of horses that differ essentially only in their location in the respective supraspinous or supra-atlantal bursae.
- ✓ This discussion is of fistulous withers but, except for anatomic details, also applies to poll evil.
- ✓ In the early stage of the disease, a fistula is not present.
- ✓ When the bursal sac ruptures or when it is opened for surgical drainage and secondary infection with pyogenic bacteria occurs, it usually assumes a true fistulous character.

Etiology:

- ✓ The condition may be traumatic or infectious in origin.
- ✓ Agglutination titers support an infectious etiology. *Brucella abortus* and occasionally *B suis* can be isolated from the fluid aspirated from the unopened bursa, and outbreaks of brucellosis in cattle have followed contact with horses with open bursitis.
- ✓ A *Brucella* titer should always be evaluated in these cases; if significant, the owners should be made aware of the public health significance.
- ✓ The inflammation leads to considerable thickening of the bursa wall.
- ✓ The bursal sacs are distended and may rupture when the sac has little covering support.
- ✓ In more chronic, advanced cases, the ligament and the dorsal vertebral spines are affected, and occasionally these structures necrose.
- ✓ In the early stage, the supraspinous bursa distends with a clear, straw-colored, viscid exudate.
- ✓ The swelling may be dorsal, unilateral, or bilateral, depending on the arrangement of the bursal sacs between the tissue layers.

- ✓ It is an exudative process from the beginning, but no true suppuration or secondary infection occurs until the bursa ruptures or is opened.

Tendonitis

(Bowed tendon)

- ✓ Inflammation of a tendon can be acute or chronic, with varying degrees of tendon fibril disruption.
- ✓ Tendinitis is most common in horses used at fast work, particularly racehorses.
- ✓ The problem is seen in the flexor tendons and is more common in the forelimb than in the hindlimb. In racehorses, the superficial flexor is involved most frequently.
- ✓ The primary lesion is a rupture of tendon fibers with associated hemorrhage and edema.

Etiology:

- ✓ Tendinitis usually appears after fast exercise and is associated with overextension and poor conditioning, fatigue, poor racetrack conditions, and persistent training when inflammatory problems in the tendon already exist.
- ✓ Improper shoeing may also predispose to tendinitis. Poor conformation and poor training also have been implicated.

Clinical Findings

- ✓ During the acute stage, the horse is severely lame and the involved structures are hot, painful, and swollen.
- ✓ In chronic cases, there is fibrosis with thickening and adhesions in the peritendinous area.
- ✓ The horse with chronic tendinitis may go sound while walking or trotting, but lameness may recur under hard work.

Tenosynovitis

- ✓ Tenosynovitis, an inflammation of the synovial membrane and usually the fibrous layer of the tendon sheath, is characterized by distention of the tendon sheath due to synovial effusion.
- ✓ It has a number of possible causes and clinical manifestations.
- ✓ The various types of tenosynovitis include idiopathic, acute, chronic, and septic (infectious). Idiopathic synovitis refers to synovial distention of tendon sheaths in young animals, in which the cause is uncertain.
- ✓ Acute and chronic tenosynovitis are due to trauma.
- ✓ Septic tenosynovitis may be associated with penetrating wounds, local extension of infection, or a hematogenous infection.

Clinical Findings

- ✓ There are varying degrees of synovial distention of the tendon sheath and lameness, depending on the severity.
- ✓ Horses are markedly lame in septic tenosynovitis.
- ✓ Chronic tenosynovitis is common in horses in the tarsal sheath of the hock (thoroughpin) and in the digital sheath (tendinous windpuffs).
- ✓ These 2 entities must be differentiated from bog spavin and synovial effusion of the fetlock.

h. Integumentary System

PATHOLOGY OF THE INTEGUMENT

Skin – largest organ of the body.

Functions:

1. affords environmental protection and serves as a close barrier.
2. regulates body temperature and blood pressure
3. produces pigments and Vitamin D.
4. Sensory perceptions
5. Stores fats, water, vitamins, carbohydrates, proteins and other substances.

Cytokines- includes IL-, CSF, TNF.. plays a role in mediating inflammation and immune response of the skin.

Histological Review of the Integument

Epidermis

Haired skin has four epidermal layers:

- Stratum comeum
- Stratum granulosum or granular layer
- Stratum spinosum or spinous layer
- Stratum basale or germinativum

Hairless skin has five epidermal layers:

- Stratum comeum or horny layer or keratin layer
 - Stratum lucidum or clear layer
 - Stratum granulosum or granular layer
 - Stratum spinosum or spinous layer
 - Stratum basale or germinativum
- Horns are epidermal outgrowth.

Dermis

- consist of COLLAGEN AND ELASTIC FIBERS

Vessels and Nerves

Hypodermis

ADNEXA, which consists of hair follicles, and glands (SWEAT, SEBACEOUS and specialized glands such as in anal glands).

CLAWS AND HOOVES are digital organs.

Exogenous Factors Affecting the Skin:

1. Infectious
2. Nutritional
3. Physical
4. Chemical
5. Actinic
6. Allergic

Endogenous Factors:

1. Immunologic
2. Congenital
3. Hereditary
4. Hormonal
5. Emotional
6. Metabolic
7. Age
8. Internal Disease

HAIR CYCLE:

Anagen –phase of hair synthesis

Catagen – transitional phase of hair cycle between growth and resting phases.

Telogen – resting phase of hair cycle.

PATHOLOGICAL CONDITIONS

Hyperkeratosis- increased thickness of the stratum corneum

– Two forms:

Orthokeratosis - or hyperkeratosis
cells are anuclear

Parakeratosis - cells contain nuclei.

- seen in zinc deficiency where there is nuclear retention of the keratin layer (swine).

DERMATITIS – inflammation of the dermis or the skin.

Acanthosis nigricans – considered a genodermatosis of young dachshund dogs.

- disease is manifested by bilateral axillary hyperpigmentation, and alopecia.

- may involve secondary seborrhea and pyoderma.

Epitheliogenesis imperfecta (aplasia cutis)- results from failure of the squamous epithelium and adnexa of skin and epithelium of oral mucosa to develop completely.

- underlying tissue is easily traumatized and becomes infected

Hypertrichosis - excessive growth of hair.

Ichthyosis - skin is alopecic and covered by thick keratin.

Solar dermatosis – acute (sunburn) or chronic (solar dermatosis or neoplasia/ skin cancer).

Solar dermatitis - UV related or actinic.

Photosensitization

- lesions occur in areas not covered by hair or fleece.

Lesions may include erythema, edema, blisters, exudation, keratitis, necrosis etc.

Forms:

a. **PRIMARY** photosensitization or primary porphyria – often due to ingestion of preformed photodynamic substances (e.g. buckwheat or fungal contaminated plants).

- administration of phenothiazine, tetracyclines, thiazides or sulfonamides also may cause primary photosensitization.

b. congenital porphyria

- may develop due to abnormal porphyrin metabolism

- inherited disorder due to an enzyme deficiency that results in abnormal synthesis of photodynamic agents, including uroporphyrin and coproporphyrin. (e.g., bovine congenital porphyria).

c. hepatogenous (or secondary photosensitization)

- is due to hepatic disease that impairs excretion of phyloerythrin, a product of chlorophyll metabolism. (e.g. caused by ingesting hepatotoxic plants

- e.g., plant lantana or fungal-contaminated plants, i.e., mycotoxin sporidesmin).

Acral lick dermatitis - psychogenic dermatitis of extremity usually a result of excessive licking and chewing.

Callus – thickened area due to friction.

(e.g. seen at pressure points or bony prominences)

Intertrigo (skin fold dermatitis)

Microorganisms causing skin disease

a. Poxviruses e.g. contagious ecthyma (orf, contagious pustular dermatitis, soremouth)

b. Herpesviruses

c. Rickettsial organisms – RMSF, SFG due to spotted fever group.

d. Dermatophilosis or streptothricosis caused by *Dermatophilus congolensis*.

- scab from affected cattle/animal will show tram-track appearance of the organisms using either Giemsa's or Gram's stains.

e. Staphylococci, streptococci, Pasteurella, Fusobacterium Corynebacteria etc.

f. Mycotic infections – Epidermophyton, Microsporum, Trichophyton. (Dermatophytes/ Dermatophytosis)

- Candidiasis.

Systemic mycoses – blastomycosis, coccidioidomycosis, cryptococcosis and histoplasmosis.

Greasy pig disease (exudative epidermitis) caused by *Staph. hyicus*.

- an acute often fatal dermatitis of neonatal piglets.

- a mild disease in older piglets.

Staphylococcus intermedius –

- primary pathogen of canine skin.

Pyoderma – cutaneous bacterial infections.

Folliculitis – inflammation of the hair follicles

Perifolliculitis – surrounding the hair follicles

Furunculosis (perforating folliculitis) – follicular rupture due to pyogenic staphylococci, parasites (Demodex, Pelodera) and dermatophytes (Microsporum, Trichophyton).

Sebaceous adenitis – inflammation of the sebaceous glands.

Hidradenitis – inflammation of the apocrine glands.

Panniculitis – inflammation of the adipose tissues.

Parasitic Infestations**Ectoparasites**

mites and ticks (which have eight (8) legs)

lice, fleas and flies (which have six legs).

Mites – Demodex, Sarcoptes, Psoroptes, and Chorioptes etc.

Ticks – soft (argasid) and hard (ixodid)

Acanthosis - thickening of the epidermis as a result of hyperplasia of the Malpighian layer, especially the prickle cell layer or spinous cell layer.

- may occur with or without hyperkeratosis.

Ballooning degeneration - isolation of the cells of the epidermis from one another, particularly in the deeper layers, following intracytoplasmic edema and vacuolization; leading to vesiculation.

-often seen in viral diseases.

e.g., vesicular stomatitis, FMD

Bulla (bleb) - cavitation in the epidermis, similar to but generally larger than a vesicle.

Dyskeratosis - an abnormality of development with distinctive alterations in epidermal cells.

Two types are distinguished:

benign - disorganization of epidermal cells, especially in the granular layer, with swollen, eosinophilic cytoplasm, sometimes containing elementary viral particles (pox, contagious ecthyma).

malignant - anaplastic changes in the epidermis manifest by hyperchromatism, changes in polarity, increase in mitotic activity, and enlargement of nuclei.

- generally considered a step toward carcinoma.

Some terms in skin pathology:

Acantholysis – separation of the keratinocytes

Alopecia- hair loss

Bulla – large blister (>0.5cm)

Blister (vesicle)- localized collection of fluid usually in or beneath epidermis.

Cornification - production of stratum corneum by epidermal differentiation.

Dermatophytosis – fungal infection of skin

Erythema – redness of skin due to congestion of capillaries.

Keratosis - excessive formation of keratin.

Lichenoid – two meanings: one clinical, one histopathologic.

- Histopathologic: refers to band-like inflammation parallel to the epidermis, with or without basal cell degeneration.

Lichenification – thickening of skin with accentuation of skin creases.

Macule – flat, circumscribed lesion of altered skin lesion

Papule – small, circumscribed elevation of skin.

Paronychia - inflammation of skin around the nails.

Pustule - small, circumscribed accumulation of pus within the epidermis.

Seborrhea - nonspecific term for signs of scaling, crusting and greasiness.

Primary seborrhea - specific term for cornification disorder.

Spongiosis -intercellular edema creating sponge-like skin appearance.

Ulcer - loss of epidermis and superficial portion of the dermis.

Urticaria – vascular reaction in dermis consisting of transient wheals (hives).

Vitiligo – acquired skin depigmentation. Loss of skin pigmentation.

Vibrissae - long, coarse hair located about the muzzle.

Wheal and Flare reactions – edema and redness in the skin resultant of hypersensitivity or allergic states.

Portals of Entry into the Skin

EPIDERMIS

Absorption through stratum corneum and epidermis

Penetrating trauma, including injection from exterior

Penetration of ultraviolet or γ-radiation

Direct contact with heat, cold, irritants, caustic substances, and microbiologic agents

ADNEXA

Penetration through follicular openings

Rupture of follicle, gland, or other structure (anal sac)

DERMIS AND PANNICULUS

Vessels (Hematogenous)

Drugs or toxins

Localization within capillary beds

Embolism

Leukocyte trafficking

Nerves

Migration from ganglion along sensory nerves via axonal flow to epithelial cells

SUPPORT STRUCTURES

Penetrating trauma from bone fracture

Extension of tumor or infection from adjacent lymph node, gland, muscle, or bone

Cutaneous Fungal Infections

SUPERFICIAL (LIMITED TO HAIR OR STRATUM CORNEUM)

Piedra

Trichosporon beigeli

CUTANEOUS (LIMITED TO HAIR, STRATUM CORNEUM, CLAWS)

Dermatophytes

Microsporum canis

Microsporum gypseum

Trichophyton mentagrophytes

Candida spp.

Malassezia spp.

SUBCUTANEOUS (USUALLY LIMITED TO CUTANEOUS AND SUBCUTANEOUS TISSUE, SOMETIMES LYMPHATICS)

Eumycotic mycetoma

Curvularia geniculata

Madurella spp.

Acremonium spp.

Pseudoallescheria spp.

Phaeococcus spp.

Dermatophyte pseudomycetoma

Phaeohyphomycosis

Hyalohyphomycosis

Sporotrichosis

Entomophthoromycosis (zygomycosis)

Oomycosis (pythiosis and lagenidiosis)

SYSTEMIC (USUALLY PULMONARY PORTAL OF ENTRY, BUT CAN AFFECT DERMIS AND SUBCUTIS)

Blastomycosis

Coccidioidomycosis

Cryptococcosis

Histoplasmosis

Cutaneous Bacterial Infections

SUPERFICIAL PYODERMAS

Superficial pustular dermatitis (impetigo)
 Superficial spreading pyoderma
 Mucocutaneous pyoderma
 Dermatophilosis
 Exudative epidermitis
 Ovine fleece rot
 Superficial folliculitis (see staphylococcal folliculitis and furunculosis below)

DEEP PYODERMAS

Staphylococcal folliculitis and furunculosis
 Abscesses

BACTERIAL GRANULOMATOUS DERMATITIS

Mycobacterial granulomas
 Granulomas caused by nonfilamentous bacteria
 Staphylococcus spp.
 Streptococcus spp.
 Pseudomonas aeruginosa
 Actinobacillus lignieresii
 Proteus spp.
 Filamentous bacterial granulomas
 Nocardia spp.
 Actinomyces spp.
 Streptomyces spp.
 Actinomadura spp.

SYSTEMIC OR TOXIC REACTIONS

Erysipelothrix rhusiopathiae
 Systemic salmonellosis, pasteurellosis, *Escherichia coli* infection
 Canine toxic shock syndrome and necrotizing fasciitis due to streptococcal or staphylococcal infection
 Clostridial dermatitis
 Clostridium novyi or *Clostridium chauvoei*
Streptococcus equi

BACTERIAL DIGITAL INFECTIONS OF RUMINANTS

Contagious foot rot
 Necrobacillosis of the foot
 Papillomatous digital dermatitis

Host Defense Mechanisms against Injury: Physical Defense Mechanisms

BARRIER FUNCTIONS

Hair follicles: Physical and thermal
 Tactile hairs and neurons: Sensory
 Claws and horns: Physical defense
 Stratum corneum: Barrier function
 Adnexal glandular secretions: Barrier function
 Apocrine glands horses and cattle: Defense against excessive heat
 Melanin: Defense against ultraviolet radiation
 Basement membrane zone: Filter to macromolecules, and barrier to invasion of neoplastic epidermal cells
 Panniculus: Barrier against temperature extremes

RESISTANCE TO MECHANICAL FORCES

Hair follicles and epidermal-dermal interdigitations:
 Anchor epidermis to dermis
 Stratum corneum: Corneocyte, corneocyte envelope, and intercellular lipid adhesion
 Desmosomes and hemidesmosomes: Intercellular and basement membrane adhesion
 Basement membrane: Anchors epidermis to dermis
 Collagen and elastic tissue: Resilience, strength, and support of adnexa
 Panniculus: Shock absorption, facilitates movement, anchors dermis to fascia

Cutaneous Parasitic Infestations

MITES

Demodex sp.
Sarcoptes sp.
Notoedres sp.
Otodectes sp.
Psoroptes sp.
Chorioptes sp.
Cheyletiella sp.
Psorergates sp.
Neotrombicula and *Eutrombicula* spp.

TICKS

Argasid (soft)
 Ixodid (hard)

LICE

Mallophaga (biting)
 Anoplura (blood sucking)

FLEAS

Ctenocephalides felis and *Ctenocephalides canis*

FLIES

Adult fly bites
 Horn fly, stable fly, horse fly, deer fly, black fly, biting gnats, mosquitoes
 Myiasis
 Calliphorids, sarcophagids, *Cuterebra* sp., *Hypoderma* sp., screwworm, *Dermatobia* sp.

HELMINTHS

Larvae
 Hookworms, *Habronema* sp., *Pelodera* sp., *Necator* sp., *Strongyloides* sp., *Gnathostoma* sp., *Bunostomum* sp.
 Filarial
 Onchocerca sp., *Stephanofilaria* sp., *Elaeophora* sp., *Parafilaria* sp., *Suifilaria* sp., *Dirofilaria* sp., *Acanthocheilonema* sp.

PROTOZOA

Leishmania sp.
 Rarely other genera

Conditions with Prominent Alopecia or Hypotrichosis

ENDOCRINE DISORDERS

Hypothyroidism
 Hyperadrenocorticism
 Hyperestrogenism
 Alopecia X of Nordic breeds*
 Hypersomatotropism
 Hyposomatotropism
 Cyclical flank alopecia (pineal gland)

NONENDOCRINE HAIR CYCLE ABNORMALITIES

Post clipping alopecia
 Telogen effluvium
 Anagen defluxion

DISORDERS ASSOCIATED WITH EXCESSIVE GROOMING

Feline psychogenic alopecia
 Feline hypersensitivity reaction

FOLLICULAR DYSPLASIA SYNDROMES AND CONGENITAL ALOPECIA AND HYPOTRICHOSIS

OTHER CONDITIONS ASSOCIATED WITH ALOPECIA

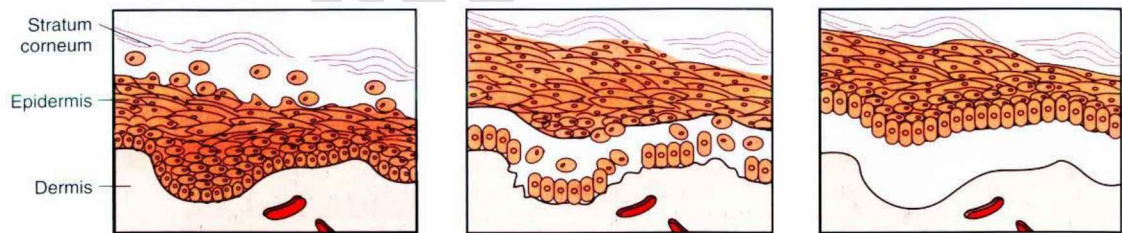
Sebaceous adenitis
 Folliculitis—infectious and noninfectious
 Feline paraneoplastic alopecia
 Poor nutrition
 Postinflammatory and posttraumatic

*Alopecia X of Nordic breeds is a group of poorly characterized dermatoses, including but not limited to castration responsive dermatosis, growth hormone responsive dermatosis, and follicular dysplasia in Siberian huskies or Alaskan malamutes.

Viral Infections of the Skin

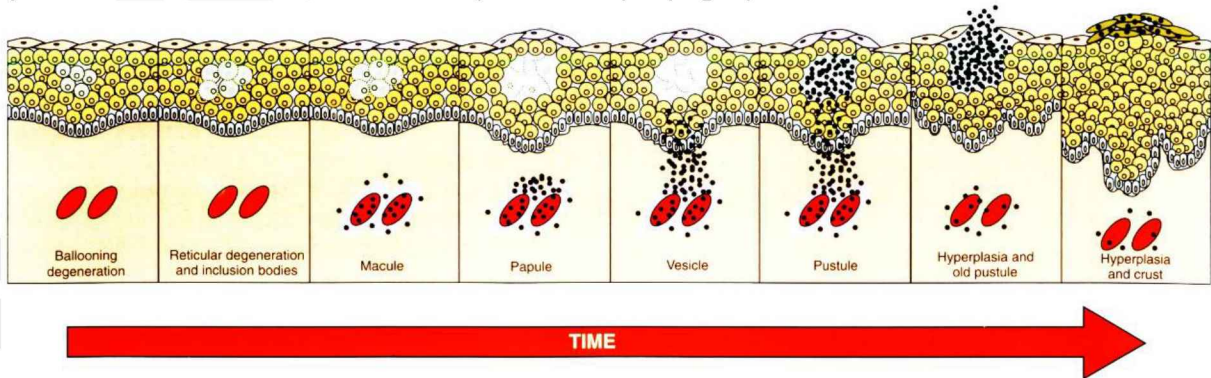
Virus	Diseases	Species Affected	Distribution
Parapoxvirus	Contagious pustular dermatitis Papular stomatitis Pseudocowpox	Sheep, goats, cattle; rarely dogs Cattle Milking cows; zoonotic	Cutaneous
Orthopoxvirus	Cowpox Vaccinia Horsepox* Equine papular dermatitis†	Some such as cowpox and vaccinia affect many species; others are more host specific	Cutaneous
Molluscipox Capripoxvirus	Molluscum contagiosum Sheeppox Goatpox	Horses, rarely dogs Most species specific	Cutaneous Systemic
Suipoxvirus	Lumpy skin disease	Cattle	Cutaneous
Unclassified poxvirus	Swine pox Ulcerative dermatosis of sheep	Pigs Sheep	Cutaneous
Bovine herpesvirus 2 (dermatotropic)	Bovine ulcerative mammillitis (bovine herpes mammillitis) Pseudo-lumpy skin disease	Cattle	Cutaneous
Bovine herpesvirus 4 (dermatotropic)	Bovine herpes mammary pustular dermatitis	Cattle	Cutaneous
Feline herpesvirus 1	Feline facial dermatitis and stomatitis	Cats	Cutaneous, oral, ocular, upper respiratory
Ovine herpesvirus 2‡ (in United States)	Malignant catarrhal fever	Cattle	Cutaneous, oral, systemic
Papillomavirus	Warts	All species	Cutaneous, oral, mucocutaneous
Papillomavirus	Fibropapilloma	Cattle	Cutaneous, genital
Papillomavirus	Sarcoid (fibropapilloma)	Horse, cat	Cutaneous
Papillomavirus	Bowen's-like disease	Cat, less in dog	Cutaneous
Papillomavirus	Pigmented epidermal plaques	Dog	Cutaneous
Picornavirus	Foot-and-mouth disease	Ruminants, pigs	Oral, cutaneous
Picornavirus	Swine vesicular disease	Pigs	Oral, cutaneous
Rhabdovirus	Vesicular stomatitis	Horses, cattle, pigs	Oral, cutaneous
Calicivirus	Vesicular exanthema	Pigs	Oral, cutaneous
Calicivirus	Feline calicivirus	Cats	Oral, cutaneous, systemic
Parvovirus	Porcine parvovirus	Piglets	Oral, cutaneous
Retrovirus	Feline leukemia virus Feline immunodeficiency virus	Cats	Secondary skin infections; cutaneous horns with feline leukemia virus

*Horsepox may be due to human or cattle orthopoxviruses.
†Virus not fully characterized.
‡Indirect evidence of viral involvement.



A. Subcorneal B. Suprabasal C. Subepidermal

Schematic diagram of the sites of vesicle formation in the skin. A, In a subcorneal vesicle, the stratum corneum forms the roof of the vesicle (as in impetigo or pemphigus foliaceus). B, In a suprabasal vesicle, a portion of the epidermis (stratum spinosum) forms the roof (as in pemphigus vulgaris). C, In a subepidermal vesicle, the entire epidermis separates from the dermis and forms the roof (as in bullous pemphigoid).



Schematic diagram of the development of a poxvirus lesion over time.

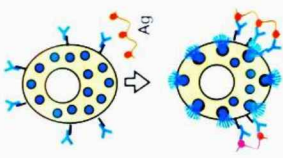
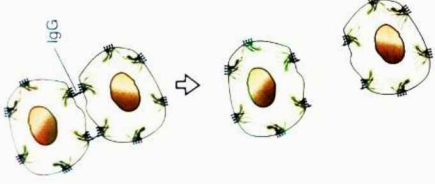
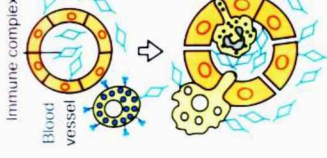
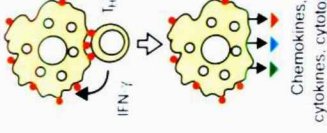
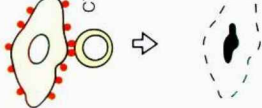
Differential Diagnoses of Selected Patterns That Can Be Recognized Clinically and Histologically

Pattern	Pustules Crusts (epidermal)	Vesicles Bullae (epidermal) to subepidermal)	Necrosis or ulceration (epidermal)	Scaling or other hyperkeratotic lesions* (epidermal)	Nodules ± draining tracts (dermal and pannicular)	Alopecia (adnexal)	Hypopigmentation or depigmentation (epidermal)
Disorders							
	Superficial bacterial infection	Pemphigus vulgaris	Vasculitis/ infarction	Primary seborrhea	Masses caused by deep infections	Folliculitis: Infectious	Vitiligo
	Pemphigus foliaceus and panepidermal pustular	Paraneoplastic pemphigus	Chemical and thermal burns	Ichthyosis	with bacteria, fungi, algae, Pythium,	Noninfectious	Uveodermatologic syndrome
	Dermatophilosis	Lupus erythematosus	Superficial necrolytic dermatitis	Zinc responsive dermatosis	migratory parasites (e.g., actinomycosis,	Postinflammatory and posttraumatic	Lupus erythematosus
	Exudative epidermitis	Subepidermal bullous dermatoses	Erythema multiforme	Sebacous adenitis	feline leprosy, mycetoma,	Endocrine alopecia	Copper deficiency
	Subcorneal pustular dermatosis	Drug reactions	Stevens-Johnson syndrome	Ear margin seborrhea	blastomycosis, pythiosis,	Idiopathic flank alopecia	Alopecia areata (healing stage)
	Foot pads*	Chemical and thermal burns	Toxic epidermal necrolysis	Vitamin A responsive dermatosis	habronemiasis abscesses)	Telogen effluvium	Inherited disorders (Chédiak-Higashi syndrome, Maltese and other coat color dilutions)
	Pemphigus foliaceus	Photosensitization	Ergot/fescue grass toxicity	Feline exfoliative dermatosis	“Sterile” nodular inflammation (e.g., foreign body reactions,	Anagen defluxion	Waardenburg-like syndrome
	Superficial necrolytic dermatitis	Viral diseases	Frostbite	and thymoma	histiocytosis, sterile	Follicular dysplasia	Piebaldism
	Lupus erythematosus		Feline indolent ulcer	Callus	pyogranuloma, xanthoma,	Congenital alopecia	Albinism
			Feline ulcerative dermatosis syndrome	Cutaneous horn	venomous bites, injection site reactions,	Feline psychogenic alopecia	Cyclic hematopoiesis
			Vesicular cutaneous lupus	Actinic dermatitis	eosinophilic granulomas)	Poor nutrition with protein deficiency	Contact with rubber
			erythematous Self-trauma		Panniculitis/ steatitis	Feline paraneoplastic alopecia	
			Epitheliogenesis imperfecta		Neoplasms		

Some of these disorders could be placed in different patterns. For instance, disorders characterized by vesicles or bullae may develop into an ulcerative pattern after the vesicles or bullae rupture.
*Hyperkeratotic disorders may also affect the nasal planum and footpads; see Box 17-2.

