COURSE CODE:	VPT 302
COURSE TITLE:	General Pathology
NUMBER OF UNITS:	3 Units
COURSE DURATION:	Three hours per week

COURSE DETAILS:

Course Coordinator:	**Dr. S.O. Omotainse.** *DVM, MVSc., PhD*
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Other Lecturers:	**Dr. M. O. Olaniyi,** DVM, MVSc**.& Dr. O. L. Ajayi,** DVM, MVSc

COURSE CONTENT:

Introduction to principles of Veterinary Pathology. Death of cells and tissues: necrosis, gangrene, infarcts; cellular deposits: gout, melanosis, calcification, icterus, photosensitization. Disturbances of growth and of circulation. Inflammation. Healing and regeneration. Types and aetiology of neoplasia. Nature and causes of disease.

COURSE REQUIREMENTS:

This is a compulsory course for all DVM students and attendance of at least 75% is required to write the examination.

READING LIST:

1. McGavin, M. Donald and Zachary, F. James. 2007. Pathologic basis of veterinary disease, 4th Ed.Mosby Elsevier.
2. Jubb, K. V. F., Kenedy, P. C. and Perma, M. 1985. Pathology of domestic animals. 3rd Ed. Academic Press, New York.

LECTURE NOTES

INTRODUCTION TO GENERAL PATHOLOGY

By Omotainse, S. O.

Pathology is the study of anatomical, physiological and biochemical changes in the host when exposed to disease agents or there is deprivation of essential factors.

CLASSIFICATION OF PATHOLOGY

•A. SUBSPECIALITIES
*General Pathology
*Systemic Pathology e.g. ***Respiratory, GIT,*** etc
*Organs
*Clinical Pathology/Chemical Pathology
*Surgical Pathology e.g. Tumour

B. RESEARCH
•Molecular pathology
•Ultra structural pathology
•Immunopathology
•Biochemical pathology
•Physiological pathology
*****Exfoliative Cytology of cells obtained from fluids, tracts, tissues e.g. of female in pregnancy diagnosis, cancer.

CELL INJURY AND DEATH
A. Cellular Adaptation
- i. Atrophy
- ii. Hypertrophy
- iii. Hyperplasia
- iv. Metaplasia

B. Cell Injury
C. Necrosis
D. Apoptosis
• **Cellular Adaptation**- adjusting their structures and functions in response to physiological and pathological conditions:
i. **Atrophy**- shrinkage of cells.
ii. **Hypertrophy**- increase in the size of cells to result in enlargement of the organs.
iii. **Hyperplasia**- increased number of cells in an organ or tissue.
iv. **Metaplasia**- transformation or replacement of one adult cell type with another.
•When cells fail to adapt, they undergo certain changes called **cell injury**. The cells so affected may or may not recover (Reversible or irreversible death)

Causes
•Anoxia (O2 deprivation)
•Physical agents
•Chemical agents
•Injection agents
•Immunological reactions
•Genetic defects
•Nutritional imbalances.

MORPHOLOGY OF CELL INJURY
Reversible.

•Cellular swelling and vacuoles formation (Hydropic changes)
•Changes at this stage are better appreciated by the EM showing blebbing of the plasma membrane, swelling of mitochondria and dilatation of endoplasmic reticulum (ER)

Irreversible (**NECROSIS**)
*Irreversible changes produced by enzymatic digestion of dead cellular elements, denaturation of protein and autolysis (by lysosomal).
*Changes are seen in the Nucleus and Cytoplasm.

Mechanisms of cell death

Certain biochemical events that take place in the process of cell death include:
•ATP depletion
•Loss of calcium homeostasis and free cytosolic calcium
•Free radicals: superoxide anions, hydroxyl radicals, hydrogen peroxide
•Defective membrane permeability
•Mitochondrial damage
•Cytoskeletal damage
•**APOPTOSIS** (Necrobiosis)
- vital process that helps eliminate unwanted cells.
-An internally programmed series of events effected by dedicated gene products.
-Removal of excess cells in developing embry

LESIONS
– Characteristic changes in an organ produced by a disease
Pathognomonic lesion: a change which is specifically characteristic of a disease e.g. Negri bodies for Rabies virus in neurons

NECROSIS
Necrosis: the local death of cells or tissues within the living organism. This should be distinguished from the term necrobiosis which is a physiological death: natural death of a cell at the end of its lifespan e.g. superficial layers of epidermis or epithelial cell of the intestinal tracts.
Death – ceasation or extinction of life.
Microscopic Features of Necrosis:
•Nuclear changes
•Cytoplasmic change
•Other change

GROSS CHARACTERISTICS OF NECROTIC TISSUES
•Loss of colour – becomes paler if not filled with blood- black if filled with haemolysed blood.

•Loss of strength [tensile strength] – inability to withstand pressure (liver, lungs) or stress (intestine)
*****Development of putrifaction when exposed to saprophytic organism (saprophytes) e.g. gangrene or PM autolysis.

Difference between Necrosis and Postmortem Autolysis

Microscopically:

•Presence of both normal and dead tissues on the same field.

•Necrotic tissues normally act as irritants to the body, therefore there is normally a zone of inflammatory reaction (cellular response) if left on the body.

•Erythrocytes in the blood vessels are normally bright red. But at postmortem, rbc
usually undergo lysis (haemolysis).

Note: The GIT b/c of the bacterial content is about the fastest to undergo PM changes.

The liver and the CNS also quickly undergo postmortem changes.

CAUSES OF NECROSIS

1. Poisons: substances that produce injury when taken into or applied to the animal body.

2. Lack of proper blood supply: cuts down the supply of nutrients and O2 e.g. thrombi (from emboli), ligatures, compressions of blood vessels by tumors.

•CAUSES OF NECROSIS CONTD-

3. Lack of nerve supply – e.g. in Sweeney-shoulder lameness
in those associated with atrophy and necrosis of the
(supraspinatus/infraspinatus) muscle of the scapula.

4. Pressure – e.g. decubitus (Bed sore) in animals: long continued pressure from adjascent tumous and abscesses, recumbency, sites of bandage/casts.

5. Thermal mechanical (physical) injury – most severe in 3rd burns, freezing, rays: sun, uv-light; accidental blow of a hammer, heat – coagulation of protein, cold – bursting of membranes, slogging of blood supply.

DIFFERENT TYPES OF NECROSIS

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

•1. Coagulative N: the outline of the dead cells are maintained and the tissues is somewhat firm. e.g. Myocardial infarction.

•2. Liquifactive N: the dead cells undergo disintegration and affected tissue is liquefied. e.g. cerebral infarction

•3. Caseous N: a form of coag. N. (cheese - like). e.g. tuberculosis lesion.

•4. Fat Necrosis: Enzymatic digestion of fat. e.g. necrosis of fat by pancreatic enzymes.

•5. Gangrenous N: Necrosis (secondary to ischemia) usually with super imposed infection. e.g. necrosis of distal limbs, usually foot and toes in diabetes.

ZENKER' S NECROSIS: Zenker's degeneration

Occurs only in striated muscle (Myocardia and skeletal)

It is a coagulation of the proteins in the cytoplasm of striated muscles.

Microscopically:

•Swollen fibers, homogeneous and hyaline in texture
•Acidophilic sarcoplasm (Reddish H&E)
•Small and dark nuclei (pryknotic)
•Loss of cross striations in fibre
Grossly – White or pale muscle: shiny and swollen
Aetiology:
•White muscle disease condition e.g. Vit E and Selinum deficiencies
•Infectious diseases like: foot and mouth disease (FMD) which is a viral disease.
Significance:
-Fibres may regenerate by proliferation of the sarcolemma nuclei.
-Necrotic area may undergo calcification

Biochemical Diagnosis of Necrosis

Following necrosis, soluble substances are circulated into the body e.g. enzymes/proteins, ions
•could specifically indicate areas of necrosis e.g.Alanine aminotransferase (ALT) is highly
concentrated in hepatocytes.

Aspartate aminotransferase (AST) is also high in striated muscles (myocardium and skeletal) and in liver cells

High level of creatinine phosphokinase will indicate kidney damage.

OUTCOME OF NECROSIS

•**Liquefaction**

•Formation of **cyst-like accumulation**.

•Liquefaction and **abscess** formation

•Necrosis area may be **encapsulated** without liquefaction

•**Desquamation (sloughing)**

•**Repair** may take place in form of replacement.

•**Calcification**

•Invasion by anaerobic organism leading to **gangrene**

•A**trophy** of the tissue.

GANGRENE

This is a clinical term applied to any **black and fowl swelling**

area that is in continuity with living tissues. It is liquefied necrotic area + invasion of saprophytes (putrefactive bacteria).
Two types of gangrene: **wet** and **dry** gangrenes.

Causes:

i. In the extremities and intestines, **interference with blood**

supply is the major cause.

ii. In the lungs and udder, **toxic products** of highly lethal bacteria are the causes.
SIGNIFICANCE OF GANGRENE: Because gangrene can spread and the bacteria and toxin produced from the decomposition can **disseminate to other parts** efforts should be made to stop the process by **amputation,** and surgical removal of affected parts e.g. intestine.

