

Veterinary General Pathology

January 14th – February 12th

Pathology Professor

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Recommended Texts

- **Robbins & Cotran Pathologic Basis of Disease** (7th ed.) by Kumar et al
3rd ed, available for check out at the Vet. School Library
- **Cell, Tissues, & Disease: Principals of General Pathology** by Majuo & Joris
- **Pathologic Basics of Veterinary Diseases** by McGavin & Zachary

Exam

- 100 points
- Material will come from notes (focusing on learner objectives) and student written questions
 - Short answer, multiple choice, matching, 1 essay?

Requirements for the Doctor of Philosophy Degree

- Page 53 Graduate Bulletin
- The Ph.D. is the highest earned degree offered by universities
- It is conferred only for work of distinction in which the student displays decided powers of original scholarship and only in recognition of marked ability and achievement
- Satisfaction of the minimum requirements of the Graduate School, as stipulated [in the graduate bulletin] in no way relieves a doctoral student of responsibility for satisfying and additional requirements deemed appropriate by the graduate faculty of the degree programs in which he or she is enrolled
- The basic requirements are:
 - 1) A student must exhibit unmistakable evidence of mastery of a broad major field (such evidence is ordinarily provided by passing a general exam)
 - 2) A student must prove ability to complete a significant program of original research by preparing a dissertation embodying creative scholarship and by passing a rigorous final examination

Introduction to Pathology

Disease:

- is essentially the “loss of ease”
- a departure from a normal state
- the better we understand the disease, the better we can diagnose & treat it

- **Diagnosing & Treating Disease**
 - Learn what's normal
 - **Anatomy:** the morphologic structure of an organism
 - **Physiology:** the study of the normal vital processes/functions of animal & vegetable organisms
 - **Histology:** the study of the minute structure of cells, tissues, & organs in relation to their function
 - **Biochemistry:** the chemistry of living organisms & of the chemical, molecular, & physical changes occurring within the living organisms
 - **Genetics:** studying the mode & consequences of transmission & generation of the components of biological inheritance

 - Learn what goes wrong
 - Structural &/or Functional changes
 - Why/how things go wrong
 - Agents that cause things to go wrong
 - Genetic
 - Microbial
 - Nutritious
 - Parasitic
 - Toxic

 - Devise a Treatment or Management Plan

Pathology:

- Pathology is the study of Disease.
 - Pathos – suffering; disease
 - Logos – study

- Pathology is the study of molecular, biochemical, functional, & morphological changes in cells, tissues, or organs in response to an **injury**
 - **Injuries** can be..
 - **Traumatic:** relating to or caused by a **trauma** (a physical or mental injury)
 - **Toxic:** poisonous
 - **Ischemic:** relating to or caused by **ischemia**
 - **Ischemia:** local loss of blood supply due to mechanical obstruction (mainly arterial narrowing or disruption) of the blood vessel

- It bridges the gap between the basic & clinical sciences
- it studies the structural & functional changes in cells, tissues, & organs
- it explains how/why the clinical signs of a disease are being manifested

Pathology (continued)

- when living cells are exposed to a noxious chemical, physical, or biological agent they are injured
- there are a limited number of the types & mechanisms of **injury**
- cells generally respond to an injury in one of the following 4 ways:
 - the cells get bigger (**hypertrophy**)
 - the cells get smaller (**Atrophy**)
 - The cells proliferate (**Hyperplasia** or **Neoplasia**)
 - The cells die (**Necrosis** or **Autolysis**)
- the problem is that there can be a lot of stimuli that cause the same type of injury

Cellular Response to Injury

Hypertrophy

- the general increase in the bulk of a part or organ, not due to tumor formation, essentially the cell size increases without increasing the number of cells. Hypertrophy can be either good or bad

Examples

- **Cardiac hypertrophy** involving the left ventricle.
 - o this patient (pt) had **systemic hypertension**.
 - o The number of myocardial fibers does not increase, but their size can increase in response to an increased workload
 - this leads to the marked thickening of the left ventricle.
 - o In this case the heart had to get bigger in order to pump enough blood to the periphery (which is good)
 - However, now the heart has to pump faster in order to pump the same amount of blood
 - This will cause the heart to get smaller which will use more energy (degenerative spiral)
 - o This is common in cats with **hyperthyroidism**



Heart

Atrophy

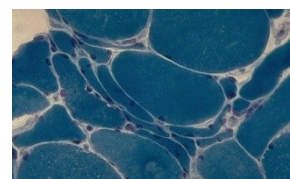
- the cells get smaller, through the wasting of tissues, organs, or the entire body, as from death & re-absorption of cells, diminished cellular proliferation, decreased cellular volume, pressure, ischemia, malnutrition, lessened function, or hormonal changes

Examples

- **Testicular Atrophy**
 - o A normal testis is shown on the left
 - o The testis at the right has undergone atrophy
- **Muscular Atrophy**
 - o Trichrome stain of muscle fibers that show atrophy.
 - o The number of cells is the same as before the atrophy occurred, but the size of some of the fibers is reduced.
 - o This is a response to injury by “downsizing” to conserve the cell.
 - o In this case, the **innervation** of the small fibers in the center was lost.
 - **Innervation:** the supply of nerve fibers functionally connected with a part