Mechanisms of Tissue Damage in Hypersensitivity or Autoimmune Diseases

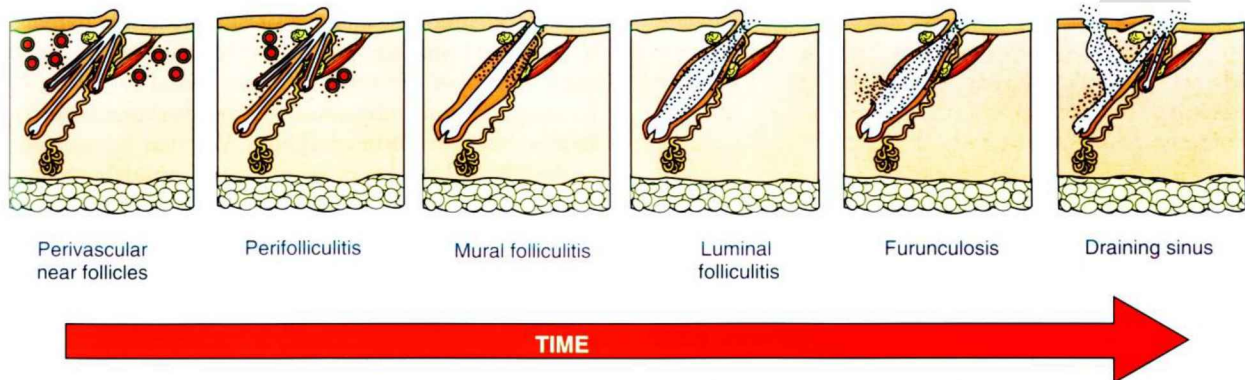
There are four types of hypersensitivity reactions (type I, II, III, IV) that cause tissue damage by immunologic mechanisms. Types I, II, and III are mediated by antibodies and are distinguished by the type of antigen and class of antibody involved. Type I responses are mediated by IgE cross-links these receptors, inducing mast-cell activation. Type II responses are mediated by IgG or IgM directed to antigens bound to the surface of the cell or part of cell membrane. The reaction can engage Fc receptor and complement mediated effector mechanisms. Type III responses are mediated by IgG or IgM directed against soluble antigens, and the tissue damage is caused by responses triggered by immune complexes. Type IV hypersensitivity reactions are mediated by T lymphocytes and can be subdivided into three groups. In the first group, tissue damage is caused by CD4⁺ T_H1 lymphocytes directed to soluble antigen bound to MHC II and that release cytokines including IFN- γ , resulting in an inflammatory response via macrophage activation. In the second, damage is caused by activation by CD4⁺ T_H2 (helper) lymphocytes directed to soluble antigen bound to MHC II and that release IL-4 and IL-5, resulting in an inflammatory response in which eosinophils predominate. In the third, damage is caused by cytotoxic T lymphocytes (CD8⁺) directed to cell-associated antigen bound to MHC I.

	Type I	Type II	Type III	Type IV	
Immune reactant	IgE	IgG or IgM	IgG or IgM	CD4 ⁺ lymphocyte, T _H 2 type (T-helper)	CD8 ⁺ cytotoxic lymphocyte
Time frame	15-30 min	Minutes to hours	3-10 hr	48-72 hr	48-72 hr
Antigen	Exogenous antigen	Antigen is bound to surface of cell or is a part of the cell membrane	Soluble antigen, endogenous or exogenous	Soluble antigen bound to MHC II-injected into skin	Cell-associated antigen bound to MHC I
(Examples)	(pollens, molds, insect salivary antigens)	(desmosomal or hemidesmosomal proteins)	(DNA, histones, ribosomes) (Streptococcus equi)	(atopic dermatitis: mites, pollens)	(contact antigen or self-antigen)
Effector mechanism	Mast cell activation	FcR γ cells (macrophages, NK cells) complement	Immune complex Blood vessel	Macrophage activation	Cytotoxicity
					
Examples of hyper-sensitivity	Atopic dermatitis, urticaria, anaphylaxis	Pemphigus, pemphigoid	Systemic lupus erythematosus Purpura in Streptococcus equi infection	Diagnosis of infections by Mycobacteria spp. and systemic fungal infections	Contact hypersensitivity Graft-versus-host disease

Examples of Pattern Diagnosis in the Skin

Component of Skin	Reaction to Injury	Pattern	Disease Examples
Epidermis	Prominent hyperkeratosis	Hyperkeratotic diseases of the epidermis	Primary seborrhea Ichthyosis Vitamin A deficiency Callus
Dermis	Interface inflammation	Interface dermatitis	Lupus erythematosus Erythema multiforme
Follicle	Inflammation of the follicular lumen	Luminal folliculitis	Infection with staphylococci, Dermatophytes, Demodex sp.
Panniculus	Predominantly neutrophilic inflammation	Neutrophilic panniculitis	Abscess Feline pansteatitis (early)

A pattern consists of two parts: a component of the skin (e.g., epidermis) + a histologic reaction of that component to injury (e.g., hyperkeratosis) = pattern (hyperkeratotic diseases of the epidermis).



Schematic diagram of the progression of folliculitis. Inflammation begins with migration of leukocytes (dots) from perifollicular dermal vessels into the perifollicular dermis (perifolliculitis). Inflammation progresses to involve the follicular wall (mural folliculitis) and then the lumen (luminal folliculitis). If the inflammation continues, the follicular wall is weakened, ruptures, and follicular contents are released into the dermis. The inflammation can extend into the deep dermis and panniculus, and/or form sinuses that drain to the surface of the skin.

Highlights on Integumentary System

Parakeratosis

- ✓ Parakeratosis is a nutritional deficiency disease of 6- to 16-wk-old pigs characterized by lesions of the superficial layers of the epidermis.
- ✓ It is a metabolic disturbance resulting from a deficiency of zinc or inadequate absorption of zinc due to an excess of calcium, phytates, or other chelating agents in the diet.
- ✓ Predisposing factors include rapid growth, deficiency of essential fatty acids, or malabsorption due to GI diseases.
- ✓ Signs are limited to the skin, although mild lethargy, anorexia, and growth depression may be seen in severe cases; there is little if any pruritus.
- ✓ The outstanding lesions are symmetrically distributed areas of excessive and abnormal keratinization of the epidermis with the formation of horny scale and fissures.
- ✓ Brown spots or papules are first seen on the ventrolateral areas of the abdomen and inner thigh, pastern, fetlock, hock, and tail regions.
- ✓ These lesions coalesce to involve larger areas until the entire body may be covered.
- ✓ The scale is horny, dry, and usually easily removed.
- ✓ Occasionally, secondary infection of the cracks and fissures causes them to fill with dark, sticky exudate and debris, which may resemble exudative epidermitis
- ✓ however, this usually occurs in younger piglets.
- ✓ Chronic sarcoptic mange and deficiencies of B vitamins or iodine must also be considered in a differential diagnosis.
- ✓ Clinical signs, skin biopsy, and low serum levels of zinc and alkaline phosphatase will help to confirm a diagnosis.

Ulcerative Dermatitis of Sheep:
(Lip and leg ulceration, Venereal balanoposthitis and vulvitis)

- ✓ Ulcerative dermatosis is an infectious disease of sheep caused by a virus similar to the ecthyma virus.
- ✓ It manifests in 2 somewhat distinct forms, one characterized by formation of ulcers around the mouth and nose or on the legs (lip and leg ulceration), and the other as a venereally transmitted ulceration of the prepuce and penis or vulva.

Clinical Findings:

- ✓ The lesion, regardless of location, is an ulcer with a raw crater that bleeds easily, varies in depth and extent, and contains an odorless, creamy pus
- ✓ Face lesions occur on the upper lip, between the border of the lip and the nasal orifice, on the chin, and on the nose.
- ✓ In severe cases, the ulcers may perforate the lip.
- ✓ Foot lesions occur anywhere between the coronet and the carpus or tarsus.
- ✓ Venereal lesions partially or completely surround the preputial orifice and may become so severe as to produce phimosis.

Seborrhea:

- ✓ Seborrhea is a skin disease in dogs that is characterized by a defect in keratinization or cornification.
- ✓ Clinically, it results in increased scale formation, occasionally excessive greasiness of the skin and hair coat, and often secondary inflammation and infection.

Etiology, Clinical Findings, and Diagnosis:

- ✓ Primary seborrhea is an inherited skin disorder characterized by faulty keratinization or cornification of the epidermis, hair follicle epithelium, or claws.
- ✓ There is usually a familial history of seborrhea, suggesting genetic factors are involved.
- ✓ The disease begins at a young age (usually <18-24 mo) and progresses throughout the dog's life.
- ✓ A diagnosis of generalized primary idiopathic seborrhea should be reserved for

dogs in which all possible underlying causes of seborrhea have been ruled out.

- ✓ Most seborrheic dogs have secondary seborrhea, in which a primary underlying disease predisposes to excessive scale, crusting, or oiliness, often accompanied by superficial pyoderma, Malassezia infection, and alopecia.
- ✓ The most common underlying causes are endocrinopathies and allergies.
- ✓ The goal is to identify and treat any underlying cause of the seborrhea.
- ✓ Palliative therapies that do not compromise the diagnostic evaluation should be instituted concurrently to provide as much immediate relief as possible for the dog.
- ✓ Underlying diseases may present with seborrhea as the primary clinical problem.
- ✓ The degree of pruritus should also be noted. If pruritus is minimal, endocrinopathies, other internal diseases, neoplasia, or certain diseases limited to the skin (eg, demodicosis or sebaceous adenitis) should be ruled out.
- ✓ Secondary infection plays a significant role in most seborrheic dogs.
- ✓ The sebum and keratinization abnormalities that are common in seborrheic dogs frequently provide ideal conditions for bacterial and yeast infections.
- ✓ The self-trauma that occurs in pruritic animals increases the likelihood of a secondary infection.
- ✓ Often, coagulase-positive *Staphylococcus* spp or *Malassezia* spp are present.
- ✓ The infections add to the pruritus and are usually responsible for a significant amount of the inflammation, papules, crusts, alopecia, and scales

i. Reproductive System

Pathology of the Female Reproductive System

Developmental Anomalies:

Criteria of defining sex

1. genetic
2. chromosomal
3. ductal
4. phenotypic

Normal mammalian chromosomes;

XX-female
XY-male

Gonadal sex is based on the histologic component of the gonad.

Ductal sex is based on whether the element is derived from the:

Mullerian (female)
or the Wolffian (male) system.

Abnormalities of chromosomal sex:

XXY (male) -Klinefelter's syndrome

XO (female)-Turner's syndrome

- or XXX female

Chimeras and mosaics – have each two or more cell types, each with different chromosomal content.

Chimera - cells come from different sources

Mosaic - cells come from a same source

Abnormalities of Gonadal Sex

Hermaphrodites - have both ovarian and testicular tissue

3 types:

1. bilateral- combined organ, ovotestis is present on both sides
 2. unilateral - combined organ, ovotestis is present on one side
 3. lateral - testis on one side and ovary in the other
- true hermaphrodites

Abnormalities of Phenotypic sex

Pseudohermaphrodites - have the chromosomes and gonads of one sex and tubular organs modified toward those of other sex.

Segmental Aplasia of the Mullerian duct system.

- Simplest form is failure to make proper connection with the urogenital sinus.

Imperfect fusion of the paired Mullerian ducts

Vagina and Vulva

Cysts- stimuli for cyst formation are hyperestrogenism

Inflammation

- In cow, it arises from Gartner's duct (Wolffian ruminants) or Bartholins glands.

Tumefaction - through a normal phenomenon of female in estrus overly large of persistent swelling is abnormal

- caused by hyperestrogenism

- poisoning in swine with mycotoxin found in moldy corn called zearalenone

Inflammatory changes;

The vulva and vagina are lined by stratified squamous epithelium are fairly resistant to infection.

Post parturient vulvitis and vaginitis

- occur during dystocia with laceration and tearing leading to infection.

Granular vulvitis -involved agent are; *Mycoplasma* and *Ureaplasma*

Infectious pustular vulvovaginitis - caused by herpesvirus.

Coital exanthema - common in equine caused by equine herpesvirus – I

Infectious bovine cervicovaginitis - or "EPIVAG" a bovine disease
- seen in Africa probably caused by the herpesvirus.

Dourine - caused by Trypanosoma equiperdum, a venereally transmitted disease of equine.

Cervicitis - concomitant with vaginitis or endometritis.

NEOPLASMS

Transmissible venereal tumor (TVT) –transmitted at coitus

Squamous Cell carcinoma - Solar radiation is the proposed cause.

Uterus:

Non - inflammatory Abnormalities:

Mechanical factors:

1. Torsion- can occur when the uterus is enlarged by
 - a.) Pyometra - Accumulation of pus in the uterine lumen.
 - b.) mucometra - Accumulation of mucus in the uterine lumen.
2. Uterine prolapse
3. Subinvolution
4. Endometrial atrophy can be due to loss of ovarian function secondary to hypopituitarism or in some species to old age or anestrus.
5. Endometrial hyperplasia- rare in mare: common in others,
 - in farm animal, influenced by , prolonged hyperestrogenism.

Adenomyosis- is the presence of nests of endometrium within the myometrium

Endometriosis - is the presence of endometrial glands in stroma in location outside the uterus.

Inflammatory lesions:

-most uterine infection begins in the endometrium

Humoral and cellular immune mechanism,

- neutrophilic infiltration consequent to chemotaxis with leukotriene B4 and substance released by bacteria.
- complement activation
- IgG allows faster opsonization
- IgG, IgM and IgG - important antibodies in the female genital tract.
- Antigens are produced in the mucosal endometrium.

HORMONAL INFLUENCES:

In normal estrus cycle, the cervix opens under the influence of estrogens, facilitating drainage.

- Leukocytes are normally increase during estrus

In general, the uterus is more susceptible to infection when it is under the influence of progesterone; Progesterone reduces the migration of blood neutrophils and reduces phagocytosis and killing of bacteria by uterine neutrophils.

-Prostaglandins (PGE in stroma, PGF epithelia) are normally produced by endometrium.

Physical factor:

Conformation - when the pelvic area is elevated, the vulva become horizontal and sucks air and contaminants including feces into the vagina and uterus, also urine.

- ascending sepsis- common in mare.

Endometritis-inflammation limited to the endometrium

Metritis- Inflammation of all layers of uterine wall

Pyometra - may occur as a sequel to endometritis or metritis.

-accumulation of pus in the uterine lumen with a closed cervix.

Leiomyomas

Carcinoma of endometrium - rare

Lymphosarcoma- enzootic from commonly caused by bovine leukemia retrovirus commonly involves tetrad of organs:

1. heart
2. abomasums
3. lymph nodes
4. uterus

PLACENTA AND FETUS

Non - Inflammatory Lesions:

Retention of fetal membranes - prevalent in cows

Twinning - most common noninfectious cause of abortion in mares

Endometrial fibrosis - sequel of endometritis

Premature placental separation

Torsion of umbilical cord

Adventitial placentation in ruminants

Hydramnios and hydrallantois - refers to excessive accumulation of fluid in the amniotic and allantoic sacs, respectively

Embryonic and Fetal death

Mummification - one of the possible outcomes of fetal death.

-fetal retention; progressively dehydrated to become firm, dry mass, colored brown or black by degraded hemoglobin and consisting of leathery skin enclosing the harder parts of the fetus. Cause is infectious or non-infectious.

Maceration - of dead fetus requires presence of organisms responsible for fetal death.

Abortion - in animal is defined as expulsion of the fetus before development is sufficiently advanced to

allow survival. The fetus maybe dead or alive. Most often it is dead.

Still birth -delivery of dead fetus at a stage of development at which it should have been viable.

Inflammatory Disorders:

Bacterial Inflammations

Venereal Agents:

1. *Campylobacter fetus* var. *venerealis*
2. *Brucella abortus*
3. *B. canis*
4. *B. ovis*
5. *B. suis*
6. *Coxiella burnetii* - a cause of Q fever in humans; cause abortion/death of a weak lamb or kid.
7. Chlamydia - enzootic abortion
8. *Leptospira* spp.; *L. hadjo* in cattle, *L. pomona* in swine
9. *Listeria* - cause of sporadic abortions in cattle, sheep and goats. *L. monocytogenes*

Fungal causes:

Aspergillus and Phycomycetes (*Absidia*, *Mortierella*, *Mucor*, *Rhizopus*)

Viral causes:

1. Herpesvirus
2. EHV-1
3. Flavivirus
4. Parvovirus in cats
5. Parvovirus in swine causes reproductive failure (but in canine, intestinal lesion).

Herpesviruses and fetal diseases:

1. Infectious bovine rhinotracheitis
 - cattle
2. Pseudorabies virus (Aujeszky's disease)
 - pig
3. Equine herpesvirus 1 or Equine rhinopneumonitis virus
 - horses
4. Caprine, canine and feline herpesviruses
 - goats, dogs and cats, respectively

Protozoal causes:

1. *Toxoplasma gondii*
2. Trichomoniasis - *Tritrichomonas fetus*

UTERINE TUBES

Hydrosalpinx - distention of uterine tubes by clear fluid.

Salpingitis - inflammation of the uterine tubes.

Pyosalpinx - pus in the uterine tubes.

OVARY

Developmental anomalies:

1. Hypoplasia of the ovaries
2. Hypoplasia with genetic or chromosomal abnormalities
3. Valvular hamartomas
4. Cysts

Acquired ovarian lesions:

1. Oophoritis - inflammation of the ovary.
2. Ovarian bursal adhesions
 - ovarian bursa - a peritoneal pouch formed around the ovary the broad ligament and the mesosalpinx.

Lesions related to cyclic changes:

- hemorrhages in the follicles
- atretic follicles - normal phenomena in any estrus
- cystic graafian follicle
- follicular cysts
- anovulatory luteinized cyst
- supernumerary follicles

Neoplasms:

- germ cell neoplasm
- dysgerminoma - a rare neoplasm
- ovarian teratoma - rare
- granulosa cell tumors - most commonly found neoplasm in large animals
 - if the stroma predominates- "thecoma"
 - if the granulosa theca cells - "luteomas"

MAMMARY GLANDS

Inflammation:

Mastitis - inflammation of the mammary gland.

Causes:

1. *Streptococcus agalactiae*
2. *Strep. uberis*, *S. dysgalactiae*
3. *Staph. aureus*
4. *Mycoplasma* spp.

Defense mechanisms:

1. Natural milking
2. Lactoferrin
 - the major iron-binding protein of secretions is a nonspecific protective factor in milk.
3. the Lactoperoxidase-thiocyanate H_2O_2 system
 - inhibits Streps, coliforms and *S. aureus*.
4. Lysozyme
5. Alternate pathway of complement activation

Immune defenses: Defense cells in the:

1. lamina propria of the teat canal
2. rosette of Furstenberg - located at the base of the teat cistern - major immunoglobulin is IgG; abundant plasma cells
3. tumor necrosis factor (TNF), IL-1 and IL-2

Humoral mechanisms:

IgG - serum derived
IgA and IgM - synthesized in the udder

Mastitides:

1. coliform mastitis
2. *Mycoplasma* mastitis - *Mycoplasma bovis*
3. Granulomatous mastitis- bovine tuberculosis

4. Tuberculous mastitis - *Mycobacterium bovis*

Iatrogenic Granulomatous mastitis
caused by:

- *Nocardia asteroides*
- *Cryptococcus neoformans*
- *Mycobacterium spp.*
- *Candida spp.*

Nonbovine species:

- *Mycoplasma agalactia*
- *Pasteurella haemolytica*
- coliforms

Pathology of the Male Reproductive System

The testes and Leydig cells are mesenchymal derivatives.

Portals of Entry to the Male Reproductive System

- Direct penetration
- Ascending infection
- Hematogenous localization
- Peritoneal spread

Wolffian ducts – male precursors; arising from the mesonephros (the primitive kidney)

- production of testosterone is regulated by chorionic gonadotropin and luteinizing hormone.

FSH stimulated Sertoli cells – produces a glycoprotein, androgen-binding protein that fosters high testosterone concentration around germ cells for progression of spermatogenesis.

Gubernaculum – facilitates descent of the testis into the scrotum.

Abnormalities in Development:

Chromosomal abnormalities –

- Sex chromosomes can be abnormal in structure or numbers (e.g. deletion of the short arm of Y chromosome and isochromosome formation).
- Duplication of one of the sex chromosomes in an animal with Y chromosome (XYY or XXY) results in male genitalia.

Gonadal Sex Abnormalities:

Hermaphrodites – abnormal gonads; possess both testicular and ovarian tissue.

- can have separate testis and ovary or one or both organs can be mixed.
- OVOTESTIS – the term for mixed gonadal organ.
- mechanism of hermaphroditism is usually unknown.

Pseudohermaphrodites

- have chromosomes and gonads of

one sex but tubular organs modified those of the other sex.

Sex reversal =

XX males – sex reversed male

XY female – gonad is streak of ovarian stroma.

Anatomical Review:

Testis

Epididymis

Spermatic cord

Prostate gland

Bulbourethral gland

Seminal Vesicle

Urethra

Penis

b. Testis

- covered by a thick, dense, fibrous capsule, *tunica albuginea*
- which in turn is surrounded by a serous membrane called the *tunica vaginalis*.

EPIDIDYMIS -the primary storage and final maturation site for spermatozoa.

Anorchism – congenital absence of the testis.

Unilateral = monorchia

Bilateral = anorchia

Cryptorchidism – refers to incomplete descent of the testis.

- more often unilateral than bilateral.
- affected animals are prone to develop neoplasia (i.e., seminoma etc.)
- XXY karyotype (Klinefelter's) syndrome is recognized in male cats; tricolor, tortoise-shell, or calico coat types.
- hypogonadism in male; characterized by testicular hypoplasia, gynecomastia etc.

Testicular degeneration

There are many specific causes:

- 1) heat
- 2) obstruction of flow of sperm
- 3) vascular impairment
- 4) fever or local heat
- 5) burdizzo castration or torsion of spermatic cord
- 6) nutritional deficiency
- 7) hormonal abnormalities
- 8) toxicities
- 9) irradiation
- 10) Vit A and Zinc deficiency

Orchitis – inflammation of the testis

Causes:

In dog:

1. *Brucella canis*
2. Canine distemper virus
3. *Escherichia coli*
4. *Proteus vulgaris*

In Stallion:

1. Equine viral arteritis
2. Equine infectious anemia virus
3. *Salmonella abortus equi*
4. *Strongylus edentatus*

In Boar:

1. *Brucella suis*
2. *Pseudomonas pseudomallei*

In Ram:

1. *Brucella ovis*
2. *Corynebacterium ovis*
3. Sheep pox virus

In Buck:

1. *Brucella melitensis*

In Bull:

1. *Brucella abortus*
2. Bluetongue virus
3. *Chlamydia psittaci*
4. *Actinomyces pyogenes*
5. Lumpy skin disease virus
6. *Mycobacterium tuberculosis*
7. *Nocardia asteroides*

NEOPLASMS:

- a. Leydig cell tumor
The most commonly testicular neoplasm in dogs and bulls.
- b. Seminoma
the second most common canine testicular neoplasm.
- c. Sertoli cell tumor –
 - the third most common neoplasm in dogs.
 - more than 50% of cases are found in dogs with undescended testis.
 - FEMINIZING effect = gynecomastia
 - The toxic effect of excess estrogen is myelotoxicity characterized by non-regenerative anemia, granulocytopenia and thrombocytopenia.

The SCROTUM

The outpouching of the perineum composed of :

- a) skin b) dartos c) fascia
 - it is fused with the parietal layer and the tunica vaginalis

Dermatitis of the scrotal skin
– common lesion

Tunica vaginalis -extension of the peritoneum that lines the scrotal sac on the parietal layer and covers the testis, epididymis and spermatic cord.

Spermatic cord

Varicocele – local dilatation of spermatic vein.

Torsion – happen with undescended testes

Inflammation occurs following castration or contamination.

Spermatocele – local distention of epididymis that contain accumulated sperm.

Immotile cilia syndrome

Seminal vesiculitis – lead to reduced fertility.

Prostate

-dogs have prominent prostate gland.

Prostatitis – inflammation of the prostate gland

Penis and Prepuce

Abnormalities:

Phimosis – constriction of the orifice of the prepuce.

Inability to retract the prepuce over the penis because of too small preputial opening

Paraphimosis – inability to replace the prepuce over the penis because of penile swelling.

Hypospadia – abnormal urethral opening on the VENTRAL surface of the penis.