INFARCTION: An infarct is a **localized area of necrotic tissue** resulting from deprivation of blood supply (**Ischaemic**). The resultant necrosis is usually a **coagulative** type and is common with areas supplied with single end-arteries e.g. kidney, brain.
•Recent infarcts are usually haemorhagic or red infarct due to back flow of blood from efferent veins into the capillaries of the necrosis area.
•Others are pale or anaemic infarct depending on their age. The paleness or redness also depends on the denseness or perviousness of the tissues.

Types of Infarcts
•**Renal Infarcts**: usually conical with the apex at the cortico- medullar junction. **Causes**: Chronic valvular endocarditis is a common cause in dogs and pigs. It is always an anaemic type.
•**Splenic infarct:** mainly shallow, subcapsular infarct that is haemorrhagic in nature. It is seen in hog-cholera (viral disease) of pigs.
•**Infarct of brain** – usually anaemic, and quickly liquefied.
•**Intestinal infarcts** are usually haemorrhagic and deadly. It usually involves a food length of the intestine. Caused by strangulation of the intestine e.g. in a hernia sac.
•**Myocardial infarcts**: not common in animals. Usually red or gray.
•**Pulmonary infarcts** – usually heamorrhagic.
•**Hepatic infarct** is rare but could occur if hepatic artery is blocked. In cattle, hepatic infarct can occur in *Clostridium haemolyticum* infection (Bacillary haemoglobinuria).
•**Mammary gland infarcts** are common in mastitis caused by highly virulent streptococci producing necrotizing toxins.

Significance of Infarction

•Area may undergo gangrene formation
•Area may undergo abscess formation
•Area may undergo scar formation
•There could be loss of function e.g. paralytic stroke as in the brain infarct.

DEGENERATIVE CHANGES

Regressive Change

Reversible disorders of cells/tissue which are not dead yet, but may lead to necrosis if insults are not removed. Cells may recover if interference to the cells is removed in time.

•**Proteineous Changes**

I. Cloudy swelling: This is the term used to describe cells that are slightly swollen due to changes in function of the cell membranes and membranes of the organelles e.g. changes is Na+ - K + pump lead to intracellular concentration of Na2, Ca2+ and decrease in K+. This will lead to influx of water.

II. **Hydropic degeneration** (Ballooning degeneration / Vacuolar degeneration)

i.e. presence of water in the cytoplasm of the cell e.g. epithelial cells. The change is seen as clear space surrounding the nucleus. Aetiology :- Nutritional and serenity, Infection – Pox and FMD viruses.

III. **Hyalin degeneration** – Deposition of homogenous, translucent, eosinophilic, solid, dense smooth materials (protein) intracellularly. It is associated with nutritional deficiencies: e.g. Vit. E def.

AMYLOIDOSIS

This is a degenerative change. **Amyloid** are amorphous, eosinophilic homogenous proteinous materials (a glyco- protein) initially deposited extracellularly under the epithelium of the blood vessels. Amyloid is made up complex structures of filaments or rods. With Congo-red it stains pink or orange to orange-red with bifringent light-green under Polaroid microscope.

CLASSIFICATION OF AMYLOID

I. On the **basis of staining** with Congo-Red
•Typical – Stains with Congo-red.
•Atypical – does not stain with congo-red

II. **primary amyloidosis** – no anticident or co-existence with any disease.
secondary amyloidosis – following chronic disease: TB, Osteomyelitis, rheumatoid arthritis, (characterized by increase IgG); hyper- immunized horse.

III. Associated with myeloma (Plasmacytoma):
Production of Bense-Jones Protein:(75 Immunoglobulin man).

IV. Isolated organ as in senile human

Clinico- pathological features of Amyloidosis

Usually a progressive phenomenon – spleen, liver &

kidneys, lymphnodes and adrenal

1. Renal: commonest and most serious type of amyloidosis. Initially in the glomeruli in general; to tubules & the
medulla in cattle & cats - Io site is intersititial. This leads to **PROTEINURIA & casts**

2. In dogs - **pulmonary artereo-thrombosis**

3. **Hepatic amyloidosis** – in Spaces of of disse. No serious dysfunction noted.

4. **GIT amyloidosis** – e.g. In monkeys (macague) – in lamina propria – leading to blunting of the villi & atrophy of crypts -> malabsorption.

5. **Splenic amyloidosis** – around the central arteries of the splenic corpuscles -> follicles – appearance of tiny white nodules (grains) 'Sago' (Tapioca droplets). In the medulla area it gives the appearance known as **'Lardaceous spleen**' – lardosis

6. **Isolated Organs**

– Islet of Langerhans – pancreas in Cat family ->diabetes mellitus;
- myocardium – man & mice.
– Respiratory tract – horse & man as tumor- like deposits.

Aetiology: Usually due to chronic activation of the Ag-Ab system as in the Io amyloidosis.

Grossly: hard opaque white deposit, mainly in spleen. Enlarged liver with pale colour

Microscopically: Stains pinkish or purplish pink with
H&E stain (Haematoxylin & eosin). Specific stain:
+Cresyl violets gives deep red;
+Congo-red gives pink. – Sharp demarcation as against gradual one in hyaline.
+Aqueous solution of I2 on slide of fresh tissue gives brown.
+Addition of dil. H_2SO_4 following I2 solution will convert brown to give blue colour.
+Periodic acid-Schiff (PAS) gives violet.
+Thioflavin T, gives green birefringence under UV light.

MUCINOUS DEGENERATION

•Excessive accumulation of mucin in the Epith. cells of mucous membranes such as lining of the G.I.T. & Resp. Tract.
-Aetiology: - mild irritants, mechanical, chemical infections.
-Mucin stains **blue** with H&E.
Pseudomucin (by adenomas & cyst adenocarcinoma) –pink with H&E.
PAS – mucins – **Rose to pink or purple-red**. Mucicarmine stains mucins – **Rose to pink or purple – red**

MUCOUS DEGENERATION

Mucous degeneration (Myxomatous degeneration) or mucoid atrophy of fat – in tissue with ct. + fat (adipose ct.) – around the coronary grove of the heart, omentum and mesentery.

Microscopically – proliferation of ct. of embryonal xtics: hyperchromatic nuclei, ovoid or spherical nuclei.
Grossly: Translucent and watery.
Aet: Mal-nutrition, toxaemia,
• ill-health indicator to meat inspectors.

GOUT

•Disturbance of purine metabolism
•Formation of crystals of Ca+ & Na+
•Urates resulting in the tissues.
•Tophi – deposits of gout in tissues.
•Occurrence – man, birds, dogs & cats
•**Birds**:-
•Articular gout
•Visceral gout.

•**Articular** & peri-articular spaces and subcuitis result in friction, irritation & pain & inflammation, Swollen joints. White chalky mass in the joint and ulceration of the surround skin.

Visceral gout:
•Metallic sheen (gloss) on the serous surfaces of the viscera; deposit of crystals in ureters (kidney), serous surfaces of the liver, pericardium and airsacs.Aet:
a) Avitaminosis A,
b) Too much of protein (Imbalance) in diet.

DISTURBANCES INVOLVING CARBOHYDRATES Glycogenic Infiltration:
Glycogen is normally found in the liver and muscles. Pathologically: found in the epith. cells lining, straight tubules, Loop of Henle of kidney. Also found in inflamed tissues.
Microscopically:
Clear spaces around nuclei
Fixing should be done with a non-aqueous fixative e.g. absolute alcohol or Carnoy's fixative to demonstrate glycogen.
Stains: Best's Carmine Stan gives Bright-pink. Grossly – usually not visible.
Significance: indicative of cellular injury.

DISTURBANCES INVOLVING FATS (FATTY CHANGE) Intracellular accumulation of lipids (usually neutral fat) in organs: liver, kidney and heart.

Microscopically: appear as vacuoles (clear, unstained spaces) spherical spaces.

Glossly: Organs are enlarged, tan or yellowish in colour,- light and friable, float in water.

Aet: interference with transport or metabolism of fat or protein synthesis.

Fatty change seen in:
•A. Liver: -periportally – in poisoning (haematogenous) – centro-lobular – as in iron def. (anorexia)
•B. Kidney – proximal convoluted tubular (PCT) and Ascending loop of Henle.
•C. Heart – fine droplets in the myocardium.

The 3 organs (A-C) could be involved simultaneously as in ketosis (Diabetes), pregnancy toxaemia (Ewes with Twins)
Also in rabbits & guinea pigs with more than 2 feotuses.

Significance/consequences of fatty change
- It is reversible if insults are removed
- Hepatic necrosis may follow if persistent
- Fat cells may be released as emboli
- Liver can rupture
- Stroma Fatty Infiltration – within the normal ct. of organs like pancreas and heart.
- Extracellular accumulation of lipid – outside cells in some situation: cholesterol released from some necrotic cells or pooled from lipo-protein and deposited in crystalline form in areas of old haemorrhage.