Dog Testes



Muscle Fibers

Hyperplasia

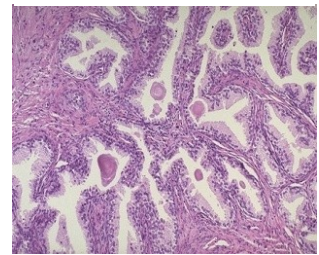
- an increase in the number of normal cells in a tissue or organ, usually resulting in the subsequent increase in the size of the surrounding part or organ. (hyperplasia excludes tumor formation)

Examples

- **Prostatic hyperplasia (XS).**
 - o Normal prostate 3-4 cm diameter.
 - o The number of prostatic glands as well as **stroma** has increased .
 - **Stroma:** the framework, usually connective tissue, of an organ, gland, etc.
 - o The pattern of increase here is **nodular** (not uniform).
 - o This change was due to **hormonal manipulation** (as opposed to a normal physiological process)
 - o Histo. view of one of the nodules of the above prostate with many glands along some intervening stroma.
 - o The cells making up the glands are normal in appearance, but there are just too many of them.



Prostate

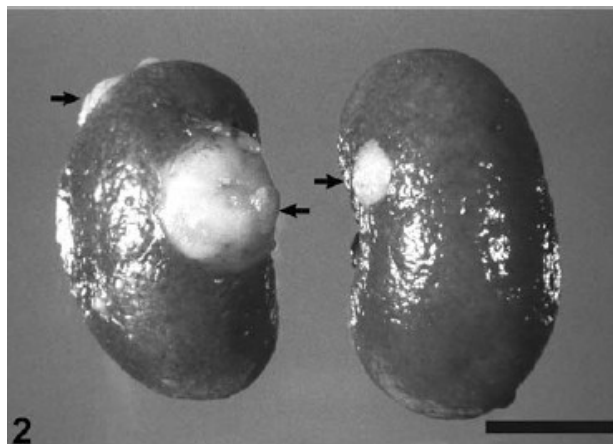


Neoplasia

- Pathologic process that results in the formation & growth of a **neoplasm**
 - **Neoplasm:** a tumor, which is an abnormal tissue that grows by cellular proliferation more rapidly than normal & continues to grow after the stimuli that initiated the growth has ceased

Examples

- **Neoplastic Kidney**
 - o 8-year old male, black-footed ferret kidney
 - o Arrow show the multiple renal tubular-cell neoplasms within the kidney
 - o Scale bar = 1cm
 - o Lair et al. (2006) Renal Tubular-cell Neoplasms in Black-footed Ferrets (*Mustela nigripes*) – 38 Cases. Vet Pathol 43: 276-280



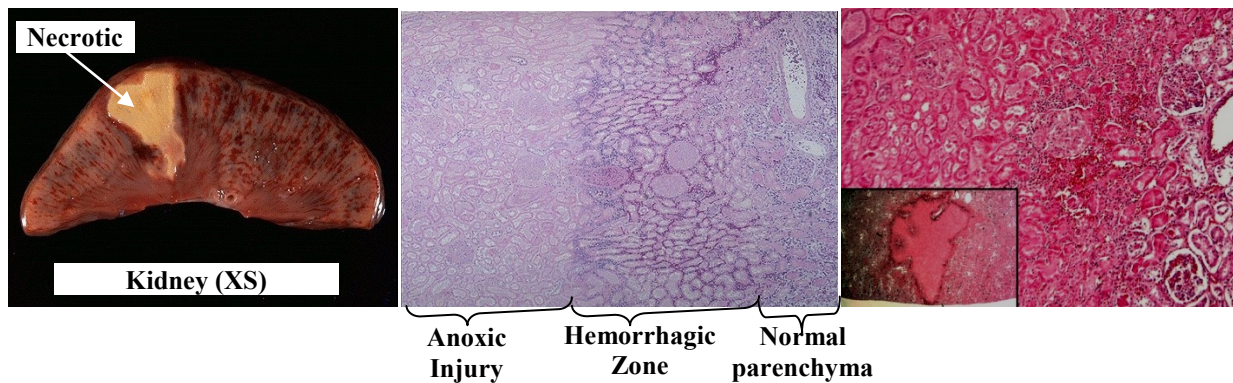
Kidney

Necrosis

- Pathologic death of one or more cells, or a portion of tissue or organ, resulting from irreversible damage
 - **Coagulative** necrosis: is when you can still see what is dead (i.e.) the dead cells
 - **Liquafactive** necrosis: when you can no longer see the cells because everything has turned into a liquid goo
 - **Casius** necrosis: everything turns into a cottage cheese consistency