Epispadia -abnormal urethral opening on the DORSAL surface of the penis.

Corkscrew penis

Rainbow penis

Balanitis – inflammation of the penis

Posthitis – inflammation of the prepuce

Balanoposthitis – both the penis and prepuce are inflamed.

Causes: Herpesvirus

Corynebacterium renale

Other agents:

Strongyloides papillosus in bulls

Larvae of *Habronema* spp. in horses

Neoplasms:

Transmissible Venereal Tumor (TVT) – common in male animals, if present, more often found at the caudal penis

Squamous cell carcinoma of the penis

-important neoplasm in horses

Fibropapilloma – common in horses

Defenses of the Female Reproductive System

Innate defenses

- Vaginal epithelium
- Cervical barrier
- Conformation
- Myometrial tone and contraction
- Drainage of secretions
- Neutrophils
- Macrophages
- Complement
- Cytokines

Adaptive defenses

- Humoral immunity including common mucosal immune system
- Cellular immunity

Innate or Nonspecific Defenses of the Mammary Gland

Physical factors

- Sphincter and keratin of teat orifice
- Flushing action of milk

Soluble factors

- Lactoferrin
- Lysozyme
- Complement
- Cytokines

Cellular factors

- Macrophages
- Neutrophils
- Natural killer cells

Common Syndromes of Abnormal Sexual Development		
Syndrome	Species	Comments
Freemartinism	Bovine, ovine	Chimerism associated with twinning
XX sex reversal	American cocker spaniels	Autosomal recessive inheritance
XX sex reversal	Polled goats	Associated with the poll gene
Male feminization syndrome	Canine	Lack of testosterone receptors
Müllerian remnant syndrome	Miniature schnauzer	Complete internal female tubular genitalia in XY males
Failure of testicular descent	All species	Discussed under male genital system
Segmental aplasia	All species	Rare anomaly often missed at clinical examination
Gonadal hypoplasia	All species	Males especially

Portals of Entry into the Mammary Gland

Ascending ductular route

- Bacteria, fungi, parasites
- Therapeutic agents

Systemic infection and localization

- Systemic fungi, viruses, mycoplasmas, mycobacteria

Lymphatic spread

- Teat lesions

Direct penetration

- Penetrating injury

Portals of Entry into the Female Reproductive System, Especially the Uterus

Ascending infection through cervix

- At insemination
- Excessive vaginal contamination
- Postpartum and with retained fetal membranes

Hematogenous

- Localization in maternofetal interface

Descending from ovary via uterine tube

Transneural with recrudescence of herpesvirus infection

j. Special Senses

PATHOLOGY OF THE EYE AND EAR

EYE

The eye is an organ of sight. It also serves as a window through which some disease processes can be observed.

Ophthalmic pathologists - specialists

Components of the eye (ocular apparatus)

- eyeball (globe), optic nerve, and accessory structures, including the eyelids, lacrimal apparatus, orbital fasciae and oculomotor muscles.

The eyeball has:

- retina
- sclera
- choroid
- cornea

All these combine to focus light on the retina.

-the eyeball has three concentric tunics:

- fibrous
- vascular (or uvea)
- nervous

- three refractive media

- aqueous humor
- lens
- vitreous

ADNEXA OF THE EYE

A. Eyelids

- lacrimal
- sebaceous glands

B. Conjunctiva

C. Nictitating Membrane

Anomalies of the Globe

- absence of the globe (anophthalmia)
- microphthalmia - abnormally small globe
- cydopia - a dev. anomaly char. by presence of a single median eye in a single median orbital fossa.
- coloboma - congenital absence of a portion of an ocular tissue is designated "typical" coloboma.

Ocular inflammations:

Ophthalmitis (ophthalmia)

- inflammation of the eye
- panophthalmitis, endophthalmitis

CORNEA

Anomalies of the Cornea

- megalocornea - excessively large cornea
- microcornea - small than normal cornea
- dermoid - piece of skin on the cornea, conjunctiva or both

Degenerative lesions and dystrophies

- keratoconjunctivitis sicca (dry eye, xerophthalmia)

Pannus— a fibrovascular tissue that invades the cornea beneath the epithelium (occurs with corneal edema and inflammations).

Keratitis - inflammation of the cornea

Corneal Ulceration

- may be due to bacterial, viral or fungal agents

Outcome of Corneal Ulceration

1) Scars

- common sequel resulting to opacity

Classification of corneal opacities Accdg. to degree of density:

nebula-faint, clouding

macula-definite, gray opacity

leukoma-dense, white opacity

2) Keratectasia

3) Descemetocoele

4) Glaucoma and phthisis bulbi

Acquired Corneal Inflammations

Chronic superficial keratitis

Superficial indolent ulcers

Infectious keratitis (keratoconjunctivitis)

- "pink-eye"
- in cattle, *Moraxella bovis*
- in sheep, Rickettsial conjunctiva

Uveitis

- involves the iris, ciliary body and choroid

Sequels of uveal inflammation

- posterior and anterior synechiae
- blockage of filtration meshwork by synechia lead to

GLAUCOMA- characterized by high intraocular fluid pressure, optic disc lesion and eventual loss of vision.

THE LENS**Anomalies of the lens**

aphakia (absence of the lens)

Cataract - opacity of the crystalline lens and its capsule.

Luxation of the lens

- dislocation/displacement of the lens.

VITREOUS BODY

- (or hyaloid body) a transparent avascular gel filling the globe posterior to the lens.

RETINA

The 9 layers of the sensory retina:

- layers of rods and cones
- external limiting membrane
- outer nuclear layer
- outer plexiform layer
- inner nuclear layer
- inner plexiform layer
- ganglion cell layer

8) optic nerve fiber layer

9) internal limiting membrane

Retinal Detachment-accumulation of fluids, exudate, blood or neoplastic cells within the potential space (a vestige of central cavity of the optic vesicle) constitutes detachment of the retina.

OPTIC NERVE

- consist of the axons of the ganglion cells of the retina and is a white fiber tract of the CNS, extending from the eyeball to the optic chiasma.

Anomalies include

- aplasia, hypoplasia, coloboma of optic nerve
- papilledema (disc edema) - swelling of nerve head
- Optic neuritis - inflammation of the optic nerve

GLAUCOMA

- A sustained increase in intraocular pressure and the changes produced in various ocular structures.

CONJUNCTIVA

Conjunctivitis - inflammation of the conjunctiva.

EPISCLERA

- a well vascularized connective tissue between the bulbar conjunctiva and the sclera.

EYELIDS

BLEPHARITIS - inflam. of the eyelids

Hordoleum- a folliculitis due to pyogenic infection of the perifollicular tissue

Chronic inflam. of meibomian or Zeis glands (chalazion)

LACRIMAL APPARATUS

Sialodacryoadenitis-inflammation of the lacrimal gland

In rats, caused by a coronavirus.

ORBIT

Exophthalmos - deviation or protrusion of the orbit.

Cellulitis - orbital inflammation

NEOPLASMS

Conjunctival or corneal neoplasms

THE EAR

- a sensory, hearing organ

composed of the external ear, middle ear and the inner ear (labyrinth).

The internal ear

The labyrinth is divided into 2:

- Cochlea - for hearing
- Vestibular system - for equilibrium

The middle ear

- includes the tympanic cavity with its contents and auditory (eustachian) tubes.

The external ear

- consist of the auricle (pinna) and the external auditory meatus, which ends medially at the tympanic membrane.

OTITIS - ear inflammation

CLINICAL PATHOLOGY

a. Laboratory Examination of Cardiovascular System

Techniques for Erythron Evaluation:

1. RBC Count
2. Hemoglobin Content
3. Hematocrit or PCV

RBC Indices:

1. Mean Corpuscular Volume (MCV)

$$\frac{\text{PCV} \times 10}{\text{RBC Count}} \quad ; \text{ femtoliters (fl)}$$
2. Mean Corpuscular Hemoglobin (MCH)

$$\frac{\text{Hb} \times 10}{\text{RBC Count}} \quad ; \text{ picograms (pg)}$$
3. Mean Corpuscular Hemoglobin Concentration (MCHC)

$$\frac{\text{Hb} \times 100}{\text{PCV}} \quad ; \text{ grams/deciliter (dl)}$$

Sedimentation Rate (ESR) – RBCs form aggregates → Rouleaux Formation; indication of inflammatory conditions or diseases. Anemia shows increased ESR.

Erythrocyte Morphology:

1. humans, cows, sheep, dogs – typically biconcave
2. horses and cats – shallow concavity
3. goats – flat

RBC Morphological Assessment:

Abnormalities in Size – Anisocytosis (variation in size)

- common in bovines (3.6 to 9.6 μ)
- dogs – largest RBCs
- goats – smallest RBCs

Abnormalities in Shape – Poikilocytosis (variation in shape); wet blood film is suggested

1. Leptocytes – RBCs with increased surface area but not volume; membrane has the tendency to fold or become distorted; commonly present in buffy coat layer
2. Target Cells (Codocytes) – have dark-staining center surrounded by clear staining area, commonly seen in dogs; seen in chronic disease process
3. Spherocytes – RBCs with more rigid membrane, therefore resisting deformation; short life span, rapidly removed from circulation
4. RBC Fragmentation – seen in hemolytic anemia and diseases with alteration in the circulation (DIC)
 - a. Keratocyte – partially fragmented RBC
 - b. Schizocyte – one or more cuts
 - c. Knizocytes – complete cut seen in hemolytic anemia
5. Acanthocytes – RBCs with rounded projections; can be seen in healthy cows or in dogs with liver disease
6. Crenation – crenated RBCs are not of clinical significance and may be due to:
 - a. delayed drying
 - b. exposure to lytic agents
 - c. presence of hypertonic solution

Erythrocyte Inclusions

1. Reticulocytes – precursors of RBCs

Reticulocytosis – increase in number of RBCs with bluish-stippling in the center of the cell

Influences in reticular count:

- a. epinephrine treatment
- b. struggling and excitement in cats – 60-80% response

Reticulocytes are not seen in horses' peripheral blood, even with severe anemia

2. Punctate Basophilia or Basophilic Stippling – characterized by the appearance of punctate aggregations of basophilic staining materials in the form of fine or coarse granules in the RBC. They can also be seen with Nucleated RBCs (NRBCs). These are attributed to degenerative changes in the cytoplasm involving RNA in the young cells. Seen in small numbers in healthy dogs.

3. Howell-Jolly Bodies – remnants of nuclear materials; appear as refractile, single- or double-spherical bodies within RBCs. It must be differentiated from blood parasites (*Anaplasma marginale*) which are located peripherally in uniform size. Common in young pigs.

4. Polychromasia of RBCs – an overall bluish-red color rather than normally red color of RBCs; associated with anemia and are usually reticulocytes. The condition is called polychromatophilia.

5. Heinz Bodies – irregularly-shaped refractile inclusions, found in healthy blood of cats; found in dogs on daily use of prednisolone

6. Nucleated Erythrocytes do not normally occur in any species of domestic animals, except in suckling pigs up to 3 months of age.

Anemia – decrease in the number of RBCs, or hemoglobin, or both

Laboratory Finding:

1. Hemolysis – rapid with great destruction of RBC. Free Hb is present in plasma → icterus (jaundice); most consistent findings associated with hemolytic anemia
2. Hemorrhage – signs of bone marrow activity is present; nucleated RBCs appear in peripheral blood, including reticulocytes from 4th-7th day after hemorrhage
3. Bone Marrow Depression – simultaneously observed with decrease in WBCs; leptocytes appear in peripheral blood smears; reticulocytes and nucleated RBCs are not observed

Polycythemia – increase in number of RBCs to more than or above normal

1. Absolute – seen in polycythemia vera and hypoxia
2. Relative – occurs as a consequence of hemoconcentration
3. Familial – inbred Jersey cows; now increase in reticulocytes, NRBCs, and thrombocytes

Assessment of Leukocytes:

1. WBC Count
2. Differential Count

Valuable findings reflected in total differential count:

1. susceptibility of the host
2. virulence of the infecting organism
3. nature and severity of the disease process
4. systemic response of the individual
5. duration of the disease process

Normal Values:

1. Bovine
 - a. aged cattle – 5,000/ μ l
 - b. newborn calves, during excitement or stress – low WBC
 - c. pregnancy (first four months) – increase in total WBC
2. Equine
 - a. hot-blooded Thoroughbreds have higher WBC count than cold-blooded
 - b. younger ones have lower WBC count than mature ones
3. Canine
 - a. total WBC highest in young dogs (15,000-16,000/ μ l)
 - b. mature dogs – 7,000/ μ l
4. Feline – total WBC count is hard to establish since they are high excitable; resistance and excitement should be considered in interpretation of results
5. Porcine – total WBC is higher than any other domestic animal species; at 6-12 weeks is 10,000-40,000/ μ l
6. Caprine
 - a. first two weeks – 8,371/ μ l
 - b. adults – approximately 11,000/ μ l
7. Ovine – 4,000-12,000/ μ l; average of 8,000/ μ l

Description of Cells:

1. Canine – monocyte is the largest cell in the peripheral blood in the species; sex buds are seen in the segmented neutrophils
2. Feline – sex buds are occasionally seen
3. Bovine – lymphocytes have variable size; the large ones have deeply indented nuclei (Reider type cell) which appears binucleate

Physiologic factors to be considered in the interpretation of leukocyte counts:

1. age of the animal – leukocyte count is low in young pigs
2. breed or species of animal
3. degree of excitement and muscular activity exhibited by the patient at the time of blood collection
4. stage of pregnancy
5. stage of estrus
6. stage of digestion

Leukopenia – decrease in number of leukocytes below the normal values; due to:

1. viral infections (early stages)
2. overwhelming bacterial infections with diminution of neutrophils
3. endotoxins from Gram-negative bacteria

4. cachectic and debilitated states
5. physical agents such as X-rays and radioactive substances
6. chemical agents
 - a. antibiotics – chloramphenicol, penicillin, streptomycin, and oxytetracycline
 - b. analgesics – phenacetin, antipyrin, aminopyrine
 - c. inorganic chemicals – lead, benzene, bismuth, and mercury
 - d. cortisone products
 - e. antihistamine
 - f. sulfonamides

7. anaphylactic shock

Leukocytosis – is an increase in the number of leukocytes above the normal upper limit; due to:

1. generalized infections
2. localized infections
3. intoxication, including those produced by metabolic disturbances, chemicals, drugs, and venoms
4. rapidly growing neoplasms
5. acute hemorrhage, particularly into one of the body cavities (thoracic, peritoneal, joint)
6. sudden hemolysis of erythrocytes
7. trauma

Neutrophilia – is usually preceded by leukopenia in systemic infections. In localized infections produced by pyogenic organisms, it is usually greater than with systemic disease.

Lymphocytosis is due to:

1. all conditions that have neutropenia
2. physiologic leukocytosis accompanied with absolute increase in lymphocytes
3. lymphocytic leukemias
4. during recovery of certain infections
5. adrenocortical insufficiency
6. sometimes occurs following vaccination
7. hyperthyroidism

Lymphopenia may be caused by:

1. certain viral diseases
2. stress
3. ionizing radiation or immunosuppressive drugs
4. ACTH
5. loss of efferent lymph

Monocytosis may be caused by:

1. chronic diseases
2. infectious disease like erysipelas and listeriosis in swine, brucellosis in other animals
3. monocytic leukemias
4. ACTH treatment in dogs
5. in association with acute stress reactions in dogs and cats
6. hyperadrenocorticism

Eosinopenia may be due to:

1. any stress condition
2. after administration of ACTH
3. hyperactivity of the adrenal gland

Eosinophilia is seen in the following conditions:

1. parasitism and allergic reactions
2. anaphylactic reactions
3. adrenocortical insufficiency

4. recovery of some acute infections
5. granulocytic eosinophilic leukemias
6. neoplasms of the ovary, serous membrane, and bone
7. splenectomy in dog
8. eosinophilic gastroenteritis in the dog
9. eosinophilic myositis
10. eosinophilic granuloma in cats
11. in association with estrus in some dogs

Basophilia is rare. If it does occur it is associated with eosinophilia and is the result of a basophilic granulocytic leukemia.

Leukocytic Response:

- Shift to the Left – an increase in the number of neutrophils in the peripheral circulation; there are two types:
 - a. Regenerative Left Shift – is characterized by an absolute increase in neutrophils accompanied by the appearance of immature neutrophils in the peripheral circulation
 - b. Degenerative Shift to the Left – there is a normal, low, or falling total leukocyte count accompanied with marked shift to the left, with absolute number of immature neutrophils exceeding the mature neutrophils

Leukocyte response to Corticosteroids:

1. Dog – 4x increase in neutrophils with 50-60% reduction in lymphocytes and disappearance of eosinophils; 3x increase in monocytes
2. Horse – increase in neutrophils and decrease in lymphocytes; no monocytosis is present
3. Cow – neutrophilia, lymphopenia, eosinopenia, and monocytosis
4. Cat – neutrophilia, lymphopenia, and some elevation of monocytes

Neoplasia of Hematopoietic Tissues:

1. Bovine – neoplasms in this species are almost exclusively of lymphocytic origin (lymphosarcoma, lymphoblastoma, lymphocytoma, malignant lymphoma, and simply as leukemia)
2. Feline – neoplasms of the hematopoietic tissues occur with some frequency and usually are of one of the following types: lymphocytic, granulocytic, and monocytic. Association with feline leukemia virus with neoplasia of the hematopoietic system is a well-established fact.
3. Canine – usually limited to the lymphocytic type, although cases of granulocytic and monocytic leukemia have been recorded
4. Equine – neoplasia of hematopoietic tissue is rare, occasionally lymphocytic
5. Porcine – lymphocytic involvement is the most common type

Laboratory Techniques in Erythrocytic Examination:

Sample Collection:

- Care must be taken to avoid hemolysis, to avoid alteration of results
- Use clean, dry paraphernalia in collecting blood
- Determinations should be done of fresh blood

Anticoagulants:

1. EDTA – dipotassium and disodium salts of ethylenediaminetetraacetic acid; acts as a chelating agent and prevents the coagulation of blood by combining with calcium. 1 mg/ml of blood is sufficient to preserve the stainability of cells. Excess EDTA in the sample can cause alteration on PCV. 1 ml/5 ml of blood.
2. Oxalates – a combination of ammonium and potassium oxalates (double oxalate) can prevent coagulation of blood by combining with calcium. 1 ml (dried)/10 ml of blood
3. Heparin – prevents coagulation of blood by interfering with the conversion of prothrombin to thrombin. A syringe rinse with 10% heparin is enough to prevent coagulation of 5 ml of blood. It is the most expensive anticoagulant and is effective for only 10-12 hours.
4. Sodium Fluoride – at a concentration of 5 mg/dl is used as an anticoagulant and preservative of glucose

A. Total Erythrocyte Count (μ l)

1. Hemocytometer Method – blood is drawn up to the 0.5 mark and diluting fluid (Hayem's) is drawn up to the 101 mark. The total number of cells in 5 squares in the center of the hemocytometer are determined and multiplied by 10,000. The inherent error is $\pm 20\%$.
2. Electronic Counting Methods – more accurate

B. Hemoglobin Determinations (gm/%)

1. Acid Hematin Method – depends upon the conversion of hemoglobin to acid hematin. 0.1N HCl is added to whole blood, and the resulting brownish-yellow mixture is matched to the standard colorimeter or comparator
2. Tallquist Hemoglobin Scale and Dare Hemoglobinometer – utilizes direct matching method
3. Oxyhemoglobin Method – utilizes the Spencer Hemoglobinometer which uses a green filter to measure oxyhemoglobin by light absorption
4. Cyanmethemoglobin Method – probably the most accurate and widely used technique for hemoglobin determination; done on a photoelectric colorimeter

C. Determination of Packed Cell Volume (%)

1. Wintrobe Method – utilizes Wintrobe tube
2. Microhematocrit Method – utilizes capillary tubes and special high speed centrifuge
3. automated estimation of PCV

Techniques for Total Leukocyte Count (leukocyte/ μ l):

1. Hemocytometer Method – the diluting fluid used are glacial acetic acid or N/10 HCl (0.1N HCl). The total number of leukocytes counted in 4 large corner squares are counted and multiplied by 50.
2. Electronic Method

Peripheral Blood Smear

- Description and estimation of cells in the peripheral blood is usually done using stained blood films. The most widely used stains in preparing blood smears are Wright and Giemsa stains. In differential counting of leukocytes, 100 leukocytes are counted. The Meander System for examining stained blood film is used to ensure that all areas of the slide are examined.

Bone Marrow Examination:

Methods of Collection:

1. Dog – iliac crest and anterolateral part of the humerus
2. Cat – anterolateral part of the humerus; preferred site is the femur
3. Cattle – rib or sternum near the center of one sternbrae (11th or 12th rib)
4. Horse – rib or sternum
5. Sheep – sternum

Preparation of the Smear:

- Films are made in a manner similar to that used in preparation of films of peripheral blood. Any polychrome stain like Wright's, Wright-Giemsa or May-Grunwald-Giemsa may be utilized. Bone marrow smears should be exposed to stains for a longer period of time than is necessary for peripheral blood smears.

Examination of the Marrow Film:

- In making a differential count of bone marrow, a minimum of 500 cells should be examined. It is preferable to count 1,000 cells.

Bone Marrow

Bone marrow produces RBC, platelets, eosinophils, basophils, monocytes, and neutrophils. It is a minor site of production of lymphocytes and plasmacytes. Bone marrow examination is indicated in the presence of:

1. leukopenia
2. non-regenerative anemia
3. thrombocytopenia
4. when abnormal cell types appear in the peripheral blood smear.

Limitations of BM examination:

1. bone marrow is difficult to obtain
2. almost impossible to make a quantitative evaluation of cellular elements
3. accurate interpretation of BM examination is dependent upon the experience and ability of the individual examining the bone marrow smear.

Cell Identification:

- Primitive cells are usually larger than mature cells
- In primitive granulocytic cells nuclei are round or oval as they mature they have slight indentation.
- In color – nuclei of young cells are rich in DNA and have red or reddish-purple tinge; as they differentiate they become predominantly blue and stains more darkly.
- Stem cells – are undifferentiated mesenchymal cells.

Interpretation of BM examination (the following should be evaluated):

1. Degree of cellularity – difficult to determine unless spicules of marrow are present.
2. Presence of all series – normally all cell series are well represented.
3. Morphologic abnormalities
4. Sequence development – mature forms exceed immature cell types.
5. M : E ratio (Myeloid : Erythroid elements) – normally 1:1
6. Abnormal cells
 - a. Hypoplasia – generalized hypoplasia is usually accompanied by decrease in the number of all cell types (pancytopenia). Seen in:
 - 1) Canine ehrlichiosis
 - 2) FeLV
 - 3) Feline panleukopenia virus infection – hypoplastic marrow
 - b. Aplasia – there is complete lack of cell production associated with:
 - 1) use of toxic drugs
 - 2) viral infection
 - 3) exposure to high doses of radiation
 - 4) plant toxins
 - c. Hyperplasia – marrow hyperplasia seldom occurs simultaneously. Inflammatory processes lead to granulocytic hyperplasia, anemia results to erythroid hyperplasia. Megakaryocytic hyperplasia occurs when there has been consumption, destruction or sequestration of thrombocytes.

Bone Marrow Findings in Diseases:

- Anemia – increased immature erythrocytes in BM. Hemolytic anemia in dogs results to increased erythropoiesis and punctate basophilia.
- Severe hemorrhagic or hemolytic anemia in cats result to more prominent prorubricyte and basophilic rubricytes, with increased number of polychromatophilic rubricytes.
- Vitamin B₁₂ and Folic Acid deficiency in cats results to megaloblastic erythropoiesis.
- Anemia in horses produces regenerative M:E ratio, and polychromatophilic and basophilic rubricytes increase.
- Lead poisoning – metarubricyte maturation is arrested
- Inflammation – granulopoiesis is marked with more prominent neutrophil hyperplasia

HEMOSTASIS AND COAGULATION

Principal factors involved in hemostasis:

1. vascular factors – ie integrity of vessel walls
 - a. vasoconstriction
 - b. exposed collagen fibers
 - c. thrombocytes
2. thrombocytes
3. clotting mechanism

Thrombocytes (blood platelets) are small, cytoplasmic fragments of megakaryocytes and are found in the circulating blood. Aside from the bone marrow, the spleen and lungs are also sites of megakaryocyte development. Normal range in various species of animals is 175,000-500,000/ μ l. Serotonin and histamines are released in the blood by disintegrating platelets which act as vasoconstrictors, and contribute to the overall hemostatic reaction. A platelet substance responsible for clot retraction is a contractile protein called thrombasthenin.

Clotting Mechanism – the mechanism for blood coagulation consists of:

1. Intravascular or Intrinsic System – Factors VIII, IX, XI, and XII
2. Extravascular or Extrinsic System – Factors III and VII. Factor VII is activated by tissue thromboplastin (Factor III) in the presence of calcium ions.

General considerations in laboratory tests for coagulation defects:

1. clean glassware and equipment should be used
2. avoid too much pressure during blood extraction

Coagulation Time:

1. Lee-White Method
2. Capillary Method
3. Activated Coagulation Time (ACT) Method – more sensitive; utilizes a diatomaceous earth as a surface-activating agent

Bleeding Time – 2-5 minutes in domestic animals

Interpretation of Coagulation Time – prolonged in:

1. Factor I, VII, IX defects
 2. Von Willebrand's Disease (sometimes normal)
 3. severe liver disease
 4. Vitamin K deficiency
 5. thrombocytopenia
 6. advance stages of DIC
 7. presence of circulating anticoagulants
 8. uremia (occasionally)
- Interpretation of Bleeding Time – prolonged in:
1. defects in blood vessel wall
 2. platelet defects
 3. severe liver disease
 4. administration of large doses of anticoagulants
 5. uremia

Platelet Counting and Evaluation:

- Pipette used for erythrocyte count is also used in counting platelets, and the diluting fluid is Rees-Ecker. The entire central ruled area of the hemocytometer is used. Number of thrombocytes counted is multiplied by 1,000 to get the total platelet count.