CHANGES INVOLVING Ca2+ METABOLISM Ca++ salts get deposited in tissue (abnormally) other than the bone and teeth – as Ca – carbonate, - phosphate, - hydroxyl-apatite, - mixture with iron-salt resulting in **Mineralization**
(**calcification** when Ca++ salt only)
Calcification
•a.**Dystrophic** calcification – deposition of Ca++ in dead or dying tissues. Not linked with increased Ca++ concn.
•b. Metastatic calcification
Result from pptn of Ca+ in hypercalcaemia
FIBRIN
Fibrin is a proteinaceous substance normally present in
•Blood clot from fibrinogen,
•In fibrinous exudates.
Microscopically :pink, interlacing materials with bead-like materials (spongy- like) – with karyolysis results in blueish-tinct b/c it will absorb the released chromatin from the environment. **Grossly:** - stringy material, dull white – usually mixed up with other exudates and dead tissues.
Consequences: It can lead to:
•Thrombi leading to regional necrosis [infarction] due to ischaemia. – ischaemic necrosis.
•Fibrin could be liquefied leading to autolysis
•Could attract fibroblasts leading to growth of fibrous c.t. – organization: resulting into **thrombi**.

FIBRINOID DEGENERATION

Occur in collagen disease of man and animals.

Aet: Ab – Ag reaction e.g. rheumatic fever.

DISTURBANCES INVOLVING PIGMENTS

Pigment are in 2 main groups:

•Exogenous,

•Endogenous.

The other group are the pigments haematogenous

CLASSIFICATION OF PIGMENTS

I. Exogenous pigments – formed outside the body:

a) – Carbon – anthracosis

b) – dust – silicosis, siderosis, asbestosis

c) – metals – argyria, lead, bismuth

d) – Tattoos

e) – Kaolin

f)– Carotenoids (lipochromes)

Exogenous pigments – those that may enter through the respiratory tracts – found in the lungs and contiguous lymph nodes draining the lungs.

•Anthracosis - presence of carbon particles (deposits) in tissues e.g. in smoky cities.

•Pneumoconiosis: accumulation of dust in the lungs

a. Silicosis – due to inhalation of silicon dioxide, as seen in people blasting rocks.

b. Siderosis: inhalation of iron dust/iron dust (iron oxide or haematite from mines). It does not elicit inflammatory reaction but always accompany silicosis.

c. Asbestosis: from asbestos factories

II Endogenous pigments – formed inside the body

•Phenolic pigments

1 – melanin

•Haematogenous pigments

1 – Haemoglobins – methaemoglobin

2 – haematin (acid-haematins) e.g. acid formalin haematin

3 – parasitic – haematin in malaria, fascioliasis

4 – Haemosiderin e.g. Heart failure cells

5 – Bile

6 – porphyrins – congenital & porphyria photosynthesitization

•Lipogenic pigments

1 – tissue lipofuscins

2 – ceroid

3 – Vit. E def. pigments

•Miscellaneous Pigments

1 – Ochronosis pigment [hereditary disease]

2 – Dublin-Johnson pigment [hereditary disease]

3 – Cloisonné Kidney

•Albinism – pathological absence of melanin. The melanocytes are unable to produce melanin. Cu is an important component of tyrosinase needed in conversion of tyrosine to – melanin. [stain] – **Fontana-silver** Stains melanin black

•**Microscopically** – Dark granule in melanophores (MQ with engulved melanin)

Significance

•Melanin is protective against sunburn

•Melanosis is not harmful

•Melanoma affects the functions of the organs concerned.

HAEMATOGENOUS PIGMENTS

Haemoglobin : Haeme + globin

Free Haemoglobin if there is breakdown of rbc converted to Haemoglobinaemia and Haemoglobinuria

If haemoglobin escapes from vessels after death to stain the tissues – 'Post-mortem imbibition' of (of perivascular tissues). Formation of met-haemoglobin, in hb poisoning, leads to oxidation of Fe^{2+} to Fe^{3+} - Chocolate brown colour. {Nitrite, chlorates and sulphates = poison}.

Nitrite poisoning – Ruminants break nitrate to nitrite – chocolate – brown colouration of lungs, kidney, muscles and mucons mbr.

•Carboxy – Haemoglobin – occurs in cobalt poisoning –> bright cherry-red blood.

•Sulphur – haemoglobin: This is a reduced haemoglobin + inorganic sulphide.

Sulphur – Methaemoglobin – gives greenish decolouration of the carcass at post-mortem examination.

•Acid formalin haematin pigment – formal-precipitated haemoglobin: seen adj. to the peptic or duodenal ulcer b/c of the presence of HCL (Hydrochloric acid haematin). Here the Fe is not stained.

CIRCULATORY DISTURBANCES By

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Circulatory System - Consists of blood, pump (♥), distribution (arteries) collection (veins) and system for exchange between blood and extravascular tissue. Lymphatics also contribute by draining fluid from the extravascular space.

Microcirculation- composed of arterioles, metarterioles, capillaries, and postcapillary venules, so called because are only visible with the microscope.

Capillary bed Enormous volume Site where fluid exudes from circulating blood

Endothelial Cells Synthesize and Secrete Glycoproteins

-The normal FUNCTION of these glycoproteins is to inhibit clot formation and to protect endothelium.
-When INJURY occurs to the endothelium synthesis and release of these glycoproteins is impaired which results in problems with hemostasis and fluid transport.
-Endothelial cells are important in fluid distribution, nflammation, immunity, angiogenesis and hemostasis.

Precapillary arterioles:
Contain small, innervated myocyte sheaths.
Contract to control blood flow (regulation of blood flow).
Postcapillary Venules:
Sites of fluid exudation.
Area particularly susceptible to some toxins.
Capillaries:
Sites of fluid exudation.

Mechanisms for Substance to Transport across Capillary Endothelium
1. Direct diffusion (ions, water and small molecules) Passive diffusion across vessel wall
2. Active transport
Occurs via special protein ion pumps embedded in plasma membranes at cell surface
3. Transcytosis
Expansion of Cell Junctions allows large molecules and excess fluids to pass into the interstitium. Movement of substances through junctions and cell membranes is generally passive in response to concentration and pressure gradients.

Fluid Distribution & Homeostasis

TOTAL BODY WATER
(65% of lean body weight) = plasma (5% lean body weight) + interstitial tissue fluid (15% lean body weight) + intracellular fluid (40% lean body weight) + transcellular fluid (5%).
Interstitium: Space between tissue compartments
-Binds most cellular and structural elements into discrete organs and tissues
-(What remains after you remove the blood and lymphatic vessels, nerves and parenchymal cells from a tissue)

Interstitium = Extracellular Matrix (ECM) + Supporting cells Extracellular Matrix: (Structural, Adhesive, + Absorptive components)
Insoluble Components
(absorptive) Collagen (Type I and IV)
Fibronectin
Elastic fibers Laminin Adhesive glycoproteins
Soluble Components
Proteoglycans Glycosaminoglycans

Interstitial Tissue Fluid: Intermediary
-all metabolic products pass to enter or leave cells
-constant exchange both with *plasma* and with *cellular fluids*.
Endothelium + underlying basement membrane allows the free passage of H2O + ions and opposes the passage of plasma proteins.

	ARTERIOLAR	VENULAR
Plasma Hydrostatic Psi	**30 mm Hg**	**17 mm Hg**
Tissue Hydrostatic Psi	**8 mm Hg**	**8 mm Hg**
Plasma Colloidal Osmotic Psi	**25 mm Hg**	**25 mm Hg**
Tissue Colloidal Osmotic Psi	**10 mm Hg**	**10mm Hg**
(30-8)-(25-10)= 7 mm Hg		**(17-8)-(25-10)= 6 mm Hg**
Net filtration Psi		**Net Absorption Psi**

Starling's equation: Hydrostatic pressure in the vascular system (aided slightly by perivascular osmotic pressure) moves fluid out of the system. Osmotic pressures of the plasma proteins, and to a lesser extent, tissue pressure around blood vessels are the forces that contain the fluid within the vascular system.

INTRODUCTION

The normal functioning of tissue and cells of the body, critically depends on normal fluids environment and on adequate blood supply. Derangement of this supporting system may be in the form of fluid imbalances (e.g. edema, dehydration) or hemodynamics disturbances (e.g. Heamorrhages, hyperemia, thrombosis and infraction.

HYPEREMIA & CONGESTION

The terms hyperemia and congestion are basically synonymous although they often are used to imply different mechanistic and anatomical information.
Hyperemia usually is used to imply an active, arteriolar mediated engorgement of the vascular bed, whereas congestion usually is used to indicate a passive, venous engorgement.

HYPEREMIA

Hyperemia may occur in any organ or tissue. It is usually associated with the first stage of reaction to insult, that is inflammation. It also occurs in physiological activities such as muscle exercise, stomach and intestine after a meal or mammary gland in lactation.

Gross Appearance

The affected area takes on the bright red colour of anternal blood. If the animal is alive the part would be warm. Increase pulsative artery may be felt which is normally perceptible.