Examples

- **Kidney (XS) Coagulative** necrosis
 - o This is the typical pattern with **ischemia** and **infarction**
 - **Ischemia**: loss of blood supply due to a mechanical obstruction of the blood vessel
 - **Infarction**: an area of tissue necrosis caused a loss of blood supply and resultant tissue anoxia.
 - o The wedge-shaped pale area of coagulative necrosis (infarction) is in the renal cortex of the kidney
 - o Microscopically, the renal cortex has undergone anoxic injury so that the cells appear pale & ghost-like.
 - o There is a hemorrhagic zone in the middle where the cells are dying or have not quite died, and then normal **parenchyma** at the far right.
 - o In this case the patient will most likely loose part of the kidney, but the remaining kidney will respond with hyperplasia to makeup for the loss & continue to function normally



Autolysis

- Enzymatic digestion of cells (especially of dead or degenerative cells) by enzymes present within them (**autogenous**)
 - **Autogenous**: originating within the organism itself

Pathology

- The following 2 biomedical phenomena are responsible for up to **70%** of human **morbidity & mortality** in the U.S.
 - **Cell Proliferation** (Hyperplastic or Neoplastic)
 - **Cell Death**

Note:
Morbidity: diseased state
v.s.
Mortality: fatal outcome

- These cellular processes underlie the following common diseases
 - **Cerebrovascular accident** (stroke) –10%
 - **Neoplasia** (cancer) – 20%
 - **Myocardial Infarction** (heart attack) – 40%
 - Cross section through a **heart** with a large **myocardial infarction** involving the anterior left ventricular wall and septum.
 - The infarct is beginning to heal, but still has a necrotic center
 - If these changes are visible, then the person has lived long enough for the changes to show up (hours to weeks)



- These phenomena and an organism's response to them (inflammation & immunity) are the main focus of **General** and **Systemic** Pathology
 - **General** Pathology: cellular and tissue levels
 - **Systemic** Pathology: organ-system level
- The 4 aspects of a disease (dz) process that form the core of pathology:
 - **Etiology** - primary cause of the disease
ex. E. coli caused food poisoning
 - **Pathogenesis** - mechanisms of development of a lesion or disease process (step by step)
ex. Person eats too many raw oysters, oysters had vibrios, vibrios caused food poisoning
 - **Morphologic changes** – structural alterations within cells, organs, or tissues associated with disease processes
 - **Clinical significance** – functional consequences of morphological changes
- We emphasize understanding etiology, pathogenesis, and tissue changes in terms of:
 - **Basic science** : pathologic anatomy, biochemistry, pathophysiology, and molecular biology
 - **Clinical relevance:** clinical signs, symptoms, and disease conditions produced

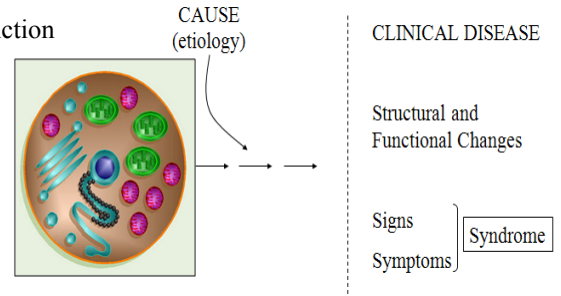
General Concept of Disease

- Functional derangements

- Abnormalities of cell, tissue, organ, system, & organism function

- Sign** – objective, seen by observer
- Symptom** – generally subjective, experienced & described by patient
- Syndrome** – “running together of symptoms &/or signs

Note: Can be both (vomiting, diarrhea, bleeding)



- Etiology – “cause” (an ancient concept; 2500BC)

- Intrinsic** factors – familial/genetic factors
- Acquired** factors – infectious, nutritional, chemical, physical
- Degree of overlap (genetic predispositions)
- Etiologies are complex and multifactorial, often involving gene-environmental interactions (atherosclerosis, neoplasia, obesity)

- Pathogenesis – mechanisms

- The study of pathogenesis is one of the main domains of pathology
 - Sequence of events in the response of cells and tissues to etiologic agents
 - Progresses from initiation of stimulus to expression of disease
- e.g.:* pollen is the cause of hay fever, but the pathogenesis of hay fever requires several steps
 - Pollen proteins are engulfed by **macrophages (mφ)**
 - Macrophage (mΦ)**: cells within tissues that originate from specific white blood cells (**monocytes**)
 - Macrophages (mφ) then pass them on to appropriate **lymphocytes** (B cells) which produce **antibodies (Ab)**
 - Lymphocytes**: white blood cells formed in the bone marrow & distributed throughout the body in lymphatic tissue undergoing proliferation
 - Antibodies (Ab)**: proteins found in blood or other bodily fluids that are used by the immune system to identify and neutralize foreign objects, such as bacteria and viruses
 - The Antibodies (Ab) then sensitize the **mast** cells, which respond to the pollen **antigens (Ag)** by releasing inflammatory agents
 - Mast cells**: resident cells of several tissue types containing many granules rich in histamine & heparin. They are intimately involved in wound healing and defense against pathogens
 - Antigens (Ag)**: molecules that sometimes stimulate an immune response