Clot Retraction – retraction of formed clot is influenced by:

1. number and function of platelets
2. fibrinogen content
3. chemical and enzymatic factors, as well as the container

Clot Retraction is Impaired in:

1. afibrinogenemia
2. thrombocytopenia – less than 100,000/ μ l
3. some coagulation defects

Classification of Anemia

	Regenerative		Nonregenerative
CBC hallmarks	Reticulocytosis (except horses) Polychromasia, anisocytosis $\pm \uparrow$ MCV, $\downarrow$ MCHC		Absence of reticulocytosis $\pm \downarrow$ MCV, $\downarrow$ MCHC (iron deficiency*)
	Hemorrhage	Hemolysis	
Causes	Trauma Hemostasis defect Neoplasia GI ulceration Parasitism	Extravascular: immune-mediated; hemoparasitism toxicosis; PK, PFK deficiencies Intravascular: immune-mediated; hemoparasitism; toxicity, enzymatic (e.g., bacterial phospholipases); hypophosphatemia; PFK deficiency (with alkalemia)	Anemia of chronic disease: $\downarrow$ iron availability; $\uparrow$ RBC turnover Altered humoral signaling: $\downarrow$ erythropoietin; endocrinopathies Ineffective erythropoiesis: immune-mediated; feline leukemia virus Primary production problem: toxicity; myelophthisis; pure red cell aplasia; pancytopenic disorders Iron deficiency*
Notes	Evaluate in concert with history, physical exam, other lab data. Fluid shift occurs within hours of hemorrhage. Regeneration takes approximately 3-4 days to become evident in blood, 7-10 days to reach maximum response.		Evaluate in concert with history, physical exam; other lab data may be indicated. Bone marrow evaluation may be indicated.

CBC, Complete blood count; GI, gastrointestinal; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; PFK, phosphofructokinase;

PK, pyruvate kinase; RBC, red blood cell.

*Iron deficiency anemia is sometimes regenerative.

Common Erythrocyte Morphologic Abnormalities

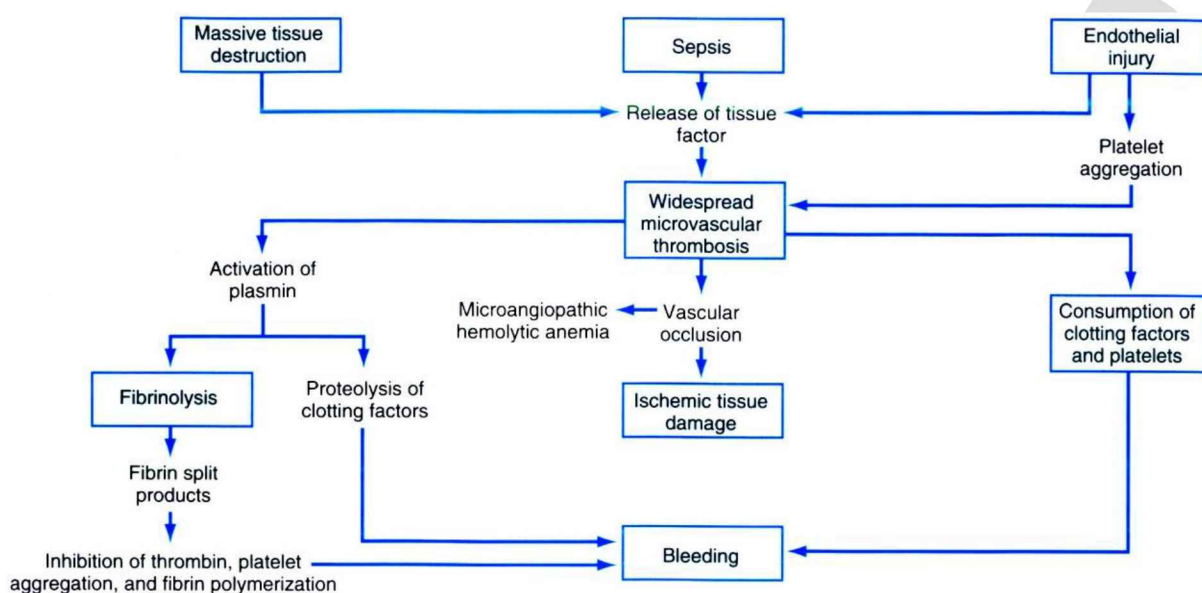
Term	Description	Condition(s) Commonly Associated with Increased Numbers of Abnormal RBCs
Macrocyte	Abnormally large	Regenerative anemia FeLV infection (cats) Congenital in some poodle dogs
Microcyte	Abnormally small	Iron deficiency Portosystemic shunts Normal in Akita and Shiba dogs
Polychromasia	Bluish color	Reticulocytosis (regenerative anemia)
Basophilic stippling	Fine punctate inclusions	Lead toxicity Regenerative anemia (especially ruminants)
Howell-Jolly body (nuclear remnant)	Small, round, blue-black inclusion, usually off-center	Regenerative anemia Splenic dysfunction
Hypochromasia	Increased pallor and deformability	Iron deficiency
Heinz body	Pale round inclusion, may bulge from cell margin; stains blue with new methylene blue	Oxidative damage
Poikilocyte	Nonspecific term for shape abnormality— specific types of poikilocytosis listed below	See below
Spherocyte	Appears abnormally small with uniform staining	Extravascular hemolysis
Schistocyte	Small, irregular RBC fragment, often crescent shaped	Microangiopathies (e.g., DIC, hemangiosarcoma, glomerulopathy) Increased RBC deformability (e.g., iron deficiency)
Acanthocyte	Few irregular projections	Abnormal lipid metabolism (e.g., liver disease) Microangiopathies (as per schistocytes) Increased RBC deformability (as per schistocytes) Common normal finding in young goats
Echinocyte	Many relatively uniform projections	Usually in vitro artifact Normal in pigs
Eccentrocyte	Eccentric staining	Oxidative damage
Leptocyte	Thin, often hypochromic and/or folded	Iron deficiency
Codocyte ("target cell")	Area of dense staining within central pallor	Liver disease
Keratocyte	Intact or ruptured "blister"	Liver disease Conditions causing schistocytosis and/or acanthocytosis

DIC, Disseminated intravascular coagulation; FeLV, feline leukemia virus; RBC, red blood cell.

Common Causes of Uniform Splenomegaly in Domestic Animals

Animal	Congestive (Bloody) Spleen	Firm (Meaty) Spleen
Horse	Septicemia Anthrax Salmonellosis (peracute) Hemolytic disease EIA (acute)	Septicemia Salmonellosis Hemolytic diseases EIA Immune-mediated hemolytic anemia Neoplasms Lymphoma Metastatic neoplasms
Cattle and sheep	Septicemias Anthrax Salmonellosis (acute) Hemolytic disease Babesiosis (acute)	Septicemia Salmonellosis Hemolytic diseases Babesiosis (subacute) Anaplasmosis Trypanosomiasis Hemotropic mycoplasmosis Neoplasm Lymphoma
Pig	Septicemia Salmonellosis (peracute) Splenic torsion	Septicemias Salmonellosis Erysipelas Hemolytic disease Hemotropic mycoplasmosis Neoplasm Lymphoma
Dog and cats	Barbiturate euthanasia or anesthesia Gastric torsion Neoplasms Hemangioma (nodular) Hemangiosarcoma (nodular)	Hemolytic disease Immune-mediated hemolytic anemia Hematopoietic neoplasia Mast cell neoplasia (cat) Lymphoma Histiocytic sarcoma Granulomatous disease Histoplasmosis Lymphoid hyperplasia (nodular) Amyloidosis

EIA, Equine infectious anemia.



Schematic diagram of the pathophysiology of disseminated intravascular coagulation.

b. Laboratory Examination of Digestive System

LABORATORY EVALUATION OF HEPATIC DISORDERS

Assessment of hepatocellular injury

A) Causes of injury: many (few examples given)

- Degenerative
- Autoimmune, anomaly
- Metabolic
- Neoplastic
- Infectious, inflammatory
- Toxic, trauma
- Hypoxia
- Chronic active hepatitis, portosystemic shunt
- Diabetes mellitus
- Lymphoma
- Tyzzers disease (Clostridium), chronic active hepatitis
- Poisons

B) Hepatocellular enzymes: leakage enzymes

1. Alanine aminotransferase (ALT)

- a. Useful in dogs, cats, primates, rabbits and rats
- b. NOT useful in ruminants, horses or pigs due to low ALT activity in the liver
- c. Cytoplasmic enzyme: rapidly released after insult by
 - i. Leakage through intact membrane, e.g., hypoxia
 - ii. Cell lysis/necrosis
- d. Magnitude of increase is proportional to number of hepatocytes injured, but NOT to the reversibility of the damage NOR to the histopathology.
- e. Continual increase of enzyme activity indicates ongoing injury; however, hepatic regeneration also can increase enzyme activity.
- f. It is suggested that a greater than 50% reduction in enzyme activity within one half-life indicates recovery (canine half-life, 2-3 days; feline half-life 3.5 hours). If massive

necrosis is present, however, enzyme activity may decrease due to loss of hepatocytes.

- g. Activity may be normal or minimally increased with hepatic cirrhosis.

- h. Increased activity (induction or leakage) occurs with use of certain drugs in absence of significant hepatocellular pathology, e.g., phenobarbital, glucocorticoids; however, both drugs also can be hepatotoxic.

- i. Muscle contains ALT, but increased activity is not often seen with muscle injury.

2. Aspartate aminotransferase (AST)

- a. SENSITIVE for hepatocellular injury in most species; however, it is not SPECIFIC as it is also found in striated muscle and erythrocytes.
- b. Primary liver enzyme used in large animals despite multiple tissue sources.
- c. Cytoplasmic and mitochondrial isoforms: the former is released by leakage or lysis, whereas the latter is only released by cell lysis.
- d. Interpret in conjunction with other liver and muscle enzymes and presence/absence of pathologic hemolysis or hemolyzed sample.
- e. Interpretation of increased AST: items d.-g. under ALT apply to AST.
- f. AST activity that approaches ALT indicates severe liver injury in dogs and cats or concurrent hepatic and muscle injury.

3. Sorbitol dehydrogenase (SDH)

- a. Liver-specific in all species, primarily used in large animals in place of ALT
- b. Located in the cytosol
- c. Interpretation of increased SDH activity: items d.-g. under ALT apply.
- d. Half-life of AST (canine half-life, 12 hrs; feline half-life, ~1.5 hrs; bovine half-life, ~2 days; equine half-life, ~2 days)
- e. Low enzyme stability *in vitro* hampers use of this enzyme.

4. Lactate dehydrogenase (LDH): found in liver and many other tissues (not SPECIFIC for

hepatocellular injury), provides little useful information.

5. Glutamate dehydrogenase (GLDH): mitochondrial enzyme that is liver-specific in all species, but not widely used in the US.

NOTE:

- Enzyme half-lives determined by methods that may not mimic what occurs *in vivo*.
- For enzymes with half-lives measured in days, recheck activity in ~4-6 days.
- For enzymes with half-lives measured in hours, recheck activity in ~2-3 days.
- For enzymes with half-lives measured in minutes, cannot be detected in serum.

Assessment of biliary disorders: cholestatic disease (impaired bile flow)

A) Causes of cholestasis

- 1) test: physical obstruction of bile flow that occurs intra- or extra-hepatic, e.g., hepatic lipidosis, gall stone
- 2) Functional impairment of bile acid secretion into canaliculus reduces bile flow, e.g., systemic bacterial infections can reduce bile acid secretion.

B) Cholestatic (inducible or biliary) enzymes: enzymes located on the canalicular membrane of hepatocyte and biliary epithelium whose synthesis is induced by cholestasis (and by some drugs).

1. Serum alkaline phosphatase (SAP or ALP or AP)

- a. Enzyme isoforms: special assays exist for isoforms; however, this is only occasionally useful in determining specific cause of increased SAP

i. Liver SAP isoform

- a. Makes up most of SAP in healthy adult animals of most species
- b. Activity increases with cholestasis and with certain drugs

ii. Corticosteroid induced SAP isoform: only present in dogs

- a. Makes up to 10-30% of total SAP in healthy dogs
- b. Increased activity of total SAP within 3-4 days upon exposure to corticosteroids and certain drugs
- c. Liver SAP isoenzyme increases first followed by corticosteroid-induced SAP isoenzyme in 7 days

iii. Bone SAP isoform:

- a. Makes up a small amount of SAP in healthy adult animals
- b. Total SAP is 2-3X higher in young growing animals due to the presence of more bone SAP, especially horses
- c. Increases with bone pathology (~2-4X), e.g., fracture healing, bone tumors, metabolic bone disease

iv. Intestinal SAP: important serum source of SAP in rodents

v. Kidney and placenta SAP: generally do not appear in serum due to very short half-lives (minutes)

b. Species differences

i. Dogs: half-life of SAP is relatively long (2-3 days), which results in the potential for marked and prolonged increases in activity

ii. Ruminant: wide reference interval results in low sensitivity for cholestasis

iii. Equine: low sensitivity for cholestasis

iv. Cats: half-life is very short (6 hrs) so even minor increases are significant

c. Increases in total SAP may indicate any of the following

i. Cholestasis: intra- or extrahepatic

ii. Exposure to steroids in dogs

a. Administration of exogenous steroids (parenteral, oral, topical)

b. Hyperadrenocorticism (endogenous)

c. Stress (endogenous)

iii. Exposure to certain drugs, e.g., Phenobarbital

iv. Bone pathology

v. Young animal

vi. Hyperthyroidism in cats (bone isoform)

vii. Colostrum ingestion in dogs

2. Gamma glutamyltransferase (GGT)

viii. Neoplasm, especially those that produce PTHrP

a. Serum GGT comes almost exclusively from liver.

b. Increased GGT activity is more **SPECIFIC** for cholestasis but less **SENSITIVE** than SAP.

c. GGT is also found in the kidney, where it is released into the urine (not blood).

d. Causes of increased GGT activity:

i. Cholestasis: intra- or extrahepatic

ii. Administration of certain drugs, e.g., steroids, phenobarbital

iii. Stress or hyperadrenocorticism (dogs)

iv. Biliary hyperplasia

v. Colostrum ingestion in calves and puppies will increase GGT activity into the low 100's IU/L

vi. Foals have higher GGT than adult horses (1.5-3X)

C) Other analytes

1. Bilirubin:

a. May or may not increase with simple cholestasis (see next section)

b. Cholestatic enzymes increase prior to an increase in bilirubin during cholestasis in dogs, whereas in cats and horses bilirubin increases first.

2. Cholesterol (hypercholesterolemia): Increased synthesis or decreased clearance, see VII.B.2.c for causes of hypocholesterolemia

3. Bile acid: may or may not increase with cholestasis

Assessment of hepatic uptake, conjugation, and secretion function: bilirubin and jaundice

A) Bilirubin metabolism

1. Source: breakdown of hemoglobin and other heme proteins occurs within macrophages primarily in liver, spleen, and bone marrow the

resulting unconjugated bilirubin (Bu) is non-water soluble and is carried in the plasma noncovalently bound to albumin.

2. Uptake: at the sinusoidal membrane of the hepatocyte, unconjugated bilirubin dissociates from albumin and is taken up by specific receptors.

NOTE: Rate limiting step in large animals: results in a larger proportion of Bu during hyperbilirubinemia whatever the cause of jaundice.

3. Conjugation: bilirubin is conjugated to amino acids/sugars, which increases water solubility and results in the formation of conjugated bilirubin (Bc).

NOTE: the very last function to be lost

4. Excretion: Bc is transported by specific transporters through the hepatocyte basal membrane into the canaliculi where it travels to the gall bladder via the bile duct.

NOTE: Rate limiting step in small animals: results in a larger proportion of Bc during hyperbilirubinemia under most circumstances.

5. Enterohepatic circulation: Bc is excreted into the duodenum with bile and metabolized by enteric bacteria to urobilinogen and then to stercobilinogen.

- a. Feces: stercobilinogen is further metabolized to stercobilin, that with Bc and urobilinogen, imparts the characteristic color to feces.

- b. Urine:

- i. Urobilinogen: some is reabsorbed by the intestine and either:

- Cleared by the liver and re-secreted in bile
- Filtered by the kidney and excreted in the urine

- ii. Conjugated bilirubin, when increased, is filtered by the kidney and appears in the urine

- iii. Unconjugated bilirubin associated with albumin is NOT filtered by the kidney and DOES not appear in the urine.

- iv. In dogs, a small amount of Bu is taken up by renal tubule cells, conjugated, and excreted in the urine, i.e., urine bilirubin of 1+ to 2+ is normal in concentrated urine in dogs, but NOT in other species.

6. Bile consists of bile acids, i.e., lipids, electrolytes, water and water-soluble wastes and is necessary to emulsify lipids for digestion.

7. Delta bilirubin: bilirubin that is covalently bound to albumin, which alters its catabolism, i.e., same half-life as albumin

8. Analysis:

- a. Serum total bilirubin (Bt) = conjugated (Bc) + unconjugated (Bu) + delta (B δ)

- b. Bu makes up the greatest portion of Bt in absence of disease.

- c. Separate measurement of conjugated and unconjugated bilirubin can be done.

- i. Direct bilirubin measurement = conjugated bilirubin (plus B δ)

- ii. Total bilirubin – direct bilirubin = indirect bilirubin

- iii. Indirect bilirubin = unconjugated bilirubin

- iv. Individual measurement of direct (conjugated) and indirect (unconjugated) bilirubin is not very useful in determining the cause of hyperbilirubinemia (see causes of hyperbilirubinemia below). It is discussed in order to highlight pathophysiologic mechanisms.

- d. Free hemoglobin in serum or plasma (hemolyzed sample) will cause a false increase in measured bilirubin.

- e. Prolonged exposure to light will falsely decrease measure bilirubin and urobilinogen.

- B) Causes of hyperbilirubinemia

1. Prehepatic

- a. Cause: increased delivery of bilirubin to hepatocytes primarily as a result of hemolytic anemia or less often secondary to massive internal hemorrhage, e.g., hemoabdomen

- b. Hyperbilirubinemia (Bt) and jaundice occurs when liver capacity to process bilirubin is overwhelmed (>30-60 fold increase).

- i. Early: saturation of sinusoidal transporter with primary increase in Bu

- ii. Later: increased conjugation and excretion with saturation of basal transporters and regurgitation of Bc into circulation (dogs and cats)

- c. Hepatocytes may sustain hypoxic injury from the anemia resulting in impaired excretion of Bc leading to further increases in Bt.

- d. Complete blood count: regenerative anemia; RBCs may have morphologic changes consistent with hemolytic disease, e.g., spherocytes, Heinz bodies, hemoparasites

- e. Serum: Increased Bt, mild to moderate, occasionally marked

- i. Early: increased Bt with Bu > Bc

- ii. Later: increased Bt with Bu = Bc (dogs and cats)

- iii. Secondary hepatobiliary disease: increased Bt with Bc $\geq$ Bu and increased ALT and SAP

- f. Urine: increased bilirubin and urobilinogen, urine is dark gold

- g. Fecal: may detect orange color from increased pigments

- h. Intravascular hemolysis results in pink or red serum and urine, if rate of hemolysis exceeds liver capacity to process bilirubin, jaundice will occur.

2. Hepatic

- a. Cause:

- i. Hepatocellular damage that impairs uptake, conjugation, or excretion of bilirubin, e.g., severe toxic or infectious hepatitis

- ii. Impaired flow of bile in intrahepatic biliary system (mechanical or functional), e.g., hepatic lipidosis, feline cholangiohepatitis

- b. Hyperbilirubinemia occurs when >50% of bile flow is obstructed

- c. Serum: increased Bt, mild to moderate

- i. Increased Bt with Bc >> Bu (dogs and cats)

- ii. Increased ALT and/or increased SAP

- d. Urine: increased bilirubin +/- urobilinogen, urine is dark gold
- e. Feces: changes are not consistent
- f. Definitive diagnosis: imaging, cytology and/or biopsy
 - 1. Post-hepatic
- a. Cause:
 - i. Partial or complete obstruction of bile duct with regurgitation of Bc into circulation and minor reduction in Bu uptake
 - ii. Leakage of bile from ruptured gall bladder or bile duct
- b. Examples: gall stone, pancreatic abscess/neoplasm, regional lymphadenopathy
- c. Usually leads to intrahepatic disease
- d. Definitive diagnosis made by imaging and exploratory surgery
- e. Serum: increased Bt, moderate to marked (dogs and cats)
 - i. Increased Bt with Bc >>> Bu
 - ii. Increase in SAP is often greater than the increase in ALT
- f. Urine:
 - i. Bilirubinuria
 - ii. Absence of urobilinogen in theory; however, dipstick is unable to detect a decreased urobilinogen
- g. Feces: acholic (gray) in small animals if obstruction is severe/chronic
- h. Definitive diagnosis: imaging and exploratory
- C) Clinical aspects
 - 1. Plasma begins to appear icteric when bilirubin is >1-2 mg/dL
 - 2. Tissue jaundice becomes apparent when total bilirubin is >2-3 mg/dL (depending on species).
 - 3. Increased bilirubin is first detected in urine (low renal threshold), followed by serum and then tissue.
 - 4. Serum bilirubin will return to normal prior to resolution of tissue jaundice.
 - 5. Hyperbilirubinemia that persists after resolution of disease may be due to longer half-life of B_o.
- D) Hyperbilirubinemia in large animals
 - 1. Horse
 - a. Higher reference interval for bilirubin than other species resulting in a more yellow color of plasma/serum
 - b. No gall bladder
 - c. Predominantly Bu (>60%) regardless of cause
 - d. Anorexia will cause mild-moderate hyperbilirubinemia (<8 mg/dL).
 - i. Increased triglycerides seen with anorexia complete with bilirubin for uptake by hepatocytes
 - ii. Lower levels of glucose reduce its availability for conjugation to bilirubin
 - e. May be mildly increased with intestinal obstruction
- 2. Ruminants
 - a. Jaundice is usually prehepatic in origin, i.e., hemolytic anemia.

- b. Hepatic jaundice occurs very late in liver disease.
- c. Predominantly Bu regardless of cause.
- d. Anorexia will cause mild-moderate hyperbilirubinemia (<1.4 mg/dL).

Assessment of hepatic function: portal clearance, synthetic function and phagocytic function

- A) Assessment of portal clearance
 - 1. Bile acids: differences
 - a. Metabolism of bile acids:
 - i. Function:
 - a. Major component of bile and necessary for emulsification and absorption of dietary lipids
 - b. Primary route of cholesterol catabolism
 - c. Toxic to cell membranes (phospholipids)
 - ii. Synthesis and secretion: made from cholesterol, conjugated to amino acids, and secreted into the bile duct by unique transporters
 - a. Cholic acid (primary)
 - b. Chenodeoxycholic acid (primary), hyocholic acid (swine)
 - c. Deoxycholic acid (secondary)
 - d. Lithocholic acid (secondary)
 - iii. Enterohepatic circulation: very efficient
 - a. Most bile acids are reabsorbed from the ileum with a small fraction de-conjugated or de-hydroxylated in the large intestine and subsequently reabsorbed.
 - b. Travel to liver in portal circulation where 95% are taken up by unique transports on the sinusoidal hepatocyte membrane
 - c. Re-conjugated and re-secreted into bile (secondary bile acids)
 - iv. Factors that affect metabolism

Factors that affect metabolism and measurement of bile acids

Factor	Potential effect on serum bile acid levels
1. Enteric bacteria	Bacterial overgrowth increases de-conjugation and thus the amount of unconjugated bile acids reabsorbed.
2. GI function	Delayed gastric emptying may alter absorption profile. Increased GI motility decreases absorption. Infiltrative ileal disease may impair absorption decreasing bile acids.
3. Gall bladder	Spontaneous contraction will transiently increase serum bile acids.
4. Meal fat content	Inadequate fat in meal may prevent gall bladder contraction.