Histology

Capillaries are dilated and filled with blood. They appear to be more numerous than before because in the normal state some of the are empty and collapsed.

CONGESTION

Congestion by its passive nature implies, that the flow of blood like the flow of vehicles on a busy street is impeded, because the element in front cannot move fast out enough. Congestion then now results in that part of the body.
Congestion may be acute and chronic
The major causes are
1. Diminished blood pressure e.g. from the failing heart or in vasodilation associated with shock.

The major cause of death (the outcome) is congestive heart failure. Chronic congestion

occur in valvular insufficiency or stenosis of mitral valve which causes chronic passive congestion of the lung. Tricuspids valvular disease cause nut meg liver.

Liver cirrhosis
Later stages of pregnancy
Hypostatic congestion (due to gravity).

Gross appearance

The area is slightly swollen and tends to have a bluish red tinge.
During life temperature may be lower than normal as contrary to hyperemia.
Evidence of post mortem hemolysis may be observed.
Considerable amount of blood may be squeeze out of cut surface.
Capillaries and vein are dilated and full of blood also the sinusoidal spaces of liver and spleen.
In chronic congestion there would be a slight or moderate increase in fibrous tissues in the wall of the vein which is due to compensatory hypertrophy.

Generalized congestion due to **right-sided heart failure** results in fluid accumulating beneath the skin, in the extremities and in the major body cavities.
The liver is congestion enlarged and there is anoxia or hypoxia around its central veins.
If anoxia persists as in chronic congestion, the hepatocytes become necrotic and the area is filled with red blood cells.
The area of the liver appears reddish blue grossly and the liver has a colour pattern of a nut meg and the term “nut-meg liver” is used to describe it.

If congestion is as a result of left-sided heart failure there would be fluid accumulation in the lungs and red blood cells will leak through the capillaries where they are engulfed by alveolar macrophages.
The break down product of the red blood cells heamosiderin appears in the macrophages as dark brown pigment and the macrophage are referred to as “heart failure” cells with chronicity, fibrosis of the lungs occurs.
The lungs are heavy and dark resulting in the term brown induration of the lungs.

HAEMORRHAGE (BLEEDING)

It occurs when red blood cells escape from the cardiovascular system into tissue space (extravasations) or when there is discharge of blood from the vascular system to the exterior of the body.

The ordinary rapid flow of blood via a break or cut in a vessel wall or heart is called **heamorrhage by rhexis**.

When the red blood cells pass via an intact vascular wall the process is called **diapedisis**.

Diapedisis is seen in anoxic blood vessels with high hydrostatic pressure or when there is defective clotting mechanism..

The causes of haemorrhage include

1) Mechanical trauma leading to breaking, cutting or crushing of blood vessel.

2. Necrosis and metabolic disturbances of the vessels wall e.g. when invaded by neoplasm.

3. Rupture of blood vessels weakens by aneurysm, antherioma, arteriosclerosis.

4. Toxic injury to capillary endothelial cells leading to destruction of tight junction or escape of blood e.g. toxin produce by septicemia infections. Hog cholera Anthrax, pasteurellosis, African swine fever.

Certain plants poison e.g. crotalaria sweet clover Brackferm

Chemical poisoning e.g. Arsenic, mercury .

Vitamin deficiency e.g. vitamin c deficiency leading to scurvy.

Disorder of clothing mechanism as we have in vitamin B deficiency.

Inflammatory process.

Pathology

Gross appearance

Heamorrhages that occur as tiny pinpoint areas of about 1 -2min foci are called **petechial heamorrhages.** Found on mucosa and serosal surfaces

- **Ecchymotic heamorrhages** are those of up to 1 – 2cm in size, and are irregular in shape.

- **Paint brush heamorrhages** refers to extensive streaking with haemorrhage as if a paint brush has been used. It is also known as **suffusion heamorrhage.**

- **Haematoma** - is bleeding within tissue reaching to a swelling i.e. accumulation of blood in an area to form a hump.

Haemocyst – This is bleeding with blood accumulation in a cavity e.g. haemopericardium, haemothorax, heamoperitoneum.

- **Purpura** – This is a clinical term applied to extensive petechial and ecchymotic heamorrhages on many serous and mucous surfaces.

The condition is seen in diseases with

a. **Disseminated intravascular coagulation (DIC)** or consumptive coagulopathies" i.e. excessive use of platelets in coagulation.

b. **Thrombocytopenia** due to increased destruction or utilization or reduced production of platelets.

During the process of dying, extensive ecchymotic & paint brush heavens are observed on epicardial and endocardial surfaces and in the tracheal mucosa of animals. These heamorrhages are refers to as agonal heamorrhages.

- **Haemorthrosis** – blood present within the joint space.
- **Haemoptysis** – Coughing up of blood clots from the trachea and branch.
- **Epistaxis** – bleeding from the nose.

The colour of heamorrhage depends on:

a. The source of blood: i. e. either arterial or venous
b. The number of red blood cells out of circulation.
c. the tissue of occurrence
d. Time tag between occurrence and visualization of the haemorrhage.

Microscopically

RBCs are visible in tissue outside the blood vessels. The red cells are either phagocytosed by an a crophages (erythrophagocytosis) or lysed and the breakdown produce which is haemosiderin is stored in macrophages or tissues.

Both erythrophagocytosis and haemosiderin laden macrophages indicate haemorrhage in tissue.

Consequences of haemorrhage

There is no serious effect of the b/d loss is small, but when large amount (about 20%) is lost rapidly death can result.

Following the loss of a considerable amount of blood, the volume of fluid is replace within an hour or 2 by withdrawal from intracellular fluid. Chromic loss of blood may cause iron deficiency anaemia.

EDEMA

Abnormal accumulation of excess fluid in interstitial tissue spaces or in body cavities.

Edema fluid is **outside** the vascular fluid compartment and **outside** the cellular fluid compartment. (**i.e.: within interstitium**)

Five Pathophysiologic Mechanisms that underlie the development of edema

1. Decrease plasma (intravascular) colloidal-osmotic pressure
2. Increase intravascular hydrostatic pressure
3. Lymphatic obstruction
4. Increased microvascular permeability
5. *Sodium retention (*increase *vascular hydrostatic ps, increase plasma colloid osmotic ps)*

Histology: Tissues are pale staining. Tissue spaces are distended by lightly staining eosinophilic fluid. Blood vessels maybe filled with erythrocytes (hyperemia). Lymphatics are dilated. The edema may be difficult to discern if the protein content is low. Collagen bundles of interstitial stroma are separated by an increase in intercellular space.

TWO TYPES OF EDEMA:
1. INFLAMMATORY
2. NONINFLAMMATORY

NONINFLAMMATORY EDEMA

Mechanisms:
1. Decrease plasma colloidal-osmotic pressure
eg: Hypoalbuminemia
Definition: HYPOALBUMINEMIA - abnormal low concentration of albumin within blood.
2. Increase hydrostatic pressure (impediment to venous blood flow). eg: right heart failure
3. Lymphatic obstruction
4. Sodium retention (increases plasma volume)

Fluid Characteristics: "protein poor"
Transudate
- low protein content < 30 g/L
- specific gravity below 1.017
- total nucleated cell count < 1.5 X 109/L

INFLAMMATORY EDEMA

Mechanism: Increased Vascular Permeability - Endothelial damage Initial reaction of the microvasculature to inflammatory or immunologic stimuli. Released mediators result in vasodilation and increased vascular permeability. Some mediators include: histamine, bradykinin, leukotrienes and substance P. The cytokines - tumor necrosis factor (TNF), interleukin-1 (IL-1) increase the gaps between endothelial cells. This mechanism will be further discussed in inflammation lectures.

Fluid Characteristics: "protein rich"
Exudate - high concentration of protein > 30 g/L
- high specific gravity > 1.025
- total nucleated cell count > 7.0 X 109/L

LOCAL EDEMA

Mechanisms:
Local **Increase** in hydrostatic pressure. Lymphatic obstruction Inflammation
Aetiology: impaired venous drainage or lymphatic blockade or inflammation
eg1: Improperly bandaged limb resulting in venous occlusion
eg2: Damage to lymphatics (surgery, neoplasm, or intravascular parasites)
eg3: Inflammation may also affect lymphatics (*lymphangitis*)

GENERALIZED EDEMA

Mechanism:
1. Increased hydrostatic pressure of blood

2. Decreased colloid osmotic pressure of plasma proteins

3. Sodium retention

Aetiology:
Heart Failure – usually right heart failure
Liver disease
Chronic renal disease
Location: ***Dependent edema***: Ventral abdominal subcutis Subcutis of the ventral cervical region Subcutaneous tissues of the limbs

TERMINOLOGY used when describing Non-Inflammatory Edema
PITTING EDEMA:
When pressure is applied to an area of edema a depression or dent results as excessive interstitial fluid is forced to adjacent areas.
ANASARCA: Swelling of the subcutis due to severe generalized edema.