- Pathognomonic

- Greek origin: Pathos (disease) + gnomon (judge)
- diagnostic for a particular disease
- a particular sign whose presence means (beyond any doubt) that a particular disease is present
- **Singular** pathognomonic are relatively **uncommon**
 - **Koplik's spots in the mouth (measles)**
 - **Palmar xanthomata (hyperlipoproteinemia)**

- Morphologic changes:

- Structural alterations that are characteristic of or diagnostic of a disease process
- **Lesion** – an abnormality or interruption of normal structure or function, or both
 - Necrosis, inflammation, neoplasia are all types of lesions
 - Wide range of overlap
 - Very few “pathognomonic” lesions
- The practice of diagnostic pathology is devoted to identifying the nature and progression of a disease by studying the morphologic changes in tissues and chemical alterations in patients
- The field has recently expanded to include molecular biologic and immunologic approaches for analyzing dz states

- Types of Diagnoses

- **Morphologic** Diagnosis:
 - Descriptive name for a lesion or disease process
 - Encompasses size, distribution, severity, time frame, organ affected, process type
 - *ex:* Canine, small intestine, enteritis, hemorrhagic, severe, segmental, acute
- **Etiologic** Diagnosis:
 - Describe lesions and proclaim an etiologic agent
 - *ex.* viral enteritis
- **Disease** Diagnosis:
 - A specific diagnosis that names the disease
 - *ex.* Parvovirus

Types of Pathology

- **General** Pathology
 - o types and mechanisms of disease (all organs)

- **Systemic** Pathology
 - o organ and system pathology

- **Anatomic** Pathology
 - o cytopathology (cells)
 - o surgical pathology (tissues)
 - o autopsy pathology
 - o also Dermatopathology, Neuropathology, other specialities

- **Morphologic** Pathology – (surgical/anatomic)
 - o **Biopsy** – “study of life”; living pieces of organism
 - o **Necropsy** – “study of the dead”
 - o **Autopsy** – postmortem study of self (same species)

- **Clinical** Pathology
 - o theoretical and technical aspects of laboratory technology that pertain to the diagnosis and prevention of disease.
 - o Deals with bodily fluids, excretions, secretions, and exfoliated cells (**cytology**)
 - o Blood work, urinalysis

- **Forensic** Pathology
 - o medicolegal pathology

Definitions

- **Disease** : departure from ease; departure from normal function
- **Pathology** : the study of molecular, biochemical, functional, and morphologic changes in fluids, cells, tissues, and organs in response to injury.
- **Clinical symptom** : a change or discomfort or pain caused by disease that can be *described* to a clinician
- **Clinical signs** : changes in behavior, excretion, secretion, or body condition that can be observed and/or measured by a clinician
- **Lesion** : an abnormal state of body chemistry, cells, or tissues.
 - Lesions may be functional or morphological or both.
 - One of the most common terms in pathology.
- **Etiology** : the cause of a disease state.
 - May be bacterial, viral, toxic, etc. (an etiological agent)
- **Pathogenesis** : the step by step progression of a lesion from the normal state to a diseased one
 - concerns the mechanisms rather than the causes
- **Prognosis**: the prediction of the outcome of a disease; must understand pathogenesis to get an accurate prognosis
- **Acute**: “coming sharply to a climax”
 - changes (good or bad) occurring rapidly
 - does not mean severe, although many acute diseases are severe
 - In real time, acute can mean anything from minutes to a few days
- **Chronic**: Means long-lasting
 - In real time, usually refers to weeks, months, or years
- **Subacute**: “not very acute”
 - Imprecise, but handy to describe certain clinical situations
- **Differential Diagnosis**:
 - The exercise of listing (in an orderly fashion) all the possible diagnoses of a given condition
 - Usually listed from the most likely to the least
 - *e.g.* : a lump on the head could be a mass of clotted blood (bruise), a tumor of the skin, a tumor of the skull, a metastatic tumor of an internal organ, an abscess, a congenital defect
- **‘Osis** : suffix for a pathological condition
- **‘Itis** : suffix for inflammation
- **‘Opathy** : suffix for pathological condition

Ten DiSC SPaCeS

- **T** – **tissue name** or type
- **N** – **number** of lesions (reasonable estimate) → Gives estimate of severity
- **D** - **distribution** of lesions → Focal, diffuse, focal to coalescing
- **S** – **size** of lesion (always metric)
- **C** – **consistency** → Firm, fleshy, hard, soft, fluctuant
- **S** – **shape** → Nodular, multinodular, umbilicated, plaque
- **P** – **pattern** → Relation to a landmark (anterior ventral pneumonia, bilateral, symmetrical)
- **C** – **color**
- **S** – **special features** (filled with pus, filled with blood)