- b. Diagnostic assay
 - i. Purpose:
 - a. Assess ability of hepatocytes to take-up, conjugate and secrete bile acids; therefore NOT indicated in icteric patient
 - b. Assess enterohepatic circulation, i.e., portal blood flow to liver
 - ii. Baseline fasting serum bile acids: normally very low (canine <5 μmol/L)
 - iii. Bile acid challenge: more SENSITIVE
 - a. Measure fasting bile acids in serum

- b. Administer small, high fat meal to stimulate gall bladder contraction
- c. Measure post-prandial bile acids in serum 2 hours later
- d. Results:
 - 1. Normal: after transient rise, bile acids return to normal post-prandial levels (canine <15.5 $\mu\text{mol/L}$) within 2 hours
 - 2. Abnormal: increase in post-prandial bile acids, fasting bile acids may be normal or increased
 - 3. A mild increase in fasting bile acids is interpreted as normal if post-prandial sample is within the post-prandial reference interval.
- iv. Free hemoglobin (hemolyzed sample) falsely decreases measured bile acids.
- v. Lipemia falsely increases or decreases results depending on the method.
- vi. Sensitivity and specificity depend on reference interval used.
- c. Causes of increased serum bile acid
 - i. Decreased clearance from portal blood
 - a. Reduced hepatic mass
 - b. Portosystemic shunt
 - ii. Decreased secretion into bile (cholestasis): more sensitive than bilirubin
 - iii. Other: minor changes may be seen with inflammatory bowel disease, hyperadrenocorticism, pancreatitis, and other extrahepatic disorders
- 2. Ammonia (NH_3)
 - a. Metabolism
 - i. Source: protein digestion, absorption from intestinal tract and deamination of amino acids
 - ii. Metabolism: NH_3 is taken up by the liver and detoxified primarily through synthesis of urea, which is then excreted in the urine
 - iii. Factors that affect metabolism: hepatic function and portal circulation
 - b. Diagnostic assay:
 - i. Purpose:
 - a. Assess hepatocellular uptake of ammonia
 - b. Assess portal circulation to liver
 - ii. Fasting plasma ammonia: ref. interval in canine, 25-94 $\mu\text{mol/L}$
 - iii. Ammonia challenge: more SENSITIVE
 - a. Measure fasting ammonia
 - b. Administer oral or rectal NH_4Cl
 - c. Measure plasma ammonia 30 minutes later
 - d. Results: post-sample similar to resting values
 - e. Contraindicated when fasting ammonia is increased
 - iv. Method: call laboratory for specifics
 - a. Collect EDTA or heparinized plasma in chilled vial.
 - b. Place in ice bath immediately.
 - c. Separate plasma in cooled centrifuge ASAP.
 - d. Run assay STAT (<4 hrs) or freeze (1-2 days) for delayed testing.
 - e. Ammonia will INCREASE in improperly handled specimens.
 - f. Free hemoglobin (hemolyzed sample) causes falsely increased ammonia.
- c. Causes of increased ammonia
 - i. Decreased clearance from portal circulation
 - a. Reduced functional hepatic mass
 - b. Portosystemic shunt
 - c. Hereditary deficiency in urea cycle enzymes (rare)
 - ii. Increased production or intake
 - a. Postprandial (transient)
 - b. Urea toxicity in ruminants (feed additive)
 - c. Improper handling of sample
 - d. Strenuous exercise (dogs and horses)
 - e. Concurrent urinary tract infection with urease-containing bacteria and urinary obstruction
- f. NH_4Cl administration
- 3. Bile acids vs. ammonia
 - a. Ammonia is more SPECIFIC for liver disease, but its labile nature makes it less convenient to perform in most settings.
 - b. Bile acid levels are affected by non-liver factor, but is easier to perform.
- 4. Dye studies: bromosulfophthalene (BSP)
 - a. Another method used to assess hepatic function and portal blood flow.
 - b. Dyes are taken up, conjugated, and secreted similar to bilirubin or bile acids.
 - c. Fallen out of favor due to technical, interpretive, and practical difficulties.
- B) Assessment of hepatic synthetic function
 - 1. Causes of loss of synthetic function (LIVER FAILURE)
 - a. Loss of hepatocellular mass (>70%): usually irreversible
 - b. Portosystemic shunt (lack of adequate blood supply)
 - 2. Substances synthesized by the liver (limited to those routinely measured)
 - a. Albumin:
 - i. Half-life in blood, 7-21 days depending on species (relatively long)
 - ii. Causes of hypoalbuminemia
 - a. Decreased production due to liver failure
 - b. Decreased intake or absorption of nutrients
 - c. Increased loss (urine, feces, exudates)
 - iii. Consequences (partial list)
 - a. Ascites/edema: hypoalbuminemia is contributor, but not sole cause
 - b. Low measured total calcium; however, ionized calcium will be normal
 - c. Altered metabolism of substances carried by albumin
 - d. Poor healing
 - e. Altered hemodynamics
 - b. Coagulation proteins
 - i. All coagulation proteins are made by hepatocytes except FVIII.
 - ii. Activation of coagulation proteins by vitamin K-dependent enzyme occurs in liver.
 - iii. Very short half-lives in blood
 - iv. Prolongation of coagulation times may occur with:

- a. Liver failure: proteins < 30% of normal levels (coagulation assays only detect MARKED decreased in proteins)
- b. Biliary obstruction (prolonged): deficiency of active vitamin K
- c. Phagocytic (Kupffer cell) dysfunction: decreased clearance of coagulation inhibitors, e.g., fibrin degradation products
- v. Coagulation panel should be performed on all patients prior to biopsy.
- vi. Parenteral administration of vitamin K may improve coagulation times in some cases allowing biopsy to be performed.
- c. Cholesterol
 - i. Causes of hypocholesterolemia:
 - a. Liver failure
 - b. Protein-losing enteropathy
 - c. Hypoadrenocorticism (rare)
 - ii. May be masked or balanced by concurrent condition that causes increased cholesterol
 - iii. See V.C.2 for hypercholesterolemia
 - d. Urea nitrogen (UN or BUN)
 - i. Causes of low BUN: liver failure, diuresis
 - ii. Consequence: contributes to polyuria, polydipsia, and isosthenuria (or minimally concentrated urine) due to impaired renal concentrating ability (inadequate hypertonicity in renal interstitium)
 - e. Glucose: may be either decreased or increased
 - i. Hypoglycemia: decreased gluconeogenesis, inadequate glycogen stores or impaired clearance of insulin
 - ii. Hyperglycemia: impaired clearance glucagon
 - f. Globulins: decreases in alpha and beta globulins may be detected by serum protein electrophoresis
- C) Phagocytic function (Kupffer cells): increased immunoglobulins (polyclonal gammaglobulinemia) due to impaired filtering function of liver and escape of antigens to lymphoid tissue

Supportive evidence of liver disease from minimum database

- A) Complete blood count: may exhibit one or more of the following depending on the specific disease present
 1. Leukogram: variable
 2. Anemia of inflammatory (chronic) disease due to iron sequestration
 3. Microcytosis: seen with PSS due to impaired iron metabolism
 4. Poikilocytosis: seen with alterations in phospholipids and cholesterol metabolism
 - a. Leptocytes ("cheerios")
 - b. Acanthocytes (sharp irregular projections), also with hemangiosarcoma
 - c. Codocytes (target cells)
- B) Urinalysis
 1. S.G. may be in range of minimal concentration or isosthenuric (See Urea, VI.B.2.d)

2. Bilirubinuria +/- urobilinogen (see Bilirubin, V.B.2-4)
3. Crystalluria: ammonium biurate crystals may form in presence of liver disease due to excessive excretion of uric acid and ammonia, especially with PSS
- C) Fecal analysis
 1. Color gray or orange (see Bilirubin, V.B.2-4)
 2. Character: steatorrhea associated with severe cholestasis due to impaired lipid absorption
- D) Fluid analysis of effusion: transudate, modified transudate, or exudates depending on type of liver disease (see lecture on cytology of effusions)

LIVER FUNCTION TESTS

Classification of Liver Function Tests:

1. tests dependent primarily on hepatic secretions and excretion
 - a. bile pigments
 - b. clearance of foreign substances
2. tests dependent upon specific biochemical functions
 - a. protein metabolism tests
 - b. carbohydrate metabolism tests
 - c. lipid metabolism tests
3. tests dependent upon the measurement of serum enzyme activity
 - a. transaminases
 - b. alkaline phosphatase
 - c. other enzymes

A. Tests dependent upon hepatic secretions and excretions:

1. Bile Pigments

a. Serum Bilirubin

The chief bile pigment found in the serum of domestic animals is bilirubin. Determination of total bilirubin is based on the van den Bergh reaction. This test is based on the ability of bilirubin to couple with diazobenzosulfochloride (Diaz Reagent) to form a characteristic red-violet pigment. Unconjugated bilirubin is insoluble in water and requires the addition of alcohol to the serum reagent mixture indirect reaction (a specific test for unconjugated bilirubin). Conjugated bilirubin is soluble in water, thus it is a direct reaction.

The accepted method for van den Bergh reaction requires the addition of alcohol to a mixture of diazo reagent and serum in order to measure serum bilirubin. The difference between the values for total and direct-reacting pigments is the indirect-reacting bilirubin.

Indications for Serum Bilirubin Determination:

- for classifying icterus in a diseased animal
- to measure the response of the liver to therapy
- assists in making an accurate prognosis

Interpretation of the van den Bergh reaction:

1) Dog

- less than 20% of conjugated, of unconjugated bilirubin are indicative of hemolytic diseases

- more than 40% of the total bilirubin is of conjugated, hepatocellular disease is probably present
- 25-35% conjugated, obstruction of the bile duct (cholestasis)

2) Horse

- up to 25 mg/dl of serum unconjugated bilirubin – liver disease
- 80 mg/dl of serum unconjugated bilirubin – indicates hemolytic anemia
- between 25 and 75 mg/dl – associated with equine infectious anemia.

Increases in unconjugated bilirubin are observed in a variety of conditions in the horse that are unrelated to primary liver disease.

- a) cardiac insufficiency
 - b) constipation
 - c) gangrenous pneumonia
 - d) hemolytic disease
 - e) primary hepatic disorder
 - f) fasting may also increase bilirubin levels.
 - g) More than 25% of total serum bilirubin (conjugated) – hepatocellular damage is suspected.
- 3) Cow – serum bilirubin levels in severe hepatic diseases in cows are only slightly elevated. It cannot be considered a sensitive indicator of hepatic dysfunction. Most hyperbilirubinemias in cattle result from excessive destruction of erythrocytes (hemolysis). There is an increase in conjugated bilirubin in cattle with biliary obstruction

4) Other animals – same as in cattle

b. Bile Pigments in Urine

- 1) Urinary Urobilinogen – refers to all substances reacting positively with Ehrlich's reagent. Urinary urobilinogen may be increased in association with hemolytic or hepatic disease. Watson's Reagent – the most common method for determining 24-hour urinary urobilinogen
- 2) Bilirubin Conjugates – only conjugated bilirubin complexes are detected in the urine, as unconjugated bilirubin does not normally pass the glomerular filter. Bilirubin conjugates are not found normally in urine of the cat, pig, sheep, and horse. Detection of urine bilirubin conjugates is relatively simple. The most easily conducted screening examination is the foam test.

Fecal Bile Pigments – fecal bilirubin appears in conditions that prevent the reduction of bilirubin to urobilinogen. This occurs:

- 1) in diarrhea
- 2) as a result of suppression of bacterial action, or
- 3) in the newborn receiving milk

Harrison's or Gmelin's Test may be used as a qualitative measure of the presence of bilirubin. Urobilinoid pigments are similar to those observed in urine are normally present in feces. The predominant pigment is stercobilin. These pigments are increased in hemolytic process

and markedly decreased in bile obstruction → feces are often clay-colored.

2. Clearance of Foreign dyes from the serum – the clearance of foreign dye in the serum may be delayed in hepatic necrosis or fibrosis that has resulted in a reduced parenchymal mass, reduced hepatic blood flow, or both.

a. Sulfobromophthalein (BSP)

- 1) Dog – BSP retention test can be valuable in assessing the functional capacity of the liver in the dog. Less than 5% retention at 30 minutes following injection is normal. Up to 10% retention can be occasionally seen in dogs with no apparent hepatic damage. Prolonged BSP retention in dogs occur in hepatic lipidoses with centrilobular necrosis, periportal fibrosis, focal hepatitis, CCl_4 poisoning, and infectious hepatitis.

- 2) Horse – a clearance method is used rather than retention method. Normal BSP clearance is 2.0-3.7 minutes with an average of 2.8 ± 0.5 minutes. Delayed BSP clearance occurs in hepatic hemosiderosis, extensive lipidosis, and CCl_4 poisoning.

- 3) Cow – 2.4-4.1 minutes with an average of 3.3 ± 0.5 minutes is normal. Same method is used as in horses, but blood samples are drawn 20 minutes after the injection of the dye. Low clearance is observed in cows with suppurative hepatitis following acute form of coliform mastitis, extensive fascioliasis with hepatic fibrosis, and hepatic abscesses.

- 4) Sheep – percentage retention method is preferable like in dogs, but blood samples are drawn following injection of dye. $6 \pm 2\%$ is normal. Slow clearance occurs in ketosis associated with hepatocellular necrosis and impediment to hepatic blood flow resulting from extensive lipidosis.

b. Indocyanine Green (ICG) – recommended for use in dogs to determine the functional status of the liver. The removal rate of this dye is exponential for the first 15 minutes following injection. The average disappearance rate of the dye from plasma was 7.6%, with a range of 5.5-9.8% per minute.

B. Tests based on specific Biochemical Functions:

1. Plasma Proteins Metabolism Test – the most accurate method for determining the relative values for plasma proteins is electrophoresis. Plasma protein alterations are not usually specific for a particular disease condition.

a. Fibrinogen – decreased plasma fibrinogen levels are associated with congenital afibrinogenemia, hepatic insufficiency and acute afibrinogenemia which may occur in shock, severe burns, and neoplasia.

- b. Albumin – hyperalbuminemia is rarely seen except in the presence of acute dehydration and shock. A decrease in total serum albumin may result from:

- 1) deficient intake of protein
- 2) deficient synthesis of albumin
- 3) excessive protein breakdown

4) loss of albumin

Absolute fall in serum albumin is found more commonly in chronic liver diseases such as subacute hepatitis or diffuse fibrosis. In acute hepatitis albumin levels are less significant. The serum globulin level is increased in both diffuse fibrosis and hepatitis. Advanced liver disease may affect coagulation test results. Factors V, VII, IX, and X are affected first. As the disease progresses, Factors I, II, and XII may also decrease.

- c. Globulin – hyperglobulinemia occurs in both viral and bacterial infections (alphaglobulins) as well as a consequence of histamine elaboration of the mast cells of tumors. Betaglobulins may be increased in hyperlipemia. Elevations in gammaglobulins in bacterial infections, viral infections, parasitism and liver diseases, also in association with lymphosarcoma and plasmacytoma. Most common cause of a deficiency in serum immunoglobulins occurs in neonates deprived of colostrum. Placental transfer of immunoglobulins is minimal in domestic animals, and all newborns are hypogammaglobulinemic at birth.
2. Carbohydrate Metabolism Test – galactose tolerance test may be successful in detecting liver damage because only the liver can utilize galactose in significant amounts, but this is time consuming in both execution and analysis, and has limited value.
3. Lipid Metabolism Test – only the determination of free esterified cholesterol of the serum has been applied to the study of hepatic diseases. Esterification is reduced in liver diseases. Decreased CE:CT (esterified cholesterol to total cholesterol) ratios were observed in dogs with leptospirosis, DM, advanced nephritis, and fatty degeneration of the liver. CE:CT ratio in normal animals is 60.
- C. Tests Dependent on the Measurement of Serum Enzyme Activity:
1. Transaminases
- a. Alanine Amino Transferase (ALT) – formerly known as Serum Glutamic Pyruvic Transaminase (SGPT). Increased values in the dog and cat is specific for hepatic diseases but not in horses, sheep, pigs, or cattle.
- b. Aspartate Amino Transferase (AST) – formerly known as Serum Glutamic Oxaloacetic Transaminase (SGOT). It is not an organ-specific test because it is present in all tissues of the body like skeletal muscle and cardiac tissues.
- c. Serum Arginase – it is of great value in testing for hepatic necrosis in horses, cattle, pigs, and sheep
- d. Iditol Dehydrogenase (ID) – is a liver-specific enzyme present in the liver in all animal species. In horses and ponies, tremendous increase of this enzyme is observed in CCl₄ and aflatoxin B₁ poisoning. In ruminants, serum ID

activity is increased in fascioliasis, hepatic lipidosis associated with Fat Cow Syndrome, and other conditions associated with hepatocyte damage.

- e. Serum Ornithine Carbamyl Transferase (OCT) – also a liver-specific enzyme used to detect liver diseases in all animal species. Elevations of serum OCT have been reported in a variety of liver disorders in cattle, horses, and swine.
- f. Lactic Dehydrogenase – an intracellular enzyme that is widely distributed in animal tissues, and released following cellular damage to the liver, lung muscle, kidney, heart, and lymphoreticular tissue. It is also present in a high concentration in erythrocytes and may also be observed in association with malignancies. It is frequently included in routine biochemical profile. Serum LDH activity is greater in young than in mature animals.
- g. Alkaline Phosphatase – are agents that hydrolyze phosphoric esters with the liberation of inorganic phosphate. Alkaline phosphatase activity is widely distributed in the body and is found in high concentration in bone (osteoblasts), intestinal mucosa, renal tubule cells, liver, and placenta. It may be higher in young animals. Measured as IU or mU/ml of serum. Serum alkaline phosphatase test is not recommended for detecting liver malfunctions in cattle and sheep due to its wide range of normal values.

Carbohydrate Metabolism and Function of the Pancreas and Digestive Tract

Blood Glucose Determination – is indicated in:

1. animals suspected of having diabetes or pancreatitis
2. animals with unexplained comas or convulsions
3. sheep or cattle in which ketosis is suspected
4. pigs suspected of having hypoglycemia associated with starvation

Glucose Oxidase Method is the most accurate method in determining blood glucose. The results of a blood glucose determination may be affected by the diet of the individual and in particular the length of time since the last feeding. In non-ruminants and young ruminants, it is advisable to use blood samples collected after a 12-24 hour fast. In older ruminants, carbohydrates given orally do not affect blood glucose levels.

Results: Increased blood glucose concentration results from either an imbalance between hepatic output of glucose and peripheral uptake of the sugar, or disturbances in the endocrine regulatory influence upon these processes. The most spectacular increase in blood glucose probably occurs in diabetes mellitus wherein blood glucose is generally above 200 mg/dl.

Although it occurs most frequently in dogs and cats, it has also been reported in horses, cattle, sheep, and pigs. Abnormal functioning of other hormone-producing organs may influence glucose levels, like:

1. increased activity of the anterior pituitary – early stages of hyperpituitarism
2. increased activity of the adrenal cortex – increased endogenous and exogenous glucocorticoids
3. excessive thyroid hormone – may increase blood glucose levels if the rate of peripheral utilization cannot keep pace with the increased hepatic output

Transitory Hyperglycemia may be associated with:

1. digestion
2. exposure to cold
3. administration of morphine or xylazine HCl
4. following general anesthesia
5. following injections of epinephrine
6. subsequent to glucose infusions
7. ingestion of large quantities of carbohydrates
8. during excitement – common in cattle, cows, and occasionally horses

Decreased Blood Glucose (Hypoglycemia) can be seen in animals:

1. with hyperinsulinism due to neoplasm of the pancreas
2. when given an overdose of insulin in the treatment of diabetes mellitus
3. with hepatogenic disorders
4. severe exertion and starvation
5. with hypothyroidism, hypopituitarism, and adrenocortical insufficiency
6. ketosis in ruminants

Glucose Tolerance Tests – indicated as a confirmatory method for the diagnosis of deviations in normal glucose metabolism

1. Oral Glucose Tolerance Test –fasted animal is given 4 g of glucose per kg bodyweight. Blood samples are taken at 30-60 minute intervals for a 3-4 hours period. Normally by the end of the 2nd hour blood glucose returns to normal levels.
2. Intravenous Glucose Tolerance Test
 - a. Low-Dose IGTT – 0.5 g glucose/kg BW
 - b. High-Dose IGTT – 1 g glucose/kg BW

Pancreatic Function Tests – exocrine pancreatic disease assumes two forms:

1. Acinar Damage
2. Acinar Deficiency

Tests used for pancreatic function:

1. Microscopic examination of feces for detection of fat, undigested protein or undigested carbohydrates
 - a. fat globules – uses Sudan III stain→ red or orange under LPO. Numerous fat globules indicate an existing pancreatic deficiency.
 - b. undigested protein – presence of yellow striated muscles indicate lack of trypsin (in animals fed with meat)

c. undigested starch – uses 2% tincture of iodine as stain→ the presence of blue particles suggests starch maldigestion

2. Examination of feces for presence of trypsin – two tests are routinely used, based on the incubation of gelatin with feces to determine the proteolytic activity present in the fecal sample.

a. Gelatin Tube Test

b. Film Test – based on the digestion of the gelatin present on exposed or fresh X-ray film, and the identification of this action by clearing of the film

3. Serum Lipase Determination – lipase activity is reflected by the release of fatty acids. Spectrophotometric studies are now available and are more accurate. Normal values are established in each laboratory. Increased values are seen in animals with necrotic pancreatitis, in dogs with renal failure, and dexamethasone injections.

4. Serum Amylase Determination – amylase activities in body fluids are measured based on determining the rate of appearance of the breakdown products of starch (Saccharogenic Method), or the rate of disappearance of starch (Amylolytic Method). Amylase activity depends on the presence of calcium ions, so the use of chelating agents should be avoided. Serum is the preferred sample. Increased levels are seen in acute pancreatitis, and in dogs with chronic primary renal failure.

5. Blood Glucose and Glucose Tolerance Determination

The glucose tolerance test measures the body's ability to metabolize glucose.

It is also known as the Oral glucose tolerance test (OGTT).

Glucose is the sugar that the body uses for energy.

Patients with untreated diabetes have high blood glucose levels. Glucose tolerance tests are one of the tools used to make the diagnosis of diabetes.

The most common glucose tolerance test is the oral glucose tolerance test (OGTT). After an overnight fast, a patient drinks a solution containing a known amount of glucose. Blood is obtained before the patient drinks the glucose solution, and blood is drawn again every 30 to 60 minutes after the glucose is consumed for up to 3 hours.

Blood glucose levels above normal limits at the times measured can be used to diagnose type 2 diabetes or gestational diabetes (high blood glucose during pregnancy). Insulin levels may also be measured. (Insulin is the hormone produced by the pancreas that moves glucose from the bloodstream into cells.)

The intravenous glucose tolerance test (IGTT) is not often used. In this test, patients are given a known amount of glucose by vein for 3 minutes, and blood insulin levels are measured before glucose and at 1 and 3 minutes. Insulin levels below a standard threshold may predict the

- development of type 1 diabetes in some patients.

6. Absorption Tests – the capacity of an animal to absorb fats may be utilized as a method for measuring pancreatic deficiency or other malabsorption syndromes. Dietary fats must be hydrolyzed to fatty acids and glycerol to be absorbed.

a. Simple Absorption Test – based on a comparison of plasma turbidity prior to and following a fatty meal. A heparinized blood sample is drawn from a fasted animal and centrifuged. The turbidities of the pre- and post-feeding samples are compared. Normally, post-feeding sample is turbid.

b. Vitamin A Absorption Test – based on the same principle as the simple fat absorption test. Vitamin A in an oil emulsion is administered orally, and absorption is determined by measurement of Vitamin A levels in the blood.

c. ¹³¹I Oleic and ¹³¹I Trioleic Absorption Tests – used to differentiate between steatorrhea caused by a deficiency of pancreatic enzymes and that caused by primary malabsorption. If steatorrhea is due to lack of pancreatic lipase, absorption of oleic acid will be normal; whereas that of triolein will be reduced. If the problem is malabsorption, both compounds will be reduced.

Causes of End-Stage Liver

 - Chronic toxicity (therapeutic agents or naturally occurring toxins)
 - Chronic cholangitis and/or obstruction
 - Chronic congestion (right side heart failure)

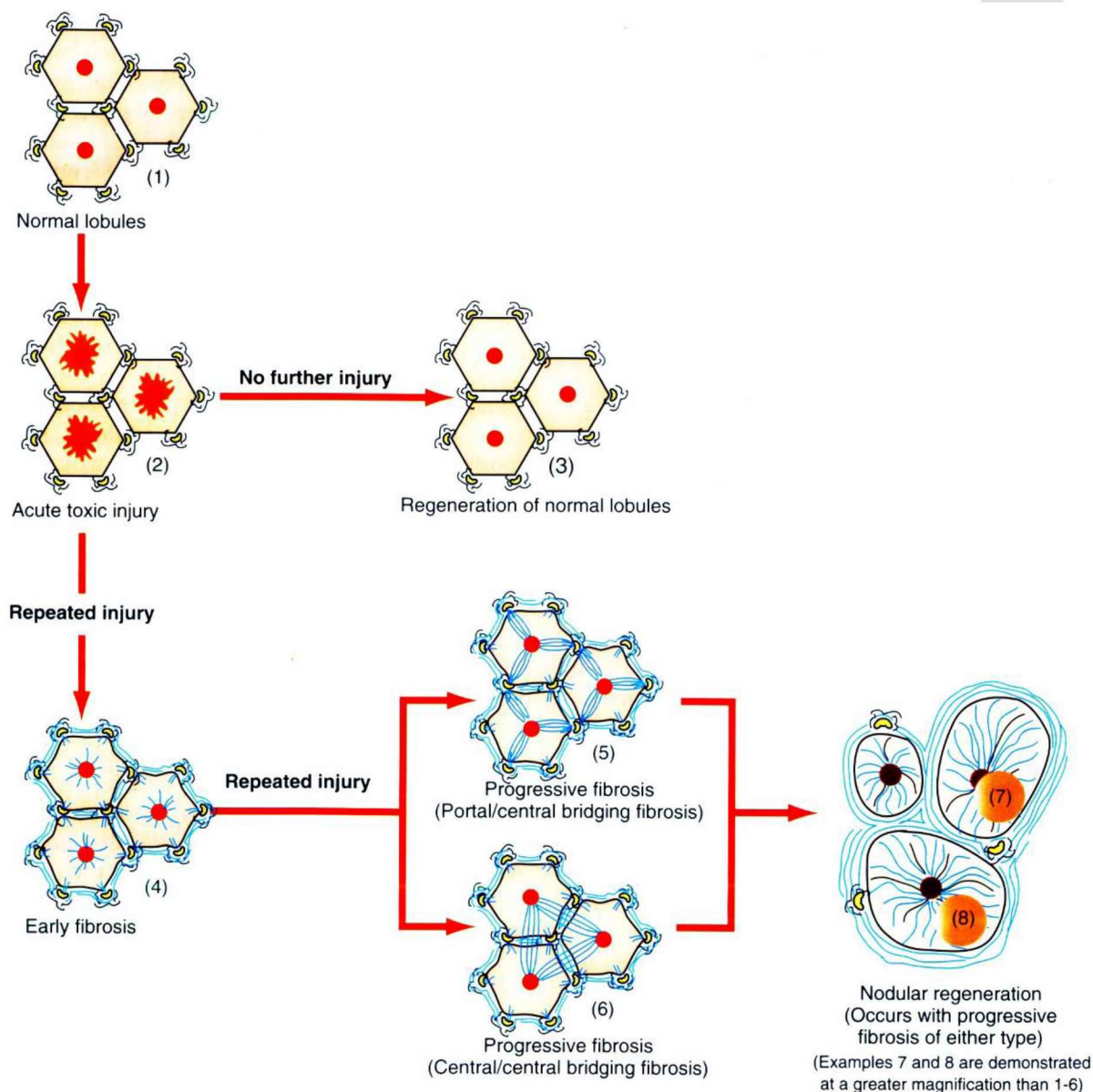
- Inherited disorders of metal metabolism (copper or iron)
- Chronic hepatitis
- Idiopathic

Selected Therapeutic Agents with Potential to Cause Hepatic Injury in Domestic Animals

- Acetaminophen
Amiodarone
Aspirin
Carprofen
Diazepam
Diethylcarbamazine-oxibendazole
Glucocorticoids
Griseofulvin
Halothane
Ketoconazole
Lomustine (CCNU)
Manganese chloride
Mebendazole
Megestrol acetate
Methoxyflurane
Naproxen/ibuprofen
Nitrofurantoin
Phenazopyridine
Phenobarbital
Phenylbutazone
Phenytoin
Primidone
Stanozolol
Tetracycline
Thiacetarsamide
Trimethoprim-sulfa

Defense Mechanisms against Injury and Infectious Agents

	Liver	Biliary System	Exocrine Pancreas
STRUCTURAL AND FUNCTIONAL BARRIER			
Skin	Yes	Yes	Yes
Rib cage	Yes	Yes	Yes
Omentum (barrier that limits access of injurious material to the organ)	Yes	Yes	Yes
IMMUNOLOGIC RESPONSES			
Kupffer cells	Yes	No	No
Resident and migrating cells (recruited monocytes), which are part of the monocyte-macrophage system	Yes	No	No
Innate and adaptive immunologic responses (including secretory immunoglobulin A), which form the body's overall immune system	Yes	Yes	Yes
BIOCHEMICAL DEFENSES			
Enzyme inhibitors that reduce the risk of premature enzyme activation and tissue injury	No	No	Yes



Schematic diagram of the effects of hepatic injury on the development of fibrosis. Acute hepatic centrilobular injury (2) that occurs only once usually resolves, and normal liver architecture returns (1, 3). Repeated bouts of injury or severe injury can initiate hepatic fibrosis (4). In the earliest stages, fibrosis may be reversible, but as fibrosis progresses it reaches a point at which repair is not likely. Fibrosis starts as fine branches of collagen deposition between portal areas or central areas or dissecting into the hepatic parenchyma (5, 6). Over time, greater amounts of collagen and other extracellular matrix are deposited and the lobular architecture becomes progressively distorted. In the end-stage liver, nodular regeneration (7, 8) and extensive, circumferential fibrosis are typical. The regenerative nodules shown here (7, 8) are at an early stage of regeneration. These nodules will often compress (7) the central vein(s) of hepatic lobules within and adjacent to those from which they arose.