HYDROTHORAX: Fluid in the thoracic cavity, (Transudate – noninflammatory fluid)
HYDROPERICARDIUM: Fluid (transudate) in the sac around the heart
ASCITES -or- HYDROPERITONEUM: Fluid in the peritoneal cavity
LYMPHATIC BLOCKAGE will result in an inability of the lymphatics to remove normal fluid excess in the interstitium resulting in edema. This may result from surgery or trauma damaging lymphatic system; neoplastic cells obstructing normal flow of lymph; parasites obstructing flow; or a hereditary malformation of the lymphatic system.
LYMPHANGIECTASIA: Dilatation of lymphatic vessels.
LYMPHEDEMA: Accumulation of lymph in subcutaneous tissues.

THORACIC DUCT OBSTRUCTIONS
Pathogenesis: Thoracic duct ruptures **chylothorax** (**Chyle** - the milky fluid taken up by lacteals from food in the intestine, is composed of lymph and triglyceride droplets)
Etiology: Trauma Neoplasia Congenital Defects Inflammation Idiopathic - unknown
Clinical Significance of Edema
Dependent upon:
a. Extent - severity
b. Location - ie. Site of accumulation
c. Duration - tissues may become more firm and distorted due to an increase in fibrous connective tissue after prolonged edema.

PULMONARY EDEMA
Note: Common cause of death in many disease processes
Definition: Accumulation of edema fluid in interstitium and alveoli of the lungs.
Sequence:
1. Fluid accumulates in interstitium →

2. Fluid disrupts the basement membranes
   Endothelial cells
   Pneumonocytes
3. Leads to fluid within alveoli →
4. Fluid drains via lymphatics →
5. Result dilated pleural lymphatics and eventual pleural fibrosis.

Mechanisms of pulmonary edema: (2)
1. **Circulatory failure**
Increase **hydrostatic psi** of blood (pulmonary veins)
Changes in pulmonary hemodynamics
Slow transudation of fluid into alveoli
Most common cause of pulmonary edema.
2. Damage to pulmonary capillary endothelium
-Inflammatory Edema
- Sudden, diffuse, direct increase **vascular permeability** (exudation)
- Usually peracute stage of inflammation.
- Followed by pneumonia - if animal survives.

GROSS: Lungs are heavy and wet; fluid may be present within bronchi and obvious on cut sections. The interlobular septa appear prominent and thickened due to the increased fluid within this space. Congestion of pulmonary parenchyma is often seen.

Histo: Edema appears first perivascularly
- Plasma exudes into alveoli
- Dilated pleural lymphatics

DEHYDRATION

Definition: Deficiency of water resulting from imbalance between the uptake and loss of water from the body. It is the opposite of edema**.**
Causes:
Uncontrolled diarrhoea
Vomiting
Renal Failure
Diabetes
Heat-stroke
Water Deprivation
Mechanism: A decrease in the total body water results in water deficit shared among plasma, intracellular, and interstitial fluid compartments. Hypovolemic shock accompanies severe dehydration as plasma water is drawn into the interstitium. Renal perfusion is reduced.
Pathological Findings: -Folds of skin pulled out from the body hesitate before returning to their normal position, "tenting." -Eyes are sunken. -Mucous membranes and subcutaneous tissues are dry and sticky.

HEMOSTASIS

Functions of normal hemostasis
Maintain blood in fluid (clot-free) state in normal vessels

Induce rapid, localized hemostatic plug at site of vascular injury
Thrombosis – inappropriate activation of hemostasis
Regulated by vascular wall, platelets, coagulation cascade

Normal hemostasis

Initial injury followed by brief period of *transient* arteriolar vasoconstriction due to reflex neurogenic mechanisms, augmented by local secretion of endothelin

Platelets adhere to exposed thrombogenic subendothelial matrix → platelet activation → platelets undergo shape changes and release secretory granules → additional platelets recruited to form hemostatic plug (primary hemostasis)

Tissue factor is exposed at sites of endothelial injury → activates coagulation cascade in conjunction with secreted platelet factors → activation of thrombin → conversion of circulating fibrinogen to insoluble fibrin (secondary hemostasis)

Permanent plug formed by polymerized fibrin and platelet aggregates → fibrinolytic mechanisms activated to limit hemostatic plug to site of injury

Intrinsic pathway – activated in vitro by activation of Hageman factor
Extrinsic pathway – activated by tissue factor exposed at sites of injury
Common pathway – intrinsic and extrinsic pathways converge at activation of Factor X
Pathways are interconnected – tissue factor (VIIa) activates Factor IX of the intrinsic pathway
Thrombin limits hemostasis by binding to protease activated receptors (PARs, 7-transmembrane G-protein coupled receptors)→ clip the extracellular end of thrombin receptor via proteolytic activation of thrombin → tethered peptide is generated that bind to the rest of the receptor and causes conformational changes to activate G-protein
Calcium ions are required for activation of Factors X, II, XIII, V → all are in the common pathway

Roles of thrombin

Activation of Factor XIII
Cleavage of fibrinogen → fibrin
Induces platelet aggregation and secretion
Activates endothelium → leukocyte adhesion molecules.
Activates monocytes

3 Natural anticoagulants regulate clotting

Antithrombins – inhibit activity of thrombin and other serine proteases. AT III is most important – activated by binding to heparin-like molecules on EC

Proteins C & S – inactivate Factors Va and VIIIa (both are Vitamin K dependent); protein C is activated by thrombomodulin

Tissue factor pathway inhibitor (TFPI) – secreted by EC; forms complex with Factors Xa and VIIa causing their rapid inactivation

THROMBOSIS

VIrchow's triad of 3 influences that predispose to thrombosis
Endothelial injury
Stasis or turbulent blood flow
Hypercoagulability

Endothelial cell injury

Dominant influence – can lead to thrombosis by itself, especially in arteries and heart where there is high flow rate
Often associated with vasculitis or atheromatous plaques.
EC loss leads to exposure of subendothelial ECM, platelet adhesion, release of TF, local depletion of PAs, and PGI2
EC does not need to be denuded or physically disturbed to incite thrombosis → imbalance of pro- and antithrombotic factors can mediate thrombosis
Significant EC dysfunction without EC loss may occur with hypertension, turbulent blood flow, endotoxin, products of cigarette smoke

Alterations in Blood Flow

Cause EC injury and dysfunction
Stasis and turbulence disrupts laminar blood flow and brings platelets into contact with endothelial cells.
Stasis prevents dilution of activated ECs by flowing blood, retards inflow of clotting factor inhibitors (resulting in thrombin buildup), and promotes EC activation

Arterial and cardiac thrombi

Arterial and cardiac thrombi – usually occur at sites of EC injury or turbulence; grow in retrograde direction from point of attachment
Lines of Zahn – laminations in wall of thrombus produced by alternation of pale platelet/fibrin layers with darker layers of RBCs; imply thrombosis at a site of blood flow.
Mural thrombi adhere to wall of underlying structures – heart chambers or aorta
Arterial thrombi are usually occlusive and firmly adherent
Most common sites: coronary a., cerebral a., femoral a.
Usually superimposed on atherosclerotic plaques or other forms of vascular injury
Gray-white, friable, composed of tangled mesh of platelets, fibrin, RBC, and degenerative leukocytes

Venous thrombi

Occur in areas of stasis; extend in the direction of blood flow
Point of attachment is usually firmest at point of origin
Propagating tail is prone to fragmentation and embolization, especially in veins
Thrombi formed in veins with sluggish flow resemble coagulated blood; may have faint, ill-defined laminations.

Usually occlusive and form long cast in the lumen – tend to contain more RBCs than arterial thrombi because they form in a static environment.
Usually occur in lower extremities.
Can be confused with postmortem clots – postmortem clots have a gelatinous dark red dependent portion from settled RBCs and yellow "chicken fat" supernatant, and are usually not attached to the vessel wall.
Red thrombi are firmer, almost always have an attachment point, and often have pale gray strands of fibrin on sectioning
Thrombi can form on heart valves – vegetations (infective endocarditis), sterile vegetations can occur in patients with hypercoagulable states
Verrucous (Libman-Sacks) endocarditis is non infective and forms from immune complexes .

Fate of Thrombus

Propagation: accumulation of more platelets and fibrin → occlusions
Embolization
Dissolution by fibrionolytic activity – only recent thrombi can be lysed; older thrombi are resistant to proteolysis
Organization and recanalization – thrombi induce inflammation and fibrosis (organization)
Older thrombi organize due to ingrowths of EC and fibroblasts, followed by formation of capillary channels and potential recanalization establish blood flow
In large thrombi/cardiac thrombi, the center of the thrombus may be degraded by enzymatic digestion of lysosomal enzymes from trapped leukocytes (rather than fibrinolysis) – ideal culture medium if bacterial seeding occurs. They usually result from degeneration of atherosclerotic plaques

Disseminated Intravascular Coagulopathy

Sudden or insidious onset of widespread fibrin thrombosis in microcirculation accompanied by rapid consumption of platelets and coagulation proteins (e.g. consumptive coagulopathy)
Followed by activation of fibrinolytic cascade → can become a bleeding disorder
Potential complications of any condition associated with widespread activation of fibrin

EMBOLISM

Detached intravascular solid/liquid/gaseous mass that is carried by blood to a distant site.
Most are thromboemboli – lodge in small vessels and cause partial to complete vascular occlusion → potential downstream ischemic necrosis (infarction).