Cell Injury & Degeneration

Disease at the Cellular Level

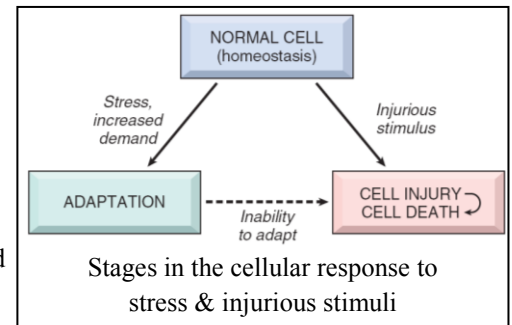
- Why do animals become sick or diseased?
- Sick cells result in sick animals
 - o Cellular dysfunction → Organ dysfunction → Animal dysfunction
 - o The problem is that we tend to get so focused on the cellular or organ dysfunction that we lose sight of the big picture (i.e. the animal dysfunction)
- **Cellular Pathology**
 - o **Rudolf Virchow**
 - Father of pathology (mid 19th century)
 - “disease can not be understood unless it is realized that the ultimate abnormality must lie in the cell.”
 - “pathology is physiology with obstacles”
 - Coined the terms:
 - **Thrombosis**
 - **Leukemia**
 - **Atrophy**
 - **Hypertrophy**
 - **Amyloid**
 - **Myelin**
 - **Teratoma**

Cellular Responses to Stress

- The normal cell is confined to a fairly narrow range of function & structure by:
 - o Genetic programs of metabolism, differentiation, & specialization
 - o Constraints of neighboring cells (one cell next to another cell)
 - o Availability of metabolic substrates
- Normal cells handle normal physiologic demands & maintain **homeostasis** (steady state)
- More severe physiologic stresses & some pathologic stimuli cause physiologic & morphologic cell adaptations
 - o Goal of cellular adaptations are usually to:
 - Achieve new, but altered, homeostasis (steady states)
 - Preserve the viability of the cell
 - Modulate function as cell responds to stimuli
 - o If the cells don't undergo some kind of adaptation the stress will usually kill them
- **Cellular Injury:**
 - o Occurs when the limits of the adaptive response to a stimulus are exceeded
 - o Occurs if a cell is exposed to an injurious agent or stress
 - o Cell injury is usually reversible to a certain point...
 - However, if the stimulus persists, or is severe enough from the beginning, the cell will reach its “**point of no return**” & will suffer irreversible cell injury & eventually cell death will occur

Normal Cells & Cellular Adaptations

- Cells have specialized functions
 - o Specialized structures based on their functions
- All cells have certain “standard” organelles
 - o Synthesis of lipids, proteins, & **carbohydrates (CHOs)**
 - o Energy production
 - o Transport of ions & other molecules
- **Cellular adaptations**
 - o Cells exist in a narrow physiochemical range of conditions
 - o **Homeostasis:** when a cell is in a homeostatic state it has tight control over its pH, electrolyte concentrations, etc.
 - o Departure from homeostasis leads to cell “damage”
 - o Cells respond to homeostatic challenges through “**adaptation**”
 - o Cell death occurs if a new level of homeostasis can not be achieved
- Examples of cellular adaptations
 - o Increase in the muscle mass with exercise
 - o Increase in the **cytochrome p450** mixed function oxidation expression in **hepatocytes**
 - People who take barbiturate drugs, or seizure meds will build up a tolerance to the medications over time, & eventually their dose will have to be increased to maintain effectiveness
 - o Cells respond (adapt) by either increasing or decreasing the content of their organelles



Cellular Responses to Injury

Nature and Severity of Injurious Stimulus	Cellular Response
Altered physiologic stimuli: <ul style="list-style-type: none"> • Increased demand, increased trophic stimulation (e.g. growth factors, hormones) • Decreased nutrients, stimulation • Chronic irritation (chemical or physical) 	Cellular adaptations: <ul style="list-style-type: none"> • Hyperplasia, hypertrophy • Atrophy • Metaplasia
Reduced oxygen supply; chemical injury; microbial infection <ul style="list-style-type: none"> • Acute and self-limited • Progressive and severe (including DNA damage) 	Cell injury: <ul style="list-style-type: none"> • Acute reversible injury • Irreversible injury → cell death <ul style="list-style-type: none"> ◦ Necrosis ◦ Apoptosis • Subcellular alterations in various organelles
Mild chronic injury	Intracellular accumulations; calcifications
Metabolic alterations, genetic or acquired	Intracellular accumulations; calcifications
Prolonged life span with cumulative sublethal injury	Cellular aging

- *Note:* decreased nutrients or decreased stimuli → muscle atrophy

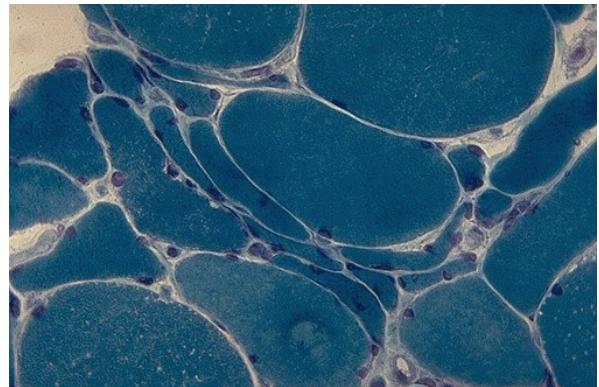
Types of Cellular Adaptation

- There are 4 types of Cellular Adaptation:

- 1) **Atrophy**
- 2) **Hypertrophy**
- 3) **Hyperplasia**
- 4) **Metaplasia**

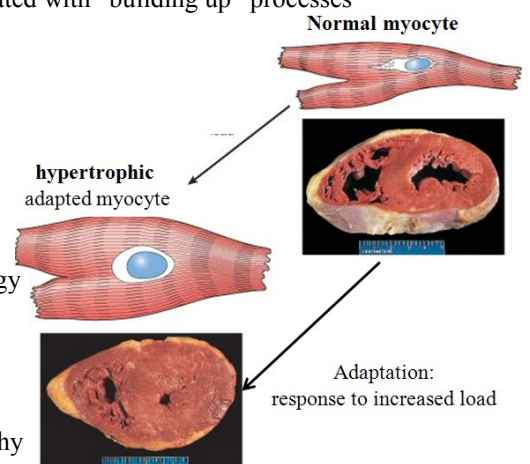
1) Cellular **Atrophy**

- Reduction in the mass of a tissue or organ, due to:
 - o Loss of cells
 - o Reduction in the size of the cells within an organ
- Adaptive response to altered demands
 - o Decreased workload
 - o Decreased nutrition
 - o Loss of hormonal stimulation
 - o Decreased blood supply
 - o Loss of innervation
- Reversible cellular change (up to a point)
- Reduced functional capacity
- Continue to control the internal environment & produce sufficient amounts of energy for metabolic state
- Prolonged cellular atrophy may lead to death of some cells
 - o Loss of muscle cells with prolonged **denervation**
 - **denervation** : loss of nerve supply
- Atrophy at the organ level may become irreversible at this point (muscle)
 - o Although it may be reversible by hyperplasia (liver)
- *ex:* **Adrenal Cortical Atrophy**
 - o Itchy dog goes to the vet for a flea allergy
 - o Dog is given **Corticosteroid (CS)** tx to inhibit the **Adrenocorticotrophic hormone (ACTH)**
 - o The cortisol reduces the ACTH levels
 - o Low ACTH causes atrophy of the **adrenal cortex** (what mediates stress responses)
 - o If the dog is abruptly taken off the CS tx the animal will go into “**Addisonian crisis**”
 - **Addisonian Crisis:** the adrenal gland is not producing enough steroid hormones
 - o This is why steroids must be gradually withdrawn, so as to allow the cells to return to their normal functioning



2) Hypertrophy

- Increase in the size of the organs/cells, which will result in the enlargement of the surrounding organs
- at the organ level, hypertrophy increases the organ size without cellular proliferation
- cell enlargement in hypertrophy is different from cell swelling (i.e. hypertrophy \neq cellular swelling)
- there are many signals indicating hypertrophy
 - o myofibrils (muscle)
 - o Mitochondria
 - o **Endoplasmic Reticulum (ER)**
- hypertrophy is an **anabolic** process
 - o **anabolic**: requires energy, often powered by ATP, generally associated with “building up” processes
- hypertrophy generally refers to muscle cells
- hypertrophy is not always advantageous to the animal
 - o point of diminishing returns
 - o Heart
 - Hypertrophy does not change the underlying problem
 - ex. **valvular stenosis**: inability to provide adequate energy or enough contraction despite hypertrophy
 - Conformational changes associated with hypertrophy
 - Decreased ejection volume
 - May eventually end up with the organ failure despite hypertrophy
 - This diagram shows over hypertrophy to the point of pathogenesis



3) Hyperplasia

- Increased number of cells in an organ or tissue, which causes enlargement of the surrounding organs
- Hyperplasia is a catabolic process
 - o **Catabolic**: does NOT require energy; passive process; generally associated with “breaking down” processes
-