Laboratory Analyses of the Liver

- ✓ Laboratory tests often detect liver disease before hepatic failure occurs.
- ✓ Routine biochemical tests such as serum enzyme concentrations are sensitive indicators of liver disease, but they do not assess hepatic function.
- ✓ Dynamic biochemical tests that assess hepatic clearance provide quantitative information regarding hepatic function.
- ✓ Tests of hepatic function are useful diagnostic and prognostic tools and provide a guide for the modification of drug-dosing regimens.

Serum Enzyme Concentrations:

- ✓ Serum concentrations of liver-specific enzymes are generally higher in acute liver disease than in chronic liver disease.
- ✓ They may be within normal limits in the later stages of subacute or chronic hepatic disease.
- ✓ Careful interpretation of laboratory values in conjunction with clinical findings is essential.

GGT

- ✓ Sequential measurements of serum γ -glutamyl transpeptidase or transferase (GGT), sorbitol dehydrogenase (SDH; also called iditol dehydrogenase, IDH), aspartate amino transferase (AST), bilirubin, and bile acids are commonly used to assess hepatic dysfunction and disease in large animals.

- ✓ Serum GGT, bilirubin and total bile acid concentrations, and sulfobromophthalein (BSP®) clearance are not sensitive indicators of liver disease in young calves.
 - ✓ Due to urinary and milk excretion of GGT and rarity of pancreatitis in large animals, increased serum GGT concentrations most commonly indicate bile duct or liver disease.
 - ✓ Some consider GGT to be the single test of highest sensitivity for liver disease in adult large animals.
 - ✓ Increase of GGT is most pronounced with obstructive biliary disease.
 - ✓ Chronic hepatic fibrosis is the only liver disease in which an abnormal increase in GGT might not be seen.
 - ✓ Neonatal foals and young horses, especially those in training, may show a nonspecific increase in GGT that is not associated with liver disease or other increases in liver enzymes or serum bile acid concentration.
 - ✓ GGT is of little value in diagnosing liver disease in neonatal calves or lambs because it is present in colostrum and milk.
 - ✓ GGT activity may also be increased with colonic displacement or administration of drugs (eg, corticosteroids, rifampin, benzimidazole, anthelmintics).
 - ✓ Some liver-derived enzymes are higher in young calves (GGT, alkaline phosphatase [AP], glutamate dehydrogenase, lactate dehydrogenase) and foals (AP, GGT, SDH, AST) because they are transiently elevated or come from sources other than the liver.
- SDH, arginase, ornithine carbamoyltransferase (OCT), AST, isoenzyme 5 lactate dehydrogenase (LDH-5), glutamate dehydrogenase (GLDH), and AP**
- ✓ are also used to assess hepatic dysfunction and disease. Arginase, SDH, and OCT are liver-specific enzymes in horses, most ruminants, and swine.
 - ✓ SDH is most predictive for active hepatocellular disease, with marked increases in enzyme activity following hepatocellular damage.
 - ✓ Mild increases in SDH can also occur with obstructive GI lesions, endotoxemia, anoxia from shock, acute anemia, hyperthermia, and anesthesia.
 - ✓ Because of their short half-lives, SDH and LDH-5 are useful in assessing acute, ongoing liver disease.
 - ✓ Arginase and GLDH are considered specific for acute liver disease because both have high tissue concentrations in the liver and short half-lives in the blood.
 - ✓ AST is highly sensitive for liver disease but lacks specificity because high concentrations come from both liver and skeletal muscle.
 - ✓ Other AST sources include cardiac muscle, erythrocytes, intestinal cells, and the kidneys.
- ✓ When CK is simultaneously measured to rule out muscle disease and the serum is not hemolyzed, increases in AST and LDH-5 are caused by hepatocellular disease.
 - ✓ AST values are often normal in chronic hepatic disease.
 - ✓ SDH and AST may be markedly increased with intrahepatic cholestasis and mildly increased with extrahepatic cholestasis.
 - ✓ Increases in AP and GGT are associated with irritation or destruction of biliary epithelium and biliary obstruction.
 - ✓ AP comes from the placenta, bone, macrophages, intestinal epithelium, and liver.
- Serum Total Bile Acid Concentration:**
- ✓ Serum concentration of bile acids is highly specific for liver dysfunction but does not define the type of insult or disease present.
 - ✓ Serum bile acid concentrations increase with hepatocellular damage, cholestasis, or shunts from the portal system to the vena cava.
 - ✓ Elevations are highest with biliary obstruction and portosystemic shunts.
 - ✓ Concentrations of serum bile acids >20 $\mu\text{mol/L}$ have a high sensitivity and positive predictive value for determining liver disease in horses but not in ruminants.
 - ✓ Serum total bile acid concentration in most normal horses is <10 $\mu\text{mol/L}$.
 - ✓ Total bile acid concentration remains increased in horses with chronic liver disease. In horses, there is no diurnal variation, no postprandial rise, and no significant hour-to-hour variation in bile acid concentrations.
 - ✓ In dairy cattle, serum bile acid measurement is of little value in recognizing fatty liver or liver disease or failure due to significant hour-to-hour variations.
 - ✓ In recently freshened cows, serum total bile acid concentrations are significantly higher than in cows in mid-lactation or in 6-mo-old heifers.
 - ✓ Total bile acid concentration may be the best single test for hepatic disease in young calves.
 - ✓ In calves, concentrations >35 $\mu\text{mol/L}$ may indicate liver disease, bile obstruction, or a portosystemic shunt.
- Serum Bile Pigments:**
- ✓ Evaluation of serum bilirubin (direct and indirect) concentration is useful for determining hepatic dysfunction in horses and ruminants.
 - ✓ Increases in bilirubin result from hemolysis, hepatocellular disease, cholestasis, or physiologic causes.
 - ✓ The indirect bilirubin increases 2- to 3-fold, while the direct bilirubin remains within the reference range.
 - ✓ In foals, indirect more than direct bilirubin may be increased with prematurity, neonatal isoerythrolysis, septicemia, or a portocaval shunt.

- ✓ Horses with hepatic disease and failure most often have significant increases in both indirect and direct bilirubin.
- ✓ With liver damage in horses or ruminants, most of the retained bilirubin is indirect (unconjugated), and the direct-to-total ratio usually is <0.3.
- ✓ Hepatocellular disease should be considered when the direct bilirubin fraction is >25% of the total bilirubin value.
- ✓ In biliary obstruction, total bilirubin concentrations are increased, with the percentage of direct bilirubin often being >25-30%.
- ✓ With bile blockage or intrahepatic cholestasis, the direct-to-total ratio may be >0.3 in horses or 0.5 in cows.
- ✓ In chronic liver disease, bilirubin concentrations are often within normal limits.
- ✓ Adult cattle and calves may have severe liver disease without any increase in serum bilirubin.
- ✓ The most dramatic increases in serum or plasma bilirubin are due to hemolytic crises rather than to liver dysfunction.

Urobilinogen:

- ✓ Urobilinogen may be detected by dipstick analysis in normal horses.
- ✓ Increased levels of urobilinogen in urine without hemolysis are suggestive of a hepatic dysfunction, portosystemic shunting, or increased production by intestinal bacteria.
- ✓ Urobilinogen in the urine indicates the presence of a patent bile duct.
- ✓ Absence of urobilinogen may indicate complete biliary blockage, liver disease, or failure to excrete bilirubin into the intestine, reduce it by intestinal bacteria, or absorb it from the ileum.

Serum and Plasma Proteins:

- ✓ Serum albumin and protein concentrations are variable in horses and cattle with hepatic disease.
- ✓ Hypoproteinemia is not common in horses with acute liver disease.
- ✓ Serum albumin is most likely to be reduced in chronic liver disease due to decreased functional hepatic parenchyma.
- ✓ Hyperproteinemia due to hyperglobulinemia (polyclonal gammopathy or increase in β -globulins) may develop in horses with severe acute or chronic liver disease.
- ✓ Plasma fibrinogen concentration may not be a sensitive test in horses with hepatic insufficiency.

Prothrombin Time:

- ✓ Abnormalities in prothrombin time (PT) are often the first detected because factor VII, a liver-synthesized vitamin K-dependent factor, has the shortest half-life.
- ✓ Serum PT may be rapidly prolonged with hepatic failure and is one of the first function tests to return to normal with recovery from acute hepatic disease.

- ✓ A normal PT determination, however, does not rule out coagulopathy due to vitamin K deficiency.
- ✓ Prolonged activated partial thromboplastin time (APTT) or other indications of coagulopathy may be noted in animals with severe hepatic disease.
- ✓ As a number of factors may influence measurement of PT or APTT values in horses, the ratio of clotting time of the animal with suspected hepatic disease to that of a normal horse's value should be >1.3 for the test to be interpreted as abnormal.

Urea, Glucose, and Ammonia:

- ✓ Serum concentration of urea may be decreased in both acute and chronic liver failure.
- ✓ Hypoglycemia is uncommon in adult horses and ruminants with hepatic dysfunction but is more likely in chronic liver disease.
- ✓ Plasma triglyceride concentrations are markedly increased in ponies, miniature horses, donkeys, and adult horses with hepatic lipidosis.
- ✓ Alterations in triglycerides, very-low-density lipoproteins, and esterified cholesterol levels are more common in ruminants than in horses with hepatic insufficiency.
- ✓ Neonatal foals have higher blood cholesterol and triglyceride concentrations than adult horses.
- ✓ Plasma ammonia levels may be increased with hepatic insufficiency but do not correlate well with severity of hepatic encephalopathy except during portocaval shunts.
- ✓ Ingestion of urea or ammonium salts may cause increases of blood ammonia and encephalopathy in horses and cattle.

Dye Excretion and Clearance Tests:

- ✓ Sulfobromophthalein (BSP®) or indocyanine green dyes can be used to assess hepatobiliary transport.
- ✓ The BSP half-life is prolonged when >50% of hepatic function is lost.
- ✓ Hyperbilirubinemia, decreased hepatic blood flow, and significant cholestasis may falsely prolong and hypoalbuminemia may falsely shorten BSP clearance.
- ✓ BSP clearance in goats is most often prolonged with generalized hepatic lipidosis secondary to pregnancy toxemia.
- ✓ Determination of BSP clearance time, rather than half-life, reportedly is more useful in detection of liver disease.

Liver Biopsy:

- ✓ Percutaneous liver biopsy is the definitive means of diagnosing hepatic disease.
- ✓ Histologic evaluation of the liver provides valuable information regarding etiology and severity of the disease process.
- ✓ Liver biopsies can also be obtained during laparoscopy, which offers the additional advantage of being able to visualize the surface

of the liver and other abdominal organs for evidence of disease.

- ✓ Samples should be placed in media for bacterial culture and sensitivity and in formalin for histologic evaluation.
- ✓ Coagulation profiles (prothrombin time, partial thromboplastin time, fibrinogen, fibrin degradation products, and optional platelet count) may be performed before liver biopsy to reduce the risk of hemorrhage.
- ✓ Liver biopsy may not be advised in an animal with clinical or clinicopathologic evidence of a coagulopathy or a hepatic abscess because hemorrhage or contamination of the peritoneal cavity may result.

c. Laboratory Examination of Urinary Disorders

Laboratory Diagnosis of Urinary Disorders

1. History and physical examination
2. Urinalysis
3. Renal function tests
4. Serum chemistries
5. Microbiology
6. Renal biopsy

Urine Collection

- A) Timing
 - morning sample is ideal for house trained pets because it provides urine produced for the last 6-8 hours
- B) Clean container:
 - Jars cleaned in dishwasher
 - sterile container
- C) Method:
 - Voided
 - collect mid stream if possible
 - Will contain cells and secretions from genital tract
 - Affected by estrus, parturition, balanoposthitis
 - Catheterized – poor technique can cause hemorrhage
 - Cytocentesis – normally produces microscopic hemorrhage
 - Off the floor or table – effects of disinfectants
- D) Preservation: Urine should be analyzed within 4-8 h; refrigeration is best preservative.

Routine Urinalysis

- A) Complete urinalysis
 1. Physical features (gross inspection)
 2. Solute concentration (specific gravity)
 3. Chemical analysis (stix)
 4. Microscopic examination (sediment)
 5. Culture
- B) Physical features
 1. Volume
 - History: increased frequency, large volume
 - Specific gravity
 - 24 hr urine volume
 2. Odor
 - Ammonia – urea splitting organisms
 - Acetone - ketones

3. Turbidity: normal urine - clear most species; horse cloudy

- a. Increased turbidity caused by:
 - Cells
 - Bacteria
 - Mucus
 - Crystals
 - Casts
- b. Descriptive terms
 - Clear
 - Hazy
 - Cloudy
 - Flocculent
4. Color: intensity varies with urine volume
 - a. Normal: pale yellow (dilute) to amber (concentrated)
 - b. Red: RBCs or hemoglobin
 - c. Red brown: hemorrhage or myoglobin
 - d. Dark amber: increased amount of bilirubin
 - e. Drugs: can produce unusual colors

C) Solute concentration

Background:

- Solutes are dissolved substances in urine that indicate kidney's ability to excrete waste products (urea, creatinine), control mineral balance and acid/base status (Na, K, Cl, HCO₃, Ca, Phos), and excrete drugs.
- In renal disease, the ability of the kidney to perform these functions is impaired and solute concentration is affected.
- Other solutes such as glucose, protein or ketones may be excreted in disease states.
- 1. Specific gravity: density of urine relative to distilled water. One ml of pure water weighs 1 gram. One ml of salt water weighs more than 1 gram because it is more dense.

Methods:

- Urinometer – requires approx. 10-12 ml of urine; not affected by turbid urines
- Refractometer – requires a few drops of urine; false increase due to turbidity or hemoglobin
- Urine dipstix – do not work in animal urines; human urines rarely go above 1.030
- 2. Interpretation of specific gravity:
 - a. Normal range: 1.001 – 1.065
1.001 – 1.080 cats
 - b. Inversely related to urine volume
 - Exceptions: diabetes mellitus: high volume, high SG; some phases of renal failure
 - Turbid urine: false increase if measured by refractometer
 - Temperature: decrease temperature will increase SG; always measure SG in urine at room temperature
 - Urine color: false increase in SG by refractometer in urine containing abnormal amounts of pigments
 - SG is increased by abnormal amounts of protein and glucose:
 - 400 mg/dl protein increases SG by 0.001
 - 400 mg/dl glucose increases SG by 0.002

- c. Specific gravity of glomerular filtrate is 1.008 – 1.012
 - Isosthenuria: 1.008 – 1.012 - Urine SG equal to glomerular filtrate
 - Hyposthenuria: < 1.008 – Very dilute urine, more solute removed than H₂O
 - Hypersthenuria: >1.030 – 1.035 – Concentrated urine, more H₂O removed than solute
 - Urine specific gravity of 1.008 – 1.012 on a random sample can be:
 1. Chance finding in a normal animal OR
 2. Indicate lack of renal concentrating ability
 - Pathologic isosthenuria that indicates a lack of concentrating ability is confirmed by:
 1. Concurrent dehydration and/or azotemia (inc BUN or creatinine)
 2. Water deprivation test
 3. ADH response test
 - Confirmed persistent isosthenuria indicates: FIXED SG
 1. 2/3 of nephrons are not functioning
 2. Absence of tubular concentrating ability
- D) Chemical analysis: Urine pH
 1. Normal values
 - Carnivores, suckling herbivores – 5.5 – 7.5
 - Herbivores – 7.0 – 8.5
 2. Method (fresh sample) narrow range pH paper; dip stix
 3. Causes of decreased urine pH
 - High protein diet (meat, milk)
 - catabolism of body protein
 - acidic fluid therapy
 - systemic acidosis – not always
 4. Causes of increased urine pH
 - a. vegetable diet
 - b. bacterial infections of urinary tract
 - c. alkaline fluid therapy
 - d. systemic alkalosis – not always
 - e. storage at room temperature
- E) Urine chemistry: Protein
 1. semiquantitative methods:
 - a. dipstix:
 - false positives in alkaline urine and/or high SG
 - trace, 1+, 2+ reactions are frequent in normal animals with high SG
 - false positive with quat ammonium, chlorhexidine, penicillin and cephalosporins
 - a. Sulfosalicylic acid test
 - equal quantities of urine and 5% SSA
 - turbidity is proportional to protein content
 - normal urine: no turbidity
 - if dipstix are used, + reaction confirmed with SSA
 - urine must be clear in order to interpret test
 2. Quantitative urine protein
 - a. 24 hr collection in metabolism cage, record volume, determine protein content.
 - b. Urine protein/creatinine ration: Protein concentration is measured against a substance (creatinine) that is produced at a constant rate

and its urine concentration varies inversely with urine volume; Pr/Cr ration does not require 24 hr or timed collection

- Measures the amount and severity of proteinuria. Therefore more quantitative than stix.
 - Proportional to 24 hr excretion
 - Can only be done on urine with inactive sediments.
 - Values: <0.5 normal; 0.5-1.0 borderline; >1.5 significant proteinuria
 - Increases can occur before azotemia is detected
 - Correlated with severity of renal lesion and progression of disease.
4. Interpretation (semiquantitative)
 - a. normal: <10 mg/dl
 - b. must be interpreted in conjunction with SG or urine volume in order to assess how much protein is lost in urine.

Urine Protein	Urine SG
3+ (100 mg/dl)	1.060 mild proteinuria
Stix	1.009 severe proteinuria

- c. Physiologic proteinuria: Transient and severity is mild
 - strenuous exercise
 - convulsions
 - neonates: transient proteinuria during first week
- d. Pathologic proteinuria
 - Renal glomerular leakage or tubular damage allows excess protein in urine.
 - Hemorrhage: plasma proteins in blood.
 - Inflammation/infection: leakage of protein accompanies inflammatory response
 - Hemoglobin, Myoglobin

<<must reevaluate urine sediment and "blood" reaction on stix to interpret>>
- F) Urine chemistry: Glucose
 1. Methods (semiquantitative)
 - a. dipstix:
 - enzymatic oxidation of glucose
 - glucose specific; more sensitive
 - false negatives: dogs; ascorbic acid in urine
 - false positives: peroxide, hypochlorite
 - b. clintest tablets:
 - copper reduction method, semiquantitative
 - detects reducing substances
 - numerous false positives
 - not affected by ascorbic acid
 2. Normal: no detectable glucose in urine

renal threshold: 180 mg/dL most species
100 mg/dL cow
280 mg/dL cat
 3. Glycosuria with hyperglycemia
 - diabetes mellitus
 - severe pancreatitis
 - hyperadrenocorticism
 - excess dietary carbohydrate

- fluid therapy
 - epinephrine response
 - immediately prior to death
 - 4. Glycosuria without hyperglycemia renal:
 - impaired tubular reabsorption
 - congenital
 - gentamycin toxicity
 false positive:
 - drugs such as ketamine
 - hematuria in cats
 - G) Urine chemistry: Ketones
 1. Methods: stix, tablets
 - a. acetoacetic acid is detected; acetone or B hydroxybutyric acid not measured
 - b. normal: negative reaction; ketones detected in urine and milk before ketonemia
 2. Ketonuria: does not indicate renal disease; occurs with abnormal carbohydrate metabolism.
 - a. Bovine ketosis
 - b. Pregnancy disease in ewes
 - c. Diabetes mellitus
 - d. Starvation; fasting; low carbohydrate/high fat diet
 - H) Urine chemistry: Bilirubin
 1. Method: stix and tablet
 - a. detects conjugated bilirubin
 - b. urine bilirubin is light sensitive – will degrade in a few hours
 - c. false positive: phenothiazine derivatives
 2. Normal:
 - a. negative most species
 - b. dog and cat have low renal thresholds
 - c. male dogs are able to conjugate bilirubin in renal tubules
 3. Interpretation: SG must be considered to determine significance
 - a. bilirubinuria
 - 1+ or 2+ frequent in normal dogs with high SG
 - hemolytic anemia: RBC destruction produces excess bilirubin
 - hepatocellular disease
 - bile stasis in liver
 - bile duct obstruction
 - b. bilirubinuria will precede hyperbilirubinemia
 - I) Urine chemistry: "Blood"
 1. Method:
 - detects HEME proteins in RBCs, hemoglobin and myoglobin
 - more sensitive to free hemoglobin or myoglobin
 2. Normal:
 - negative; false positive with hypochlorite
 - consider method of collection: catheter or cystocentesis can cause hemorrhage
 3. Positive reaction:
 - hemoglobinuria
 - hematuria +/- inflammation
 - myoglobinuria
 differentiation of heme pigments in urine:
 - urine color
 - urine sediment
 - plasma color
 - CBC
 - muscle enzymes (AST, CK)
- Urine Sediment**
- A) General features:
1. extremely important part of urinalysis
 2. urine chemistry and SG important for interpretation
 3. method of collection and history affect sediment
 4. sample storage can influence sediment results
- B) Normal urine: minimal sediment
- C) Method:
1. centrifuge urine, slow speed, 5 min.
 2. discard supernatant
 3. mix sediment, place 1 drop on slide, coverslip
 4. examine on 10x and 40x, especially along edge of coverslip
 5. unstained vs. stained; reduce microscope light
- D) Components of urine sediments
- cells
 - casts
 - crystals
 - microorganisms
 - parasites
- E) Cellular elements:
1. squamous cells
 2. transitional cells
 3. caudate epithelial cells
 4. renal tubular cells
 5. erythrocytes <<4-5/HPF
 6. leukocytes <<5-8/HPF
 7. sperm, bacteria
- F) Crystals
1. General features:
 - a. seldom have clinical significance
 - b. numbers of crystals are usually meaningless
 - c. concentration, acidity, temperature affect crystal number and morphology
 - d. correlation between crystals and uroliths
 2. Normal crystals
 - a. triple phosphates
 - b. Ca carbonate
 - c. bilirubin
 - d. oxalates
 3. Abnormal crystals
 - a. cystine
 - b. oxalate
 - c. ammonium urate (biurate)
 - d. amino acid
 - e. drugs
- G) Fat droplets
1. normal in cats
 2. causes:
 - lipemia – diabetes mellitus, fat in diet, hypothyroidism, obesity
 - catheter lube
- H) Casts
1. Features:
 - a. formed in distal tubules and collecting ducts
 - b. number of casts not reliable indicator of disease
 - c. type of cast is determined by material in lumen and indicates nature of disorder

Sources

vagina, prepuce,
urethra
urethra, ureters
renal pelvis
kidney tubules

2. types:
 - a. hyaline
 - b. cellular – renal, RBC, WBC
 - c. coarse granular
 - d. fine granular
 - e. waxy

LABORATORY EVALUATION OF KIDNEY FUNCTION

- A) General principles:
 1. determine:
 - nature or type of disease
 - extent of disease or dysfunction
 - prognosis
 2. limitations:
 - reserve capacity of kidney
 - sensitivity & specificity of test
 - importance of serial tests
- B) Blood urea nitrogen
 1. Synonyms: urea, urea nitrogen, SUN
 2. Source:
 - synthesized in liver from NH_3 – AA catabolism, GI absorption
 - distributed in total body water
 3. Excretion
 - a. kidney
 - glomerular filtration
 - tubular reabsorption: varies inversely with urine flow thru tubules
 - b. herbivores – urea metabolized by GI flora
 4. Normal: 10-30 mg/dL
 5. Serum or plasma urea values: balance of production and excretion
 - a. factors affecting urea production
 - i) functional hepatic mass
 - ii) dietary protein
 - iii) catabolism of body tissue
 - iv) drugs
 - b. factors affecting urea excretion:
 - i) changes in GFR
 - ii) metabolism in rumen and large intestine
 6. Decreased BUN concentration:
 - a. chronic liver disease
 - b. protein malnutrition
 - c. hyperadrenocorticism, anabolic steroids
 - d. GI metabolism in herbivores
 7. Increased BUN concentration:
 1. increased urea production
 - a. high protein diet
 - b. rapid catabolism of body tissue – necrosis, infection, fever, GI hemorrhage
 - c. drugs
 2. decreased excretion
 - a. prerenal
 - b. renal
 - c. postrenal

Creatinine

- A) Source:
 - produced in muscle at a fairly constant rate from creatine

- distributed in total body water
 - diffuses slower than urea
- B) Excretion:
 1. kidney:
 - *glomerular filtration
 - tubular secretion – minimal
 - small amount of enteric degradation
 - C) Normal values: <1-2 mg/dL, false inc. due to ketones
 - * therapeutic diuresis will cause BUN to decrease more rapidly than creatinine
 - D) Serum or plasma values: affected by fewer variables than BUN
 1. no tubular reabsorption – not affected by tubular flow rate
 2. minimal influence of diet
 3. not affected by protein catabolism
 4. not metabolized in liver or rumen
 5. relative size of muscle mass may have small effects on creatinine values
- Better indicator of GFR than BUN
- E) Increased creatinine concentration
 1. decreased GFR
 - prerenal
 - renal
 - postrenal

Laboratory diagnosis of azotemia

- A) AZOTEMIA – increased blood levels of nonprotein nitrogen (BUN and creatinine)
 - B) Prerenal azotemia
 1. causes:
 - dehydration
 - shock
 - cardiovascular disease
 - inc. dietary protein
 - protein catabolism
 2. features:
 - a. inc. serum BUN and creatinine
 - b. inc. urine specific gravity
 - dog: >1.030
 - cat: >1.035
 - horse, cow: >1.025
 - absence of glomerular disease
 - c. inc. PCV and TP
 - d. signs of dehydration
 3. azotemia improves with fluid Rx if caused by dehydration
 - kidney may be damaged if cause is not corrected
 4. prerenal azotemia is often superimposed on renal and postrenal azotemia
- C) Renal azotemia
 1. cause:
 - a. acute or chronic renal disease
 - 75% of nephrons must be nonfunctional
 - b. prolonged prerenal or postrenal disorders
 2. features:
 - a. inc. serum BUN and creatinine
 - b. urine specific gravity – depends on type and stage of renal disease

Persistent isosthenuria: 1.008 – 1.012

OR

Range of minimal concentration	Suspect range
dog: 1.013 – 1.030	1.030 – 1.040
cat: 1.013 – 1.035	1.035 – 1.040
horse, cow: 1.013 – 1.025	

- c. urine chemistry and sediment
- d. signs of dehydration
- e. PCV and TP are variable
- D) Postrenal azotemia
- 1. causes:
 - obstruction of urine flow or leakage of urine due to perforation
 - usual due to calculi, trauma, tumors
- 2. features:
 - inc. serum BUN and creatinine
 - urine specific gravity variable
 - PCV and TP reflect hydration status
- E) Other laboratory changes associated with renal dysfunction
 - phosphate
 - calcium
 - potassium
 - acid-base
 - amylase
 - cholesterol
 - clearance test: creatinine, electrolytes, dyes

URINALYSIS

Urine Collection:

1. Natural Voiding – midstream catch; difficult to obtain urine and usually gets contaminated
2. Catheterization – periurethral areas should be carefully cleansed with soap and water prior to passing the catheter. Addition of lubricant or chemical sterilant may alter results of urinalysis.
3. Cystocentesis (in dogs and cats) – especially indicated for bacterial culture as well as urinalysis. This is only performed when the bladder contains a sufficient volume of urine so that it is readily palpable, and will permit needle puncture without risk of damage to the bladder or other structures. A 5-20 ml syringe with a 20-24 gauge, 1½ inch needle can be inserted a few centimeters cranial to the neck of the bladder instead of into the vertex.
4. Manual Compression – can be applied in small animals to obtain urine with the patient in either a standing or a recumbent position.