Pulmonary thromboembolism

Rarely, a paradoxical embolus may pass through a septal defect and enter the systemic circulation rather than lodging in the lungs

Obstruction of >60% of the pulmonary circulation can cause sudden death, cor pulmonale, or cardiovascular collapse.
Because of the dual blood supply in the lungs, pulmonary hemorrhage occurs more often than infarction following embolization.
Obstruction of small end-arteriolar branches is more likely to cause infarction.
Multiple emboli over time can cause pulmonary hypertension with right heart failure.

Systemic thromboembolism – emboli travel in the arterial circulation, most often from intracardiac mural thrombi, aortic aneurysms, thrombi on atherosclerotic plaques, and a small amount from paradoxical emboli.
Major sites – lower extremities and brain
Less common sites – kidney, spleen, and intestine.
Infarcts occur downstream of obstructed vessel.
Fat embolism – most are secondary to long bone fracture. Clinical signs are uncommon.
Fatty embolism syndrome is characterized by sudden onset of pulmonary insufficiency, neurologic signs, anemia, and thrombocytopenia beginning 1-3 days after injury
Signs are associated with mechanical obstruction and biochemical injury from release of FFA from fat globules that cause EC injury.
Air embolism – caused by thoracic wall injury, obstetric procedures, rapid decompression in deep sea divers (bends, usually nitrogen gas bubbles)

Amniotic fluid embolism – uncommon complication of labor/postpartum with 20-40% mortality. (1 in 50,000 deliveries in people)

INFARCTION

Area of ischemic necrosis caused by occlusion of arterial supply or venous drainage
Most often caused by thrombi/emboli and arterial occlusion
Less common causes – local vasospasm, extrinsic compression of vessel (tumor), mechanical twists (torsion/volvulus), entrapment in hernia sac, traumatic rupture of blood supply
Venous thrombosis usually causes obstruction and congestion, not infarction
Bypass channels open rapidly after the thrombosis to provide outflow which in turn improves arterial inflow.
Venous infarcts are more likely to occur in organs with a single venous outflow channel (testis/ovary)
Infarcts are classified by their color and presence/absence of microbial infection: red/white; septic/bland
Red (hemorrhagic) infarcts occur with:
Venous occlusions (ovarian torsion)
In loose tissues such as lung – allow blood to collect in infarcted area

In tissues with dual circulation (lung, small intestine) – blood can flow into area from unobstructed vessel but perfusion is not sufficient to rescue ischemic tissues
In tissues previously congested due to sluggish venous flow

When flow is reestablished to a site of previous arterial occlusion and necrosis
White (anemic) infarcts occur with:
Arterial occlusions in solid organs with end-arterial circulation
Solidity of tissue limits amount of hemorrhage that can seep into affected area from adjoining capillary beds
Most infarcts are wedge-shaped with occluded vessel at the apex and the periphery of the organ forming the base (if it is a serosal surface there is often a fibrinous exudate)
Lateral margins may be irregular.
Initially, margins of all infarcts are poorly defined and slightly hemorrhagic
Margins become better defined with time by a narrow rim of hyperemia representing inflammation at the edge of the infarct.
In solid organs, extravasated RBCs from hemorrhage are lysed, hemosiderin may remain in macrophages.
White infarcts from arterial occlusions become paler and more sharply defined with time.
Red infarcts in spongy organs have extensive hemorrhage – never becomes pale, but may become firm and brown as hemoglobin is degraded into hemosiderin pigment.
Histologically – ischemic coagulative necrosis
Microscopic lesions may not be present if infarct is acute
Margins of infarcts become inflamed and well-defined over hours to days
Reparative response begins in the margins where stromal architecture has been preserved.
Most infarcts healed by scar tissue. An exception is the brain, where ischemic injury results in liquefactive necrosis.
Septic infarctions can develop following embolization of septic vegetations or when bacteria seed necrotic tissue. Infarct is converted to an abscess with increased degree of inflammatory response.

Factors that influence development of an infarct
Nature of the vascular supply
Dual blood supply limits damage (lung and liver)
Renal and splenic vessels are end-arterial – obstruction usually causes infarction
Slowly developing occlusions are less likely to cause infarction – allow time for development of alternative perfusion pathways (e.g. anastomoses).
Susceptibility of cells to hypoxia varies – neurons and myocardial cells are sensitive to ischemia; fibroblasts can live after hours of ischemia

SHOCK

Cardiovascular collapse – final common pathway for severe hemorrhage, trauma/burns, large myocardial infarction, massive PTE, sepsis

Systemic hypoperfusion caused by reduction in cardiac output or in effective circulating blood volume → hypotension, impaired tissue perfusion, cellular hypoxia → eventual irreversible tissue injury

General categories of shock

Cardiogenic shock – pump failure due to arrhythmia, myocardial damage, tamponade, outflow obstruction

Hypovolemic shock – loss of blood/plasma volume

Septic shock – systemic microbial infection

Neurogenic shock – anesthesia or spinal cord injury due to loss of vascular tone and pooling of blood

Anaphylactic shock – generalized IgE-mediated hypersensitivity response associated with systemic vasodilation and increased vascular permeability

Septic shock

Usually caused by endotoxemia – release of endotoxins from degraded cell walls during inflammatory response.

At very high levels, septic shock occurs

Systemic vasodilation

Diminished myocardial contractility

Endothelial injury and activation → systemic leukocyte adhesion and alveolar capillary damage

Activation of coagulation system → DIC

Hypoperfusion induces multiorgan system failure

Stages of hypovolemic shock

Nonprogressive phase:

Reflex compensatory mechanisms are activated and organ perfusion is maintained

Neurohormonal mechanisms maintain CO and BP → baroreceptor reflexes, catecholamine release, rennin-angiotensin axis, ADH, sympathetic stimulation

Net effect is tachycardia, peripheral vasoconstriction, renal conservation of fluid

Progressive stage

Tissue hypoperfusion and onset of circulatory and metabolic imbalances → acidodosis

Lactic acidosis due to onset of anaerobic glycolysis → decreased pH blunts the vasomotor response → vasodilation, pooling of blood in microcirculation, decreased CO, EC injury from anoxia increases risk for DIC

Decreased urine output and patient confusion when organs begin to fail

Irreversible stage

Cellular and tissue injury is so severe that survival is not possible even if hemodynamic effects are corrected.
Lysosomal leakage from cellular injury, decreased myocardial contractility is worsened by production of NO, complete renal shutdown from tubular necorsis

Morphology of shock
Changes are characteristic of hypoxic injury – may be present in any tissue, especially brain, heart, lungs, kidneys, adrenals, GI tract
Brain may develop ischemic encephalopathy
Heart – focal or widespread coagulation necrosis +/or contraction band necrosis
Cardiac lesions are usually more widespread and severe in shock than observed in reperfusion after irreversible injury or catecholamine administration
Kidneys – extensive tubular ischemic injury → oliguria, anuria, electrolyte dysfunction
Lungs – more resistant to hypoxic injury, can develop shock lung if caused by trauma or sepsis → diffuse alveolar damage
Adrenal gland – similar changes seen in all forms of stress; depletion of cortical lipid indicative that inactive vacuolated cells of cortex have been converted to metabolically active cells using lipids for steroid synthesis.
GI tract – patchy mucosal hemorrhage and necrosis → hemorrhagic enteropathy
Liver - fatty change with central lobular hemorrhagic necrosis due to hypoperfusion
Hypovolemic and cardiogenic shock – skin is cool, clammy, and cyanotic
Septic shock – skin may initially be warm, flushed due to peripheral vasodilation

DISTURBANCES OF GROWTH AND NEOPLASIA BY

Aplasia / agenesis:
Complete failure of an organ to develop during embryogenesis.
In many cases that involve vital organs the animal may not survive to extra-uterine life but where paired structures are involved such as the kidneys or gonads, or non-vital organs such as tail or limbs, the change becomes evident.

Hypoplasia:
This is the failure of an organ or part of an organ to develop to normal size.

Atrophy:
A shrinkage or reduction in size of an organ to less than its former / normal size.

This differs from hypoplasia in that it had previously attained its normal size before shrinkage while hypoplastic organs never attained the normal size.

Hypertrophy:
An increase in size of an organ or tissue to more than its former / normal size.

The increase in this case as distinct from the phenomenon in hyperplasia is usually due to an increase in the **size** of individual component cells and NOT **number**

Hyperplasia:
This is an absolute increase in number of cells usually due to an increase functional demand.

Usually only a single cell type in a tissue is affected.

METAPLASIA:
This is the replacement of one type of fully differentiated issue by another fully differentiated type.
This process is rather a substitution than a transformation. E.g change of columnar or cuboidal epithelium into stratified squamous epithelium has been observed in the tracheo-brochial tree in response to chronic irritations.
Squamous metaplasia is a common feature in Vitamin A deficiency.