4) Metaplasia

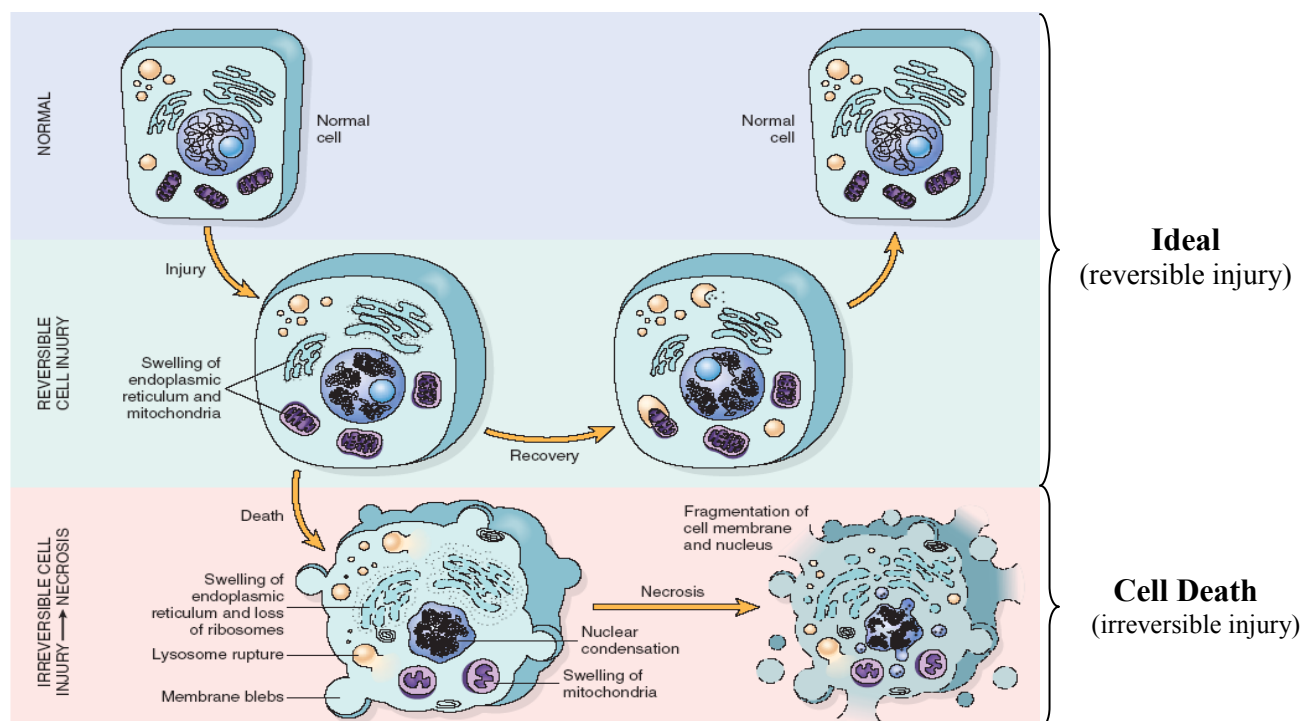
- Transformation or replacement of one adult cell type with another

Cellular Injury

- **Cell Injury:** any change resulting in loss of the ability to maintain the normal or adapted homeostatic state
- At some point, a stimulus exceeds the cell's ability to adapt, causing cell injury to occur
 - o We hope this injury will be reversible
- The cell will eventually become unable to balance the processes that regulate its internal environment
 - o Morphologic changes that we recognize as cell injury or degeneration
- The extent of cell injuries vary
 - o Severity of stimulus
 - ex. 1st & 2nd degree burns are reversible because the cells can adapt & heal; where as, 3rd degree burns are irreversible since the cell is too injured to heal resulting in cell death
 - o Type of cell involved
 - o Metabolic state at the time of the injury
- Reversible vs. Irreversible Cell Injury
 - o **Denegeration:** reversible cell injury
 - o The distinction between reversible cell injury (degeneration) and cell adaptation may be unclear in some cases

Morphology of Cellular Injuries

- Histologic Slides represent a single time point
 - o May not be able to determine if a cell is getting worse or getting better
 - o May not be able to determine whether the injury would have been reversible or not, at any given point in time
- Morphologic changes lag behind functional changes
 - o Cells will have changes in their functions before we can actually see them

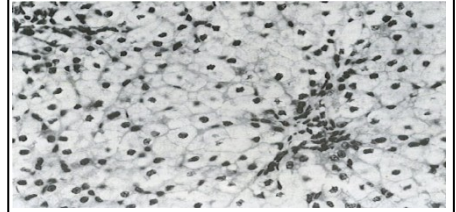


Hallmarks of Cell Degeneration: Cellular Accumulations

- Cell Swelling

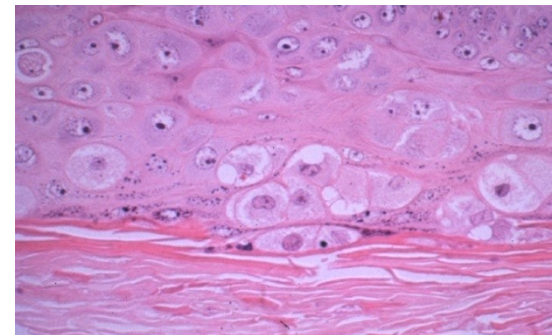
- o Early, almost universal sign of injury
- o Cells enlarged (swollen) due to a loss of volume control
- o Swelling causes the adjacent structures to become compressed
 - Causes a loss of **sinusoids** (small blood vessels) in the liver
- o Swelling results from the loss of control of the ions/water, resulting in a net uptake of water into the cell
- o Swelling is often seen when there is a loss of energy control or production
- o Not incompatible with life of the cell (depending on severity) & if often mild & rapidly reversible
- o Cell swelling also occurs in lethal injuries

Severe cell swelling. These hepatocytes are severely swollen & vacuolated. As a result, sinusoids are obliterated. These vacuoles mostly reflect markedly distended cisternae of the endoplasmic reticulum, but an increase in lipid vacuoles contributes to this appearance