Storage and Preservation of Urine Samples

- Urine examination should be done as soon as possible after collection.
- If it is impossible to complete an analysis on freshly collected urine, the specimen can be stored at refrigerator temperatures, but should be warmed to room temperature prior to examination. A crystal of thymol can be used to preserve urine specimens. Formalin can also be used to preserve

cells and casts, but chemical analysis should be done first before adding formalin.

Gross Examination of Urine

1. Urine Volume – affected by:
 - a. water and other fluid intake
 - b. environmental conditions
 - c. diet
 - d. size of the animal
 - e. activity of the animal
 - 1) dog: 12-30 ml/lb BW q24h
 - 2) cat: 4.5-9 ml/lb BW q24h
 - 3) cattle: 8-20 ml/lb BW q24h
 - 4) horse: 2-8 ml/lb BW q24h
 - 5) swine: 2-14 ml/lb BW q24h
 - 6) sheep and goat: 4.5-18 ml/lb BW q24h
2. Urine Color – depends on the concentration of urochromes present.
 - a. Pale urine can be seen in diabetes mellitus, diabetes insipidus, increased water intake, pyometra, diuretic phase of toxic nephrosis, advanced amyloidosis, primary renal glucosuria, hyperadrenocorticism, generalized pyelonephritis, and acute and chronic generalized nephritis. This may also be seen in patients following administration of ACTH or parenteral administration of fluids.
 - b. Dark urine can be seen in association with dehydration, fever, decreased blood pressure, terminal renal disease, circulatory dysfunction with edema, and reduced fluid intake
 - c. Horse urine is normally yellow when excreted, but may turn deep brown upon standing as a result of oxidation by pyrocatechin.
3. Transparency – can be recorded as clear, flocculent, or cloudy. Urine excreted from most species of animals is clear except in horses, which is normally thick and cloudy owing to the presence of calcium carbonate crystals and mucus. Pathologically, cloudy urine is observed in the presence of leukocytes, erythrocytes, epithelial cells, bacteria, mucus, fats, and crystals.
4. Urine Odor – not diagnostic. Ammoniacal odor is due to the action of the presence of urea-splitting organisms.
5. Specific Gravity – measurement of the relative amount of solids in solution, and is an indication of the degree of tubular reabsorption or concentration by the kidney. Normal values range from 1.015-1.045. Many factors influencing the amount of solute in urine must be considered in the interpretation of results. Transient increase is seen in decreased water intake, hyperventilation, when subjected to high environmental temperatures, and in animals with high fever.
 - a. Increased concentrations of urinary solids which results to increased specific gravity may occur in cases of dehydration, hypovolemic shock, edema associated with circulatory failure, burns with considerable extracellular fluid loss, and addition of excessively large quantities of solids.

- b. Decreased values are seen in cases following administration of corticosteroids, ACTH, diuretics, and parenteral administration of fluids.

Chemical Examination of Urine

1. Urine pH

- Acidic urine is normal in carnivorous animals, nursing calves and foals, and animals on diets containing excessive amounts of protein. Pathological increased may be associated with starvation, fever, or acidosis (both metabolic and respiratory).
- Alkaline urine is normal in herbivorous animals, or carnivorous animals on a high vegetable diet. It occurs in cystitis or obstructive lesions affecting the urinary bladder.
 - a. bovine – alkaline (7.4 to 8.4)
 - b. ovine – alkaline
 - c. caprine – alkaline
 - d. porcine – acidic or alkaline
 - e. canine and feline – acidic (6 to 7)

2. Protein – urine that is voided from the body does not normally contain detectable protein. Its presence is always considered pathologic except during the time of parturition, during the first few days of life, following strenuous exercise, or during estrus.

- Robert's Reagent – consists of 1 part concentrated nitric acid in a solution of magnesium sulfate; is one of the old and reliable methods to detect proteinuria.
- Physiologic transient proteinuria may follow:
 - a. excessive muscular exertion
 - b. emotional stress
 - c. excessive ingestion of protein
 - d. convulsions
- Abnormal protein in urine can be seen in:
 - a. renal proteinuria which may occur in nephritis and pyelonephritis
 - b. post-renal proteinuria seen in cystitis, vaginal and preputial discharges, prostatitis, pyelitis, urethritis, and urolithiasis
 - c. nephrosis due to severe renal damage from certain drugs and chemicals

3. Glucose – not present in normal urine. Colorimetric strip tests are done using the glucose oxidase, peroxidase and orthotoluidine reagents. High concentrations of ascorbic acid in canine urine may interfere with the test for urinary glucose. Emotional glucosuria may occur in conditions like fear, excitement, and restraint. Glucose may appear urine in the following diseases:

- a. diabetes mellitus
- b. acute or chronic pancreatitis accompanied by hyperglycemia
- c. hyperthyroidism
- d. hyperactivity of the adrenal cortex
- e. chronic liver disease
- f. hyperpituitarism with hyperglycemia
- g. increased intracranial pressure

- h. enterotoxemia in sheep due to *Clostridium perfringens*

4. Ketone Bodies – includes acetoacetic acid, acetone, and betahydroxybutyric acid. Ross Test is most widely utilized for detection of ketone bodies. In small animals, the principal cause of ketosis is diabetes mellitus. However, high fever and starvation may result in ketonuria of small puppies and kittens. Ketosis in ruminants occur when carbohydrate metabolism does not keep up with the carbohydrate needs of the body.

5. Blood

Hemoglobinuria – presence of free hemoglobin in urine; seen in:

- a. leptospirosis
- b. piroplasmosis
- c. photosensitization
- d. chemical hemolytic agents
- e. severe burns
- f. incompatible blood transfusions

Hematuria – presence of blood in the urine; seen in:

- a. pyelonephritis
- b. ureteritis
- c. cystitis
- d. urolithiasis
- e. pyelitis
- f. trauma to urinary bladder, kidney, or urethra
- g. prostatitis
- h. neoplasms of the kidney, bladder, or prostate
- i. parasites – *Diocotophyma renale*, *Capillaria plica*, and *Dirofilaria immitis* larvae
- j. acute nephritis

Microscopic Examination of Urinary Sediments:

1. Organized Elements

- a. Leukocytes – occur only as a result of pathologic processes. Seen in nephritis, pyelonephritis, pyelitis, urethritis, and cystitis.
- b. Erythrocytes
- c. Epithelial Cells – normally seen in urine, but presence of large numbers is suggestive of active tubular degeneration
- d. Microorganisms – bacteria, yeasts, fungi, protozoa
- e. Casts – principally formed in the lumen of the distal tubules, ascending loop of Henle, and collecting tubules of the kidneys. Cylinduria is the term for the presence of casts in urine; this condition is always pathologic.
 - 1) Hyaline Cast – mild form of renal irritation
 - 2) Granular Cast – in association with advanced irreversible renal disease like amyloidosis and chronic nephritis
 - 3) Waxy Cast – chronic lesions of the tubules and degeneration
 - 4) Renal Failure Cast – larger than granular cast; indicates obstruction or loss of more than one nephron
 - 5) Epithelial Cast – implies desquamation of epithelium

- 6) Erythrocytic Cast – indicates hemorrhage into the renal tubules and in association with trauma
- 7) Fatty Cast – appear as refractile bodies; indicates degenerative tubular disease associated with deposition of lipoidal material in the renal tubules
- 8) Leukocytic Cast – indicates presence of suppurative process
- 9) Cast-like Objects (Cylindroids) like mucous threads
- 10) Parasites
 - a) *Capillaria plica* – bladder worm of dog, cat, and fox
 - b) *Stephanurus dentatus* – swine kidney worm
 - c) *Diocotophyma renale* – giant kidney worm of dog and mink
- 11) Spermatozoa

2. Unorganized Elements – fat droplets, crystals, pigments

RENAL FUNCTION TESTS

Non-protein nitrogenous substances – urea, creatine, creatinine, uric acid, ammonia, amino acids

1. Blood Urea Nitrogen (BUN) – indicated:
 - a. whenever decreased kidney function is suspected
 - b. as a technique for measuring peripheral perfusion of tissues in animals subject to hypovolemic shock
 - c. as a routine pre-laboratory screening test

Methods:

- 1) Chromatographic Technique
- 2) Dipstick Method
 - Decreases in the rate of excretion of urea nitrogen produce an increase in the concentration of urea nitrogen. Azotemia resulting from decrease in excretory rate may be pre-renal (as a consequence of decreased blood flow), renal (nephritis), or post-renal (obstruction or rupture of the excretory pathway for urine).
2. Creatinine – a non-protein nitrogenous substance formed during muscle metabolism of creatine and phosphocreatine, and excreted by glomerular filtration. Methods used are Alkaline Picrate Method and Lloyd's Reagent. Interpretation of creatinine levels is similar to that for BUN levels. Conditions such as fever, toxemia, infection, and drug administration do not as readily influence creatinine levels.
3. Dye Excretion Test – most commonly uses phenolsulphthalein (PSP). An abnormal decrease in urinary excretion of this dye may occur because of poor renal perfusion, which may be due to general renal disease, dehydration, congestive heart failure, and hypoadrenocorticism.

Common Nephrotoxins of Domestic Animals

HEAVY METALS

Mercury
Lead
Arsenic
Cadmium
Thallium

ANTIBACTERIAL AND ANTIFUNGAL AGENTS

Aminoglycosides:

Gentamicin
Neomycin
Kanamycin
Streptomycin
Tobramycin

Tetracyclines
Amphotericin B

GROWTH-PROMOTING AGENTS

Monensin

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Aspirin
Phenylbutazone
Carprofen
Flunixin meglumine
Ibuprofen
Naproxen

MYCOTOXINS

Ochratoxin A
Citrinin

PLANTS

Pigweed (*Amaranthus retroflexus*)
Oaks (*Quercus* sp.)
Isotropis sp.
Yellow wood tree (*Terminalia oblongata*)

OXALATES

Ethylene glycol (antifreeze)
Halogeton (*Halogeton glomeratus*)
Greasewood (*Sarcobatus vermiculatus*)
Rhubarb (*Rheum raphaniticum*)
Sorrel, dock (*Rumex* sp.)

VITAMIN D

Vitamin D supplements
Calciferol-containing rodenticides
Cestrum diurnum
Solanum sp.
Trisetum sp.

ANTINEOPLASTIC COMPOUNDS

Cisplatin

d. Pathology and Laboratory Examination of Endocrine System

Mechanisms of Endocrine Disease

1. Primary hyperfunction of the endocrine glands
2. Secondary hyperfunction of the endocrine glands
3. Primary hypofunction of the endocrine glands
4. Secondary hypofunction of the endocrine glands
5. Endocrine hyperactivity secondary to diseases of other organs
6. Hypersecretion of hormones or hormone-like substances by nonendocrine tumors

7. Endocrine dysfunction due to failure of target cell response.
8. Failure of fetal endocrine function
9. Endocrine dysfunction resulting from abnormal degradation of hormones
10. Iatrogenic syndromes of hormone excess.

Primary hyperfunction

- may be due to hyperplasia or neoplasia.
 - e.g., hyperthyroidism in cats
 - "insulinoma" - an insulin-producing tumor of pancreatic islet cells; uncontrolled secretion of insulin leads to hypoglycemia.
 - functional tumors may have secondary effects on other endocrine glands either by positive or negative feedback.
- e.g., ACTH-producing tumor of the pituitary leads to (secondary) hyperplastic adrenal cortex, causing Cushing's disease.

- a functional (primary) adrenal cortex adenoma suppresses ACTH secretion, leading to (secondary) atrophy of other cortical tissue.

Secondary hyperfunction

- the increased activity (and usually increase in size) of an endocrine gland is an exaggerated response to factors to which it is normally sensitive.
- e.g., Cushing's disease due to adrenal cortical hyperplasia (secondary to an ACTH-producing tumor of the pituitary).
- e.g., Parathyroid gland hyperplasia which is usually a response to some other abnormality (diet or renal disease) leading to altered blood calcium and phosphate levels.

Primary hypofunction

- may be due to failure of normal development of an endocrine tissue or following destruction of an endocrine gland.

Secondary hypofunction

- diminished stimulation by pituitary trophic hormones will lead to atrophy in target endocrine gland.
- e.g., Disease in pituitary TSH results to atrophy of thyroid gland. However, if the TSH pituitary secretion is by itself secondary to TRH disease of the hypothalamus then a tertiary effect is on the target thyroid gland.

Pituitary Tumors

- most common diseases of the pituitary.

Non-functional

A tumor which is not functional may have local effects. May lead to reduced synthesis of various pituitary hormones, depending on the site, but rarely cause clinical signs (e.g., hypothyroidism or hypoadrenocorticism).

Functional tumors

- result in excess hormone secretion

The most common clinical consequence is Cushing's disease: hyperadrenocorticism results from adrenal cortical hyperplasia due to an ACTH-

producing pituitary tumor (most common functional pituitary tumors in dogs); the pituitary tumor may be microscopic and the gland may not be grossly enlarged- canine pituitary microadenoma.

Primary hypofunction

- may be due to failure of normal development of an endocrine tissue or following destruction of an endocrine gland.

Secondary hypofunction

- diminished stimulation by pituitary trophic hormones will lead to atrophy in target endocrine gland.

e.g., Disease in pituitary TSH results to atrophy of thyroid gland. However, if the TSH pituitary secretion is by itself secondary to TRH disease of the hypothalamus then a tertiary effect is on the target thyroid gland.

Pituitary hypofunction

Panhypopituitarism; dwarfism - e.g., Juvenile pituitary hypoplasia is rare but is seen particularly in German shepherd dogs (GSDs).

Pituitary hyperfunction

Acromegaly (overgrowth of connective tissue, visceral parenchyma and bone)

Diabetes insipidus

Diabetes insipidus is characterized by excretion of large amounts of dilute urine due to a failure of normal resorption of water by renal tubular epithelial cells.

result of lack vasopressin production

result of failure of the renal tubule epithelial cells to respond to vasopressin; in such cases vasopressin levels are normal or may even be elevated (nephrogenic diabetes insipidus associated with chronic renal failure or nephrocalcinosis / hypercalcemia).

Central and nephrogenic diabetes insipidus can be distinguished by the response, or absence of a response, to exogenous vasopressin.

ADRENAL GLAND

Hypoadrenocorticism

Addison's like disease is associated with lack of secretion of both glucocorticoids and mineralocorticoids (most cases are idiopathic). Inadequate glucocorticoids has effects on blood sugar, blood profiles and the skin:

hypoglycemia – this is due to reduced gluconeogenesis and increased sensitivity to insulin.

- lymphocytosis and eosinophilia due to hyperplastic lymphoid tissues
- skin hyperpigmentation which may be due to increased ACTH (acting like MSH) or melanocyte stimulating hormone.

Lack of mineralocorticoids:

- hyperkalemia due to potassium retention may lead to cardiac arrhythmia.

reduced blood volume due to sodium and chloride ions and water excretion.

This leads to:

- hemoconcentration
- dehydration/circulatory shock
- polyuria/polydipsia
- prerenal uremia.

Combination of these features lead to acute coma – an “Addisonian Crisis”.

Hyperadrenocorticism

- often termed Cushing's disease and is due to increased glucocorticoids.
- seen most commonly in older dogs

Canine Cushing's disease

Clinical changes are a result of the combined hormonal effects on carbohydrate, fat and protein metabolism, electrolyte homeostasis and anti-inflammatory effects.

Signs in affected dogs.

- alopecia
- polydipsia and polyuria
- polyphagia,
- muscle weakness
- poor wound healing
- liver enlargement
- dystrophic calcification (of skin, lung and muscles).

Polydipsia and polyuria - is probably due to an effect of the pituitary tumor on the secretion of antidiuretic hormone (vasopressin).

damage to the medullary “satiety center” may account for increased appetite. Increased cortisol will also inhibit vasopressin secretion and increase appetite.

Increased cortisol leads to increased gluconeogenesis and reduced glucose utilization leading to hyperglycemia and signs of diabetes mellitus.

Dystrophic calcification of proteins modified during increased metabolism. Muscle weakness clinically indicates increased catabolism and reduced protein synthesis.

Hypercholesterolemia (increased in about 90% of canine Cushing's) results from increased lipolysis of body fat.

Hepatomegaly results from hepatic swelling due to accumulation of intracellular lipid and/or glycogen.

“hypercoagulable state” leading to thrombosis; may include glomerular loss of antithrombin III and/or increased concentrations of various coagulation factors, fibrinogen and plasminogen.

Adrenocortical neoplasia

Primary and secondary tumors of the adrenal cortex are rare in any species.

they occur in older animals, particularly dogs.

ADRENAL MEDULLA

Neoplasia

Pheochromocytoma - tumor of the adrenal medulla. may be unilateral or bilateral; and may be small or large, may be benign or malignant (malignant form: same name, pheochromocytoma) rare, but cases occur in dogs and bulls. Catecholamine excess leads to the following vague and intermittent clinical signs:
hypertension
hypertension
tachycardia
cardiac hypertrophy
weakness and collapse
ascites or edema of hindlimbs resultant of caudal vena cava compression.

THYROID GLAND

GOITER – non-inflammatory and non-neoplastic enlargement of the thyroid gland.

Diffuse thyroid hyperplasia may also indicate hypothyroidism; it may be a result of increased stimulation by TSH if there is iodine deficiency leading to reduced circulating T3/T4. In adult animals there is little clinical significance but there may be effects in the offspring of affected females.

Canine hypothyroidism

- grossly, small and histologically, atrophic thyroid. There may be: lymphocytic infiltration (lymphocytic thyroiditis) or fat and fibrous tissue replacements (idiopathic follicular atrophy).

Hypothyroidism

Clinical signs that may be seen include:

- a. lethargy and obesity
- b. atrophic skin disease with myxedema
- c. infertility; normochromic/normocytic anemia
- d. increased CPK (due to a hypothyroid myopathy)
- e. hypercholesterolemia due to failure to metabolize lipid in the blood.

Feline hyperthyroidism (“thyrotoxicosis”)

- commonly occurring in older cats (senile uninodular or multinodular hyperplasia, sometimes termed adenomatous hyperplasia).

High circulating T3/T4 levels have a range of effects:

1. polyphagia but weight loss (with increased frequency and volume of fecal discharge).
2. polyuria/polydipsia
3. hyperactivity
4. tachycardia and cardiomegaly

Thyroid neoplasia

Follicular cell adenoma

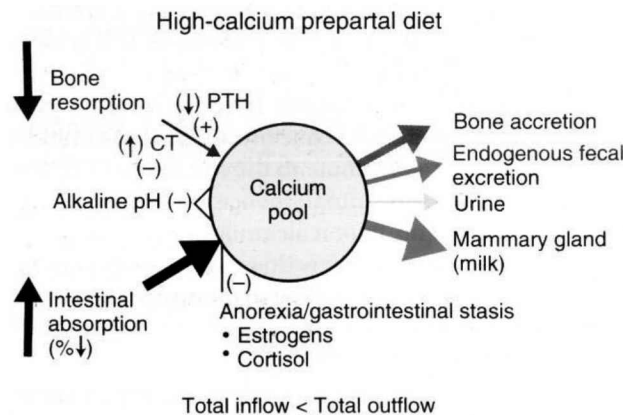
- functional and may occur in cats, rare in dogs.

Follicular cell carcinoma

- more common in dogs than cats
- tumors are usually unilateral but multinodular.
- rarely functional but are locally invasive and metastasize.
- poorly differentiated with a high mitotic rate.

Parafollicular/C-cell tumors

- rare; clinically hypercalcemia, excess resorption in bones.. etc.



Schematic diagram of calcium homeostasis in cows fed a high-calcium prepartal diet. In this case, calcium homeostasis is primarily dependent on intestinal calcium absorption. The rate of bone resorption is low, and parathyroid glands are inactive. Anorexia and gastrointestinal stasis that often occur near parturition interrupt the major inflow of calcium into the extracellular fluid calcium pool. Outflow of calcium with the onset of lactation exceeds the rate of inflow into the calcium pool, and cows develop a progressive hypocalcemia and paresis. CT, calcitonin; PTH, parathyroid hormone.

PANCREAS

There are four main islet cell types:

- alpha cells - produce glucagon
- beta cells - produce insulin; most numerous islet cells
- delta cells - produce somatostatin (growth hormone release inhibiting factor)
- F or PP cells produce pancreatic polypeptide.

Diabetes mellitus

the clinical syndrome resulting from hyperglycemia most commonly due to insulin deficiency. most cases of diabetes mellitus are a result of loss of/damage to beta cells or an effect on insulin.

Changes in the pancreas are varied depending on the precise pathogenesis.

- In some cases there will be interstitial fibrosis, reflecting chronic pancreatitis, with areas of loss of islet cells.
- Amyloid deposition obliterating normal islets common in cats, is typical of amyloid deposition and is commonly seen in cats -
- immune-mediated destruction of islet cells by autoantibody.

Cases of diabetes are usually classified into two main types (types 1 and 2) in humans; while there are similarities with the condition in animals, the classification in humans does not perfectly apply to disease in dogs and cats.

Type 1 diabetes (insulin dependent; [in humans] juvenile onset).

- autoimmune destruction of islet cells lead to failure of production of adequate insulin.
- this is the most common mechanism in dogs but not in cats.

Type 2 diabetes (non-insulin dependent; [human] adult onset)

- there may be reduced insulin secretion or peripheral insulin resistance.
- may be due to decreased effectiveness of secreted insulin (e.g. due to antibody)
- or decreased expression of insulin receptors on target organs.
- this the most common form of diabetes in cats where islet amyloid deposition is commonly found.

Chronic hyperglycemia reduces insulin secretion and there is loss of beta cells ("glucose toxicity")

Other mechanisms include destruction of pancreatic islet tissue, due to neoplasia or pancreatitis

Other diseases resulting in insulin resistance, particularly other endocrinopathies (Cushing's disease, acromegaly and to a lesser extent hyperthyroidism in cats).

Insulin-resistance and hyperinsulinemia occurs in obese dogs but does not necessarily progress to diabetes mellitus.

Fat

- accumulation of fat in the liver (fatty change of hepatocytes) leads to hepatomegaly; there is also vacuolation of renal tubular epithelial cells. Increased ketones in the blood (and urine) may lead to ketoacidosis, dehydration/circulatory shock and diabetic coma.

Protein

- lack of insulin reduces protein synthesis; protein is also broken down to compensate for failure of normal glucose metabolism. There is muscle wasting.