Dysplasia: (Dys – disordered plassein – to form)
A disordered / abnormal development of cells and tissues.
Dystrophy is sometimes erroneously used to describe this change.
Microscopically, dysplasia is characterized by disruption of orientational relationships and variation in shapes and sizes of cells

Anaplasia:
This is a reversal of cells to a more primitive and less differentiated type. Synonyms include: De-differentiation or undifferentiation.
Dysplasia and anaplasia are reversible cellular changes and are usually considered as precursors of neoplasia.

AN OVERVIEW OF NEOPLASIA

The term neoplasia literally means new growth and the mass of cells that composes the new growth is known as a neoplasm. Neoplasms represent growth disturbances in which the regulatory mechanisms of cell contact inhibition, differentiation, and mitosis are defective.
5. Explain the manner in which benign and malignant neoplasms grow and/or spread.
6. Explain the means by which neoplasms metastasize.
7. Explain the mechanism by which RNA viruses cause neoplastic transformation of cells.
8. Explain the mechanism by which DNA viruses cause neoplastic transformation of cells.

9. Explain the similarities and differences between the oncogene theory and the provirus theory of neoplastic transformation.
10. Explain the most likely mechanism by which chemical carcinogens and radiation cause neoplastic transformation of cells.
11. List and briefly explain those factors which predispose an animal to neoplasia.
12. Briefly discuss the clinical effects of benign and malignant neoplasms.
13. Briefly discuss the procedures employed to diagnose neoplasia.
14. Discuss the differences and similarities between the following, based on gross and/or microscopic features.
granuloma vs. adenoma -- adenoma vs. adenocarcinoma
sarcoma vs. carcinoma -- hyperplasia vs. neoplasia

KEY WORDS

The student should be able to define, spell correctly, and use the following terms.

neoplasm
neoplasia
cancer
tumor
cellular differentiation
Anaplasia
Aplasia
oncology
benign neoplasm
malignant neoplasm
Metastasis
Sarcoma
undifferentiated neoplasm
carcinoma
papilloma
adenocarcinoma
polyps
squamous cell carcinoma
Teratoma
Teratology
rhabdomyoma
leiomyoma
Pleomorphism
hyperchromatism
mitotic figures
Encapsulation
growth by expansion
growth by infiltration
Papova
hematoma
-- hematogenous
-- lymphogenous
-- tumor emboli
-- implantation
-- transplantation
-- carcinogens
-- oncogenic viruses
-- oncornaviruses
-- reverse transcriptase
-- RNA-dependent DNA polymerase
-- genome
-- transcription
-- provirus
-- virions
-- type "B" virus particle
-- type "C" virus particle
-- productive viral infections
-- permissive cells
-- procarcinogens
-- cocarcinogens
-- mutagen
-- the "Ames Test"
-- hyperplasia
-- metaplasia
-- precancerous lesions
-- carcinoma-in-situ
-- contact inhibition
-- leukemia
-- needle biopsy
-- granuloma

GENERAL CONSIDERATIONS

Definitions

Before embarking on the study of neoplasia, some of the commonly used terms should be clearly understood. In addition to the terms listed below, other terms are introduced throughout the section.

Oncology

Refers to the study of or science of neoplastic growth.

Neoplasia

literally means **"new growth"** and the mass of cells composing the new growth is a neoplasm. **(The term "new growth" does not adequately define an neoplasm.**)

Neoplasm

Refers to a new abnormal growth or mass of tissue whose growth rate exceeds and is uncoordinated with that of normal tissue, which serves no useful purpose, and which persists in the same excessive manner after cessation of the evoking stimuli which caused the change.

Definitions

Tumor

Originally referred to any swelling but currently used almost exclusively to refer to a neoplastic growth.

Cancer

The common term used for all malignant neoplasms.

Benign neoplasm

A neoplasm that tends to grow slowly, is well differentiated, does not metastasize, and is usually non-life threatening.

Malignant neoplasm

A neoplasm that tends to grow rapidly, is poorly differentiated, often metastasizes, and frequently causes death of the host.

Metastasis

Refers to the transfer of disease manifestations from one organ to another. It is used mainly to refer to the secondary growth of a malignant neoplasm in an organ or site remote from the primary site.

Differentiation

Refers to the process where by one form, typically the immature, develops into another, usually the mature. As it relates to cells, this generally involves the development of immature cells into mature ones.

Anaplasia

Literally means **"to form backwards"** but refers to the tendency of a neoplasm to be composed of less differentiated/mature cells.

NOMENCLATURE

Unfortunately, the nomenclature of neoplasms does not follow any single consistent pattern. However, most benign tumors end with the suffix **"oma."** Malignant neoplasms of connective tissue are generally named by attaching the term "sarcoma" to the name for the essential cell. Malignant neoplasms of epithelial origin end with the term **"carcinoma" (there are exceptions)**. Attaching the suffix **"oma"** to the cell type constituting the neoplasm works

well with mesenchymal benign neoplasm **(those arising in muscles, bones, tendons, cartilage, fat, vessels, lymphoid and fibrous tissue)** because:
(1) the cells usually closely resemble their normal counter parts and
(2) the various adult mesenchymal cells are sufficiently distinctive to be readily differentiated from one another. However, benign neoplasms of epithelial origin defy such easy classification. These neoplasms are variously classified, some on the basis of their cell or origin, others on microscopic architecture and still others on their gross patterns. Adenoma is the term applied to the benign epithelial neoplasm which forms a glandular pattern and/or is derived from glands (**but not necessarily reproducing glandular patterns).**

EXAMPLE 1:
A benign epithelial neoplasm that arises from the intestinal lining cell growing in the form of gland-like structures would be termed an adenoma, as would a mass of adrenal cortical cells growing in no distinctive pattern, but merely producing a small benign new growth.
Benign epithelial neoplasms producing microscopically or grossly visible **"finger-like"** or **"wart-like"** projections from epithelial surfaces are referred to as papillomas or polyps. Those that form large cystic masses **(as in ovaries**) are ***referred*** to as cystomas or cystadenomas.
The nomenclature for malignant neoplasms essentially follows the same pattern used for benign neoplasms with certain additions. Malignant neoplasms of connective tissue origin are called sarcomas.
EXAMPLE 2:
A malignant neoplasm of fibroblasts is a fibrosarcoma. One composed of fat cells is a liposarcoma. Malignant neoplasms of epithelial cell origin (**derived from any of the three germ layers**) are called carcinomas. A carcinoma with a glandular growth pattern microscopically is termed an adenocarcinoma. One producing recognizable squamous cells **(arising from any of the stratified squamous epithelia of the body)** is termed a squamous cell carcinoma.
Also, it is a common practice to specify, when possible, the organ of origin (**e.g., renal adenocarcinoma, bronchogenic squamous cell carcinoma, etc.**). A malignant neoplasm may be composed of very primitive, undifferentiated cells and must be designated merely as an undifferentiated malignant tumor or, when possible, undifferentiated carcinoma or undifferentiated sarcoma.
The term teratoma is used to designate a tumor composed of a variety of cell types representative of more than one germ layer.

CRITERIA FOR DIFFERENTIATING BENIGN FROM MALIGNANT NEOPLASMA

The differentiation of benign from malignant is the most important judgement the veterinarian is called upon to make relative to neoplasia **(upon this decision are based the treatment of the lesion and the outlook**

for the animal). Benign and malignant neoplasms are most commonly distinguished on the basis of:
(1) the degree of cellular differentiation or cellular anaplasia,
(2) the rate of growth and
(3) the mode of growth and spread. Anaplasia and metastasis are the **"hallmarks"** of malignancy.

1) Cellular Differentiation and Anaplasia

Differentiated neoplastic cells are those that resemble their normal cell of origin and include the extent to which they achieve their fully mature morphologic and functional characteristics. The closer the resemblance to their normal cell of origin, the better the differentiation. However, the greater the departure from the characteristics of the normal, the poorer the differentiation. The terms undifferentiated or anaplasia refers to poorly differentiated cells. In general, all benign neoplasms are well-differentiated. However, malignant neoplasms range from well-differentiated to those consisting of primitive appearing undifferentiated cells. Remember, even well-differentiated malignant neoplasms generally have some degree of anaplasia. Anaplastic or undifferentiated neoplasms are invariable malignant, and are composed of cells that have lost some or all resemblance to their normal counterpart.

On the other hand, benign neoplasms are extremely well-differentiated and closely resemble the normal cells. Oftentimes, only the massing of these cells into a nodule discloses the neoplastic nature of the lesion (mitosis is extremely scant and such neoplasms never metastasize).
Anaplasia (undifferentiated cells) is characterized by the features listed below:
1. Pleomorphism (**variation in size and shape of cells and nuclei)**.
2. Hyperchromatism **(nuclei contain abundance of dark-staining chromatin)**.
3. Enlarged nucleoli.
5. Formation of tumor giant cells **(in some instances).**
4. Increased mitosis with abnormal mitotic figures.