Carbohydrate

- glucose uptake and phosphorylation is inhibited; there is polyphagia and fat and protein are catabolized as alternative energy sources.
- lack of glucose uptake leads to hyperglycemia; the renal threshold is exceeded and glucosuria occurs leading to polyuria/polydypsia and predisposing to cystitis and ascending urinary tract infection.
- metabolism of glucose to sorbitol and fructose in the lens of the eye leads to influx of water and separation of the lenticular fibers; this results in

opacity (cataract formations) and occurs in about 70% of diabetic dogs.

Islet cell neoplasia

Insulinoma

most common

Amyloid production within the tumor tissue is common.

many of the tumors are malignant with metastases to lymph nodes and the liver.

Clinical signs due to hypoglycemia include:

confusion

stupor

convulsions and coma.

- less severe after feeding.

Glucagonomas

- excess secretion may lead to hyperglycemia

in some cases, may present clinically as diabetes mellitus.

DISORDERS OF THE ENDOCRINE PANCREAS

I. Physiology of the endocrine pancreas: Islets of Langerhans

A) Alpha cells secrete glucagon

1. Secreted when blood glucose is low

2. Stimulates glycolysis and gluconeogenesis increasing blood glucose levels

B) Beta cells secrete insulin

1. Secreted when blood glucose is high

2. Stimulates uptake of glucose by insulin-dependent cells (primarily myocytes and adipocytes) decreasing blood glucose levels

C) Delta cells secrete somatostatin: inhibitory regulator of pituitary tropin secretions (growth hormone, thyroid stimulating hormone, adrenocorticotropin hormone, prolactin).

D) F cells secrete pancreatic polypeptide: inhibits pancreatic bicarbonate and protein secretion.

II. Diabetes Mellitus (DM)

A) Types of diabetes mellitus

1. Type I (formerly insulin-dependent diabetes mellitus, IDDM)

a. Progressive loss of pancreatic beta-cell function with absolute insulin deficiency

- Autoimmune-mediated destruction of islets

- Chronic, recurrent pancreatitis with destruction of islets

b. Impaired glucose transport into most cells

c. Accelerated hepatic gluconeogenesis and glycogenolysis

d. Typically sudden onset with persistent clinical signs

2. Type II (formerly noninsulin-dependent diabetes mellitus, NIDDM)

a. Peripheral insulin resistance (decreased insulin sensitivity) with or without impaired insulin secretion results in relative insulin deficiency.

b. Factors that increase insulin resistance:

i Obesity

ii Male sex

iii Inactivity

iv Concurrent illness

c. Causes of impaired insulin secretion:

i Islet amyloidosis (common cause of DM in cats)

ii Acute pancreatitis

iii Glucose toxicity (persistent hyperglycemia)

d. Usually gradual, progressive onset with clinical signs that wax and wane resulting in insulin dependent and non-insulin dependent episodes.

3. Other (formerly) Type III or secondary diabetes mellitus)

a. Hyperadrenocorticism:

- Results in insulin resistance and glucose intolerance due to excessive glucocorticoids

- 5-10% of dogs and 80% of cats with hyperadrenocorticism will have DM.

b. Gestational diabetes:

- Insulin resistance and glucose intolerance in pregnant bitches, and less frequently in nonpregnant diestral bitches, due to progesterone

- May resolve during metestrous or result in clinical DM

c. Pancreatic adenocarcinoma: 9-18% of cats will have DM

d. Drugs that antagonize insulin: progestins, corticosteroids

e. Acromegaly (hypersomatotropism or excess growth hormone): induces marked insulin resistance

f. Congenital: e.g., inherited early-onset DM characterized by aplasia of islet betacells (Keeshonden)

B) Occurrence of diabetes mellitus

1. Dogs

a. Type:

- Type I DM is most common

- Other: gestational/diestrus, hyperadrenocorticism, drugs

b. Signalment

- Usually > 7 yrs

- Females affected twice as often as males

- Commonly seen in Poodles, Dachshund, Min, Schnauzer, Beagles, Pulik, Cairn terrier, Miniature Pinscher

- Genetic basis proven in Samoyed, Min, Poodle, Keeshond, Golden Retriever, Rottweiler

c. Clinical presentation: sudden onset, rapidly progressive over several weeks

2. Other species: DM is not frequently diagnosed in other species and is often of the secondary type, i.e., associated with presence of insulin antagonists.

C) Pathophysiology of clinical signs:

1. Hyperglycemia is primarily a result of impaired glucose utilization, but also results from gluconeogenesis leading to muscle atrophy from catabolism of protein for amino acid precursors. Glycolysis also contributes to hyperglycemia.

2. Once the renal threshold for glucose is exceeded (180-220 mg/dl in dogs and 290 mg/dl in cats) glycosuria occurs resulting in osmotic diuresis → polyuria and polydipsia (PU/PD).
 3. Hormone-sensitive lipase (normally inhibited by insulin) is activated to release nonesterified fatty acids from adipose tissue → weight loss. Ketonuria may occur secondary to excessive lipolysis.
 4. impaired glucose utilization by satiety center combined with weight loss stimulates the appetite → polyphagia.
- D) Diagnosis of diabetes mellitus
1. Consistent clinical presentation
 2. Persistent fasting hyperglycemia with concurrent glycosuria
 - See Table 1 for differentials for hyperglycemia.
 - Cats frequently develop a stress hyperglycemia, which can be as high as 300-400 mg/dl; however, most do not develop a concurrent glycosuria.
 3. Minimum database performed to detect concurrent or complicating disorders
 - a. Complete blood cell count
 - Usually normal in uncomplicated DM
 - Inflammatory leukogram may reflect concurrent disease
 - Cats may exhibit increased numbers of Heinz bodies without a hemolytic anemia.
 - b. Chemistry panel (always separate serum from red cells within 30 minutes to prevent artificial decrease in glucose levels due to utilization by red cells)
 - Hyperglycemia
 - Increase in liver enzymes (ALT, AST, ALP, GGT) may be due to diabetes or concurrent hepatic or pancreatic disease
 - Hypercholesterolemia
 - Hypertriglyceridemia due to increased lipolysis
 - Recommend measuring lipase and amylase, as well as thyroxine (T4) in cats
 - Other abnormalities due to concurrent disease
 - c. Urinalysis and urine culture
 - Glycosuria
 - Proteinuria, hematuria, pyuria, bacteriuria may be present if a lower urinary tract infection is present
 - May be mildly ketonuric

Causes of hyperglycemia in the dog and cat

- Diabetes mellitus*
- "Stress" (cat)*
- Post prandial (semi-moist food)
- Hyperadrenocorticism*
- Drug therapy* (corticosteroids, progesterone, megestrol acetate)
- Acromegaly (cat)
- Diestrus (bitch)
- Pheochromocytoma (dog)
- Pancreatitis

- Exocrine pancreatic neoplasia
- Renal insufficiency
- Acute colic
- Endotoxemia (initial phase)
- Glucose-containing fluids, esp. TPN mixtures
- Laboratory error

* common causes

4. Additional tests to diagnose diabetes and monitor therapeutic response
 - a. Glycosylated proteins
 - Non-reversible binding of glucose to blood proteins
 - The concentration of glycosylated protein is proportional to blood glucose and reflects mean blood glucose over the life span of the protein
 - Useful for differentiating stress hyperglycemia from true DM in cats and for "spot checks" of glycemic control during insulin therapy
 - Interpretation:
 - Use reference interval by your lab (note units)
 - Results within reference interval suggest normoglycemia or transient hyperglycemia
 - Increased levels usually indicate sustained hyperglycemia
 - Specific reference intervals for normal, transient hyperglycemia, and diabetes overlap with each other (see reference intervals below)

Glycosylated hemoglobin

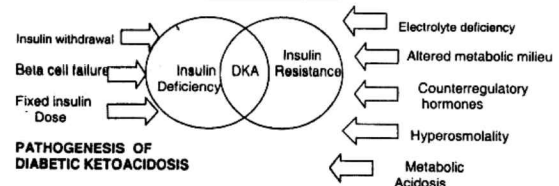
- Reflects blood glucose levels over previous 3-4 months.
- EDTA whole blood specimen, stable up to one week at 4°C.
- Affinity chromatography is preferred method.
- Results affected by conditions that affect red cell life-span and by the hematocrit (Hct).
- Reference interval (normal): dogs 2.1-4.3%, cats 0.9-2.6%.
- Diabetic interval: dogs 3.6-14.1%; cats 1.9-6.2%.

Fructosamine (serum proteins)

- Reflects blood glucose levels over the previous 1-3 weeks
- Measured in serum, specimen can be frozen
- Automated colorimetric assay
- Severe hypoalbuminemia or hypertriglyceridemia, hemolysis, lipemia, or icterus can affect results.
- Ill cats without DM may have mild increases in fructosamine.
- Reference interval (normal): dogs 170-340 $\mu\text{mol/L}$, cat 210-380 $\mu\text{mol/L}$
- Transient hyperglycemia: cats 200-410 $\mu\text{mol/L}$
- Diabetic interval: dogs 330-750 $\mu\text{mol/L}$, cats $\geq 340 \mu\text{mol/L}$
- b. Glucose curves:
 - Measurement of sequential blood glucose levels over 10-12 hours in response to a dose of insulin
 - Evaluates time of onset, peak, and duration of insulin activity

- Aids in the selection of an appropriate insulin dose for an individual patient
- Response may be affected by the stress of hospitalization, especially in cats
- c. Baseline insulin levels:
 - Insulin levels above the reference interval suggest residual beta cell function; however, low levels cannot differentiate between Type I and Type II.
 - Most human assays work in dogs and cats, but should be validated for each species.
- d. Provocative testing (intravenous glucose tolerance test, glucagon tolerance test, arginine response test)
 - Used to evaluate residual beta cell function and thus, theoretically, differentiate between Type I and Type II DM
 - Protocol: measure insulin over time in response to an exogenously administered insulin-secretoagogue (glucose, glucagon, arginine)
 - Type II diabetics should have normal to increased insulin levels in response to a stimulus; however, Type II diabetics with glucose toxicity will have low insulin levels.
 - Type I diabetics have insulin levels below normal in response to a stimulus.
 - Rarely needed to diagnose DM and does not reliably differentiate between Type I and Type II DM in most cats and dogs.
- e. C-peptide analysis:
 - C-peptide is a portion of the pro-insulin molecule that is secreted in equal amounts with insulin.
 - C-peptide is theoretically detectable in Type II DM and undetectable in Type I.
- 5. Glucometers: **FOR YOUR INFORMATION ONLY**
 - a. Patient-side, hand-held device to measure whole blood glucose quickly and conveniently
 - b. Quality control and calibration must be followed in order to obtain reliable results!
 - c. Results will vary with unit and operator.
 - d. Whole blood glucose will differ from serum glucose; values correlate best at lower glucose concentrations.
- 6. Additional tests to diagnose diabetes and monitor therapeutic response
 - a. Blood glucose results are usually lower than with other assay methods; this is designed to prevent hypoglycemia in people who adjust their own insulin dose based on glucometer readings.
- III. **Diabetic Ketoacidosis (DKA)**
 - A serious complication in diabetic patients usually triggered by a systemic illness
 - A. Pathogenesis of diabetic ketoacidosis
 1. Insulin deficiency: absolute or relative
 2. Counter-regulatory hormone excess (glucagon, catecholamines, cortisol, growth hormone): contributes to insulin resistance and raises blood glucose by stimulating protein catabolism and lipolysis and promoting gluconeogenesis and glycogenolysis.

3. Ketogenesis: excessive triglycerides from lipolysis are shunted to ketone formation; ketones serve as an alternative energy source for some cell types.
4. Fasting: anorexia causes a decline in inhibitors of ketogenesis and reduces peripheral utilization of ketones resulting in ketoacidosis.
5. Dehydration: a result of osmotic diuresis, decreased intake, vomiting, diarrhea, and hyperventilation; leads to prerenal azotemia and decreased glomerular filtration rate (GFR) reducing excretion of glucose, ketones, and hydrogen ions.



The pathogenesis of KDA, illustrating the interaction of insulin deficiency and insulin resistance necessary in the development of the ketoacidotic state. Adapted from Nelson and Feldman.

- B. Consequences: severe systemic illness with profound weakness
 1. Osmotic diuresis due to glycosuria and ketonuria results in:
 - Loss of body water leading to marked dehydration and subsequent poor perfusion and tissue hypoxia.
 - Loss of total body electrolytes (Na, K, Cl) that further impairs renal concentrating ability.
 2. If water loss exceeds electrolyte loss, serum concentrations of electrolytes may actually be increased even though total body levels are depleted (hypertonic dehydration).
 3. Accumulation of ketoacids results in high anion gap metabolic acidosis.
 4. Hyperosmolality (hyperglycemia, $\pm$ hyponatremia) leads to cellular dehydration and neurologic signs.
- C. History and physical exam
 1. Most common in previously undiagnosed diabetics, but also seen in insulin-treated diabetic patients
 2. Classic signs of DM may or may not be reported by the owner.
 3. Systemic signs increase in severity as disease progresses and are related to precipitating disease and worsening metabolic derangements.
 - (lethargy, anorexia $\rightarrow$ dehydration, vomiting, depression $\rightarrow$ moribund state)
- D. Diagnosis
 1. An ill, diabetic patient with ketones in the urine and acidosis due to ketonemia
 2. The following tests are needed for immediate assessment and treatment of any critical patient:

Test Results in DKA patient

PCV/T.P. Relative polycythemia and hyperproteinemia due to dehydration

Blood glucose (BG). Blood glucose can be 500-1000 mg/dl (BG > 500 mg/dl occurs when reduced GFR prevents excretion of glucose)

BUN or creatinine. Prerenal azotemia; ketones may interfere with some creatinine assay methods.

tCO₂/arterial blood gas Low tCO₂ and pH, metabolic acidosis due to ketoacids, lactic acid, and possibly uremic acids

UA/culture. Glycosuria, ketonuria (β -hydroxy butyrate and acetate, the major ketones in animals, are not detected by urine strips), S.G. may not be maximally concentrated owing to osmotic diuresis AND increased refraction caused by glucose, +/- urinary tract infection

Electrolytes. Total body deficits in Na, Cl, and K; however, the values measured initially may be high, normal, or low depending on the severity of hypertonic dehydration and extent of electrolyte loss in urine. Potassium may be increased due to poor distal tubular flow (site of excretion) and absence of insulin.

3. Complete minimum data base should be performed to assess concurrent conditions:

Hemogram. Stress or inflammatory leukogram; cats may exhibit increased Heinz bodies without a hemolytic anemia; evidence of disseminated intravascular coagulation may be seen.

Chemistry panel. Assess liver and pancreatic function, mineral balance (calcium and phosphorus), cholesterol, albumin. Absence of insulin impairs reabsorption of phosphorus from renal tubules and may lead to hypophosphatemia.

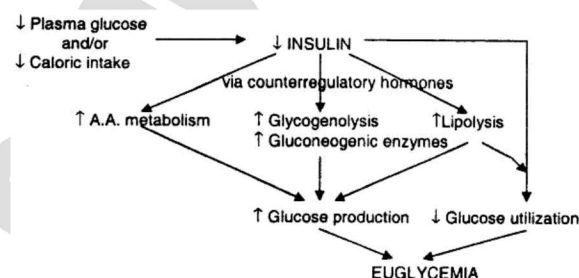
Osmolality. Hyperosmolality due to hypernatremia, hyperglycemia, and azotemia

4. Monitoring of therapy: frequent measurement of electrolytes, glucose, minerals, PCV/TP.

IV. Insulinoma

A. Pathophysiology

1. Glucose up-take by pancreatic beta cells is insulin-independent. When blood glucose exceeds 110 mg/dl, insulin is secreted by the beta cells. When glucose falls below 60 mg/dl, insulin secretion is suppressed and counter-regulatory hormone secretion is increased (early and most important hormones are catecholamines and glucagons; late hormones: cortisol and growth hormone). See figure.



The hormonal and substrate changes whereby euglycemia is maintained (and hypoglycemia prevented) in normal subjects during fasting. The fall in plasma insulin is the key hormonal change resulting in increased glucose production and decreased glucose utilization. The decline in plasma insulin is, in turn, a result of a small decrease in plasma glucose (5-10 mg/dl) and/or decline in caloric intake.

2. Functional ISLET CELL TUMORS autonomously secrete insulin (as well as other polypeptides, including pancreatic polypeptide, somatostatin, glucagons, serotonin, gastrin, and corticotropin) regardless of blood glucose concentration; surges in insulin secretion also can be stimulated by eating, excitement, and exercise resulting in a sudden onset of hypoglycemia and manifestation of signs.

3. Insulin inhibits hepatic glycogenolysis and gluconeogenesis and interferes with attempts of counter-regulatory hormonal to restore euglycemia while promoting continued glucose uptake by insulin-sensitive tissues. This results in profound hypoglycemia.

4. Insulinomas are usually small (≤ 1 cm), single, pancreatic masses with microscopic metastases present at the time of diagnosis; common metastatic sites include lymphatics, lymph nodes, liver, mesentery, and omentum.

B. Signalment, history, signs, and physical findings

1. Signalment

▪ Seen infrequently in dogs; mean age in dogs is 9 yrs.

▪ Breeds that may be predisposed include Boxer, Irish setter, German shorthaired pointer, Weimaraner, standard poodle, fox terrier, German shepherd dog

▪ Very rare in cats

▪ Common in ferrets

2. History and Symptoms:

a. Symptoms are usually intermittent and associated with fasting, excitement, exercise, and eating.

b. Two types of signs:

i Sympathetic nervous system: behavioral changes, hunger, shaking, trembling, muscle fasciculations; often occur before neural signs

ii Neuroglycopenic: weakness, ataxia, depression, seizures, status epilepticus, coma

c. Outcome of early hypoglycemic event:

i Resolution of signs due to restoration of euglycemia by counter-regulatory mechanisms or food intake

ii Progression to severe symptoms

3. Physical examination: unremarkable; weight gain may be seen due to the anabolic effects of insulin

C) Diagnosis

1. Tentative:

- a. Whipple's triad is supportive but nonspecific for a diagnosis of insulinoma:
 - i Signs of hypoglycemia occur after fasting or exercise.
 - ii Demonstrate subnormal blood glucose.
 - iii Symptoms relieved by administration of glucose.
- b. Hypoglycemia detected on a fasted blood glucose during symptomatic episode
- c. Non-fasted, random glucose measurement frequently reveals hypoglycemia.
2. Definitive:
 - a. Demonstration of inappropriately high insulin level in the presence of hypoglycemia
 - i Perform serial measurements of fasting blood glucose in hospital (glucometer); when glucose falls below 60 mg/dl, draw a serum sample for insulin and confirm low glucose by chemistry analyzer; feed patient gradually after completion of test.
 - ii Separate and freeze serum immediately; make sure reference laboratory has a validated insulin RIA for species of interest.
 - iii Normal insulin is 5-20 μ U/ml (canine).
 - iv High or normal insulin in the face of hypoglycemia is abnormal.
 - v If first pairing is nondiagnostic, repeat or perform exploratory.
 - vi A high insulin alone is not useful, insulin must be interpreted in the light of glucose levels.
 - vii Identification of a pancreatic mass at laparotomy.
 - viii Glucose-to-insulin ratio, and amended insulin-to-glucose ratio do not provide any additional sensitivity or specificity.
 - ix Provocative tests are time-consuming, expensive, and potentially dangerous and are no better than paired insulin-glucose (glucagon tolerance, intravenous glucose-tolerance, tolbutamine-tolerance, epinephrine-stimulation, calcium-infusion).
3. Minimum database usually doesn't provide a definitive diagnosis of insulinoma; however, it is important to rule out other causes of the observed symptoms and hypoglycemia. See Table 2.
 - a. Hematology and urinalysis usually normal.
 - b. Chemistry often normal except for hypoglycemia; may have mildly elevated liver enzymes
 - c. Radiographs and ultrasound used to rule out other diseases and to evaluate for metastatic disease.

Classification of fasting hypoglycemia. From Nelson and Feldman.

 - I. Endocrine (too much insulin or too little counter-regulatory hormones)
 - A) Excess insulin or insulin-like factors
 1. Insulin-producing islet cell tumor
 2. Extrapancreatic tumors producing and secreting insulin-like substances

3. Iatrogenic insulin overdose
- B) Growth hormone deficiency
 1. Hypopituitarism affecting several tropic hormones
 2. Monotropic growth hormone deficiency
- C) Cortisol deficiency
 1. Hypopituitarism
 2. Isolated ACTH deficiency
 3. Hypoadrenocorticism
- II. Hepatic (decreased glucose synthesis)
 - A) Congenital
 1. Congenital shunts
 2. Glycogen storage disease
 - B) Acquired
 1. Vascular shunts
 2. Chronic fibrosis
 3. Hepatic necrosis: toxins, infectious agents
- III. Substrate (decreased intake or excess utilization)
 - A) Extrapancreatic tumors that utilize large quantities of glucose
 - B) Fasting hypoglycemia of pregnancy (pregnancy toxemia)
 - C) Puppy hypoglycemia = ketonemia (alanine deficiency?)
 - D) Uremia
 - E) Severe malnutrition/inadequate diet or feeding schedule in neonates
 - F) Severe polycythemia/leukemia
 - G) Sepsis
- IV. Artifact and laboratory error (delayed serum separation)

LABORATORY EVALUATION OF THE EXOCRINE PANCREAS

I. Exocrine function of the pancreas

A) Production and secretion of digestive enzymes

1. Proteases:

Secreted as inactive precursors (zymogens)

Activated in intestine to:

- Trypsin
 - Chymotrypsin
 - Carboxypeptidase
 - Elastase
2. Amylases
 3. Lipases

B) Secretion of bicarbonate to neutralize gastric HCl

II. Diseases of the exocrine pancreas

A) Inflammation and necrosis

B) Exocrine insufficiency

C) Neoplasia

III. Inflammation and necrosis

A) Occurrence of pancreatitis: dogs, cats; rare in other domestic species

B) Causes: idiopathic; associated with high fat diet, some drugs (e.g., glucocorticoids, sulfas), trauma, ischemia

C) Pathogenesis: Zymogens activated prematurely in pancreas → autodigestion of pancreas

D) Hemogram: variable

- Dehydration may be indicated by elevation of PCV/TP.
 - Leukogram may reflect inflammation (mild neutrophilia or marked leukocytosis with left shift or even a severe left shift with neutropenia) or stress.
 - If DIC develops secondary to pancreatitis, thrombocytopenia may be present.

E) Serum biochemical abnormalities result from damage to the pancreas, organ damage from release of pancreatic enzymes and inflammatory mediators, and fluid imbalance secondary to vomiting.

 - Fasting hyperlipemia
 - Serum amylase activity
 - Tissue sources
 - Pancreas
 - Duodenal mucosa (likely source of normal basal levels)
 - Kidney degrades and excretes amylase
 - Interpretation of hyperamylasemia
 - Occurrence
 - Pancreatitis – 80% of cases have increased amylase
 - Renal disease (decreased clearance)
 - Intestinal perforation
 - The higher the serum amylase activity (>3x increase or >3-4x increase if renal insufficiency is present), the more likely it is that pancreatic disease is present.
 - Serum amylase values may be normal in animals with pancreatic disease.
 - Interpret in conjunction with lipase values and clinical and radiographic/ ultrasonographic signs.
 - Serum lipase activity
 - Sources: pancreas, gastric mucosa
 - Inactivation: kidney, other
 - Interpretation of hyperlipasemia
 - Occurrence
 - Pancreatitis
 - Intestinal perforation
 - Renal disease
 - Slight increase following administration of glucocorticoids
 - Three-fold increase in serum lipase activity is supportive of pancreatitis; values may be normal in pancreatitis.
 - An ELISA for serum lipase based on its immunoreactivity (not activity) has been developed recently for dogs and cats (cPLI and fPLI, respectively). This test is very promising in the diagnosis of pancreatitis in both species.
 - Serum trypsin (TLI)
 - Test measures immunoreactivity of trypsin (not activity)
 - Increased value strongly suggests pancreatitis; however, animals with renal insufficiency may have increased TLI because of decreased excretion.
 - Currently, results of test are not available for 7-10 days, but more rapid turn-around time is pending.
 - Electrolyte abnormalities are variable (depending on vomiting, etc.)
 - Hypocalcemia (multifactorial)
 - Hyperglycemia – transient or persistent if diabetes mellitus is a sequel
 - Hepatic enzymes (SAP, ALT) may be elevated owing to release of proteases into portal circulation and subsequent structural and functional changes in hepatocytes.
 - ± Hyperbilirubinemia; if present due to functional damage from proteases or mechanical obstruction of bile duct secondary to inflamed pancreas.
 - Prerenal azotemia

F) ± Metabolic acidosis

G) Peritoneal effusion: suppurative, nonspecific peritonitis

H) Acute vs. chronic pancreatitis: Recurrent bouts of pancreatitis may lead to exocrine pancreatic insufficiency or diabetes mellitus (especially in cats).

I) Pancreatitis in cats

 - Three forms: necrotizing form, distinct suppurative form, and chronic mild interstitial form
 - Laboratory tests
 - Increased serum trypsin (fTLI): most sensitive test available for diagnosis of pancreatitis in cats.
 - Serum lipase activity is increased in some cats; measuring amylase activity typically is not helpful. *fPLI (serum lipase; see above) is a promising new test that measures the amount, not the activity, of lipase based on its immunoreactivity.
 - Hyperglycemia (except suppurative form)
 - Stress
 - Concurrent diabetes mellitus
 - Hyperbilirubinemia with concurrent cholangiohepatitis
 - May develop exocrine insufficiency with chronic bouts of pancreatitis

Primary Hyperfunction of an Endocrine Gland

Neoplasia	Hormone	Lesion/Sign
Adipophil adenoma (pituitary gland)	Growth hormone	Acromegaly
Adrenal cortical adenoma/carcinoma	Estrogen	Feminization
Pheochromocytoma (adrenal medulla)	Norepinephrine	Hypertension
Thyroid follicular cell adenoma	T ₄ , T ₃	↑ Basal metabolic rate
C-cell adenoma/carcinoma (thyroid gland)	Calcitonin	Osteosclerosis
Parathyroid gland chief cell adenoma	Parathyroid hormone	Fibrous osteodystrophy
Pancreatic β-cell adenoma/carcinoma	Insulin	Hypoglycemia