2) Rate of growth

In general, benign tumors (well-differentiated) grow slowly over a period of years at a rather steady pace. Most malignant neoplasms grow rapidly, sometimes at an erratic pace, eventually to spread and kill the host. Remember, there are exceptions to this generalization. Benign neoplasms, for example, may enter periods of long dormancy when they apparently do not enlarge. Others may achieve a certain size and apparently cease growing or decrease in size. Although most malignant neoplasms progressively enlarge, some may shrink in size and others may remain dormant for periods

of time. However, as a rule of thumb, the more anaplastic the neoplasm, the more numerous the mitoses and the more rapid the growth.

3) Mode of Growth and Spread

The mode of growth and capacity to spread clearly differentiate malignant from benign neoplasms.

1. Encapsulation

Nearly all benign neoplasms grow as localized expansive masses enclosed within a fibrous capsule. Such neoplasms remain localized to their site of origin and do not disseminate throughout the body. Although encapsulation is a characteristic of benign neoplasms, the lack of a capsule does not make a neoplasm malignant.

Malignant neoplasms are almost never encapsulated and are characterized by infiltrative, erosive growth which extends into adjacent tissues (**normal anatomic boundaries are not recognized).**

2. Metastasis

Metastasis refers to the spread of neoplastic cells from one part of the body to another by way of the bloodstream **(hematogenous**) or lymph channels **(lymphogenous)**. As neoplastic cells infiltrate, they may erode into blood vessels or lymphatics, become detached and act as emboli. Thus, when these cells become lodged in other tissues, they may grow and develop into secondary tumor nodules **(metastases**). Neoplastic cells traveling by way of the bloodstream usually lodge in the first capillary bed they encounter. The lungs and liver are probably the most common sites for lodgement. Cells traveling by way of the lymph channels usually lodge in sinuses of the regional lymph nodes. There is a tendency for epithelial neoplasms to metastasize by way of lymphatics and for connective tissue neoplasms to metastasize by way of the bloodstream (**there are exceptions)**.

Metastasis is a **"hallmark"** of malignancy. All neoplasms that metastasize are malignant, although all malignant neoplasms do not metastasize ***(for example,* malignant glial cell neoplasms of the central nervous system and basal cell carcinomas of the skin are highly invasive neoplasms but they rarely metastasize).**

3. Implantation

Refers to the transfer of neoplastic cells from one serous or mucous surface to another by direct contact. Body cavities (**peritoneal, etc.**) are commonly involved.

Because of their lack of cohesiveness, neoplastic cells growing on epithelial surfaces are prone to shed into the surrounding spaces. Implantation is a feature of some malignant neoplasms.

Transplantation refers to the mechanical transport of neoplastic cells by instruments and gloved hands.

This is a significant potential hazard during cancer surgery.

In summary, benign and malignant neoplasms are most commonly distinguished on the basis of:

(1) the degree of cellular differentiation,

(2) the rate of growth and

(3) the mode of growth and spread.

Benign neoplasms are characterized by:
(1) well-differentiated cells that resemble their normal fore bearers,
(2) slow and progressive growth that may come to a stand still or regress,
(3) growth by expansion with the formation of a capsule and
(4) absence of metastasis.

Malignant neoplasms are characterized by
(1) anaplasia or poorly differentiated cells,
(2) rapid and often erratic growth with many abnormal mitotic figures,
(3) growth by infiltration as well as by expansion and a well-defined capsule is almost always absent and
(4) frequent metastasis.
Anaplasia and metastasis are the **"hallmarks"** of a malignant neoplasm. Lymphatic channels are the most common pathway for the initial spread of carcinomas, whereas sarcomas tend to spread by way of the bloodstream (**there are exceptions)**.
Significant features of benign and malignant neoplasms are listed in the following tables

CAUSES OF NEOPLASIA

There have been numerous theories advanced to explain the cause of neoplasms. The numerous agents capable of producing neoplasia naturally and experimentally can be grouped as follows:
(1) oncogenic viruses,
(2) carcinogenic chemicals,
(3) radiation and
(4) other agents.

Oncogenic Viruses

In animals, there are various neoplasms in which a viral cause has been definitely established. Viral oncogenesis was actually observed before viruses were known when ***Ellerman and Bang (1908***) demonstrated that a sarcoma of chickens could be passed to other birds in cell-free material. Since then, a great many oncogenic viruses have been identified that can be divided into DNA and RNA viruses. Viruses may influence the development of neoplasia by inserting themselves into the host genome directly or indirectly as DNA sequences, resulting in transformation of cells.
The 3 biologic forms of oncornavirus are
(1) leukemia virus,
(2) sarcoma virus and
(3) a mouse mammary tumor virus (**the leukemia and sarcoma viruses are type C viruses, whereas the mouse mammary tumor virus is a type B particle)**. Leukemia viruses have been isolated from several species including mice, chickens and cats. Sarcoma viruses have been isolated from the chicken, mouse, rat, cat and wooly monkey.
Studies on the mode of oncornavirus transmission revealed that both somatic and germ cells of animals may harbor unexpressed type C viral genome

(virogene). This suggests that oncornaviruses may remain latent within apparently normal cells. Two major theories have been proposed to explain this finding:
(1) oncogene theory and
(2) provirus theory

DNA Oncogenic Viruses:
There are three groups of DNA viruses known to have strong oncogenic potential in animal systems:
(1) papova viruses,
(2) adenoviruses and
(3) herpesviruses.
All three groups have the ability to become integrated into the DNA of host cells, causing neoplastic transformation. The papova viruses include the polyoma virus, simian virus 40 and the papilloma viruses. The herpesviruses induce a variety of tumors in several vertebrate species, including Marek's disease in birds, reticulum cell sarcoma in marmosets and owl monkeys and renal adenocarcinomas in frogs. When a DNA oncogenic virus infects the cells of its normal host, a productive infection occurs and numerous virus particles are released. The cell is usually lysed **(the normal host cells are said to be permissive since they permit the virus to complete its life cycle)**. However, when cells not the natural host of the virus are infected, virus particles are not produced and the cells often undergo neoplastic transformation. Such cells are said to be **"nonpermissive"** and the infection is "nonproductive" and **"transforming."** The host cell is the major determinant of the pathway that will be followed. The sequence of events in the **"transformation"** reaction between DNA viruses and the host cells takes place in two stages, **"early"** and **"late."**
The **"early"** stage includes entry of the virus into the cell and removal of the protein envelope from the DNA. Thereafter, the viral DNA is integrated into the genome of the host cell. In nonpermissive cells, **"early"** viral genes are expressed, leading to the synthesis of a viral coded protein called tumor or T-antigen. The T-antigen has been shown to bind to DNA and in some way modify expression of the viral genome so as to block the production of virus particles and instead produce alterations in the cell membrane characteristic of neoplastic transformation. The "late" stage of viral infection, involving genes that code for the viral capsid proteins required for the production of infectious virions, is suppressed in cell transformation.
There is no need for reverse transcriptase in neoplastic transformation by DNA viruses **(reverse transcriptase is a feature only of the oncogenic RNA viruses).** In contrast to the situation with RNA viruses, when DNA viruses induce cellular transformation there is no release of infectious virions.

Chemical Carcinogens

Chemical carcinogens **(compounds capable of producing neoplasms**) are numerous, but the best known are hydrocarbons, alkylating agents, azo dyes

and aromatic amines. The student should be reminded of the following pertinent facts relative to chemical carcinogens:

1. Chemical carcinogens include both man-made and natural products of extremely diverse chemical structure.
2. Chemical carcinogens are of two classes:
(1) direct-reacting carcinogens and
(2) procarcinogens **(which require chemical or enzymatic activation).**
3. All carcinogens are highly reactive electrophiles that bind covalently to nucleophilic residues in DNA, RNA and cellular protein.
4. The binding of chemical carcinogens to DNA is random in terms of gene specificity, as well as in terms of the nature of the genetic injury.
5. The binding of chemical carcinogens to RNA involves all forms of RNA, but particularly tRNA.

1. The effects of chemical carcinogens are dose-dependent, additive and irreversible **(the larger the cumulative dose, the greater the incidence of neoplasia)**.
2. There is a lag period between exposure and the appearance of tumors.
3. The cellular changes that trigger carcinogenesis are transmitted to daughter cells.
4. Cellular proliferation enhances carcinogenesis.

5. Neoplasms induced by the same chemical carcinogen often display antigenic diversity as well as a diversity of phenotypes in terms of histiologic patterns, degree of differentiation, cell surface properties and other attributes of neoplastic transformation. 6. Cocarcinogens or promoters are agents which by themselves have little if any carcinogenic effect, but they augment the action of either direct-reacting carcinogen or procarcinogens.
7. Most chemical carcinogens are mutagens, but not all mutagens are necessarily carcinogenicThe study of chemical carcinogenesis has contributed more to the understanding of neoplasia than any other experimental approach. The following facts are basic to chemical carcinogenesis.