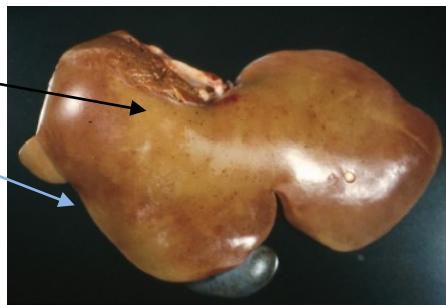
o Altered staining characteristics

- Pale, cloudy appearance
 - Cloudy swelling, hydropic degeneration
- Cytoplasmic vacuoles (**vacuolar degeneration**)
 - Distended organelles in the endoplasmic Reticulum
 - Lipid droplets



o Gross appearance of the swelling

- Organ is often pale
- Enlarged, swollen
 - Rounded margins
 - Heavy
 - Wet
- Bulges on cut surface



o Effect of the cellular swelling

- Varies by organ
 - **Brain:** swelling has severe effects due to pressure necrosis
 - **Liver:** decreased blood flow, resulting in decreased function
 - **Pharynx:** airway obstruction
 - **Muscle:** few detrimental effects due to swelling

- Fatty Change

- o Fatty change is a sort of sub-set of cell swelling
- o It has nothing to do with **adipose** (fat) tissue
- o It's the accumulation of neutral fats, ie. **Triglycerides (TG)** in a cell
- o It is a common change in injured cells
 - Especially cells that **metabolize lots of lipids**
 - **Hepatocytes**
 - **Myocardial cells**
 - **Renal tubular epithelial cells**
 - **Diabetes mellitus**
- o Sick cells tend to accumulate TG & undergo fatty change
- o **Gross appearance**
 - Yellow discoloration (kidney/liver)
 - Enlarged (liver)
 - **Hepatocytes** are chocked full of fat
- o **Microscopic appearance**
 - Small to large
 - Clear
 - Non-membrane bound
 - Intracytoplasmic vacuoles
 - Nuclei are pushed to the cell periphery
- o **Pathogenesis**
 - Overload
 - Increased mobilization of fats (anorexia)
 - *ex.* Fat Cats stop eating
 - Diabetes mellitus
 - *ex.* animals with diabetes mellitus also stop eating
 - Injury to Cells
 - Toxins
 - Anoxia
 - Deficiencies
 - Methionine
 - choline
- o **Lipidosis**
 - Normal in young animals (milk diet)
 - Normal following fatty meals



- Glycogen Accumulation

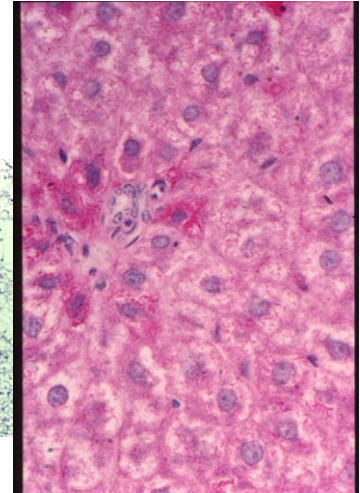
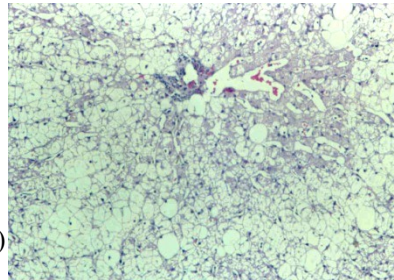
- o Glycogen is normally found in cells, but accumulates through several pathogenic mechanisms
 - Severe prolonged hyperglycemia
 - Presence of high levels of glucocorticoids
 - Lysosomal storage diseases

o Gross Appearance

- Swollen organ
- Rounded margins (liver)
- Increased pallor

o Microscopic Appearance

- Enlarged cells
- Increased pallor
- No nuclear displacement (nucleus in the center of the cells)



o Pathogenesis

- **Prolonged, severe hyperglycemia**
 - Diabetes mellitus
- **Increased corticosteroids**
 - **Cushing's Syndrome:** Pituitary Syndrome involving too much steroid production
 - **Iatrogenic:** something we have done to the patient (we caused it)
- **Enzyme deficiencies**
 - Glycogen storage diseases
 - Defects in a step of glycogen breakdown

Fatty Changes	Glycogen Accumulation
<p>- nuclei are pushed to the side of the cells</p>	<p>- nuclei are in the center of the cells</p>
<p>Microscopically it is difficult to differentiate fatty liver from glycogen accumulation (often need special stain is needed to differentiate between the two)</p>	

- Lipofuscin & Ceroid

- o Can't tell them apart Grossly, so you must stain them first
- o Oxydized product from membrane lipids
- o Yellow to brown coloration
- o **Lipofuscin**: brown pigment granules representing lipid-containing residues of lysosomal digestion

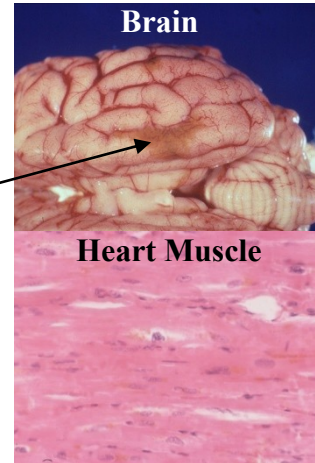
- Considered a “wear & tear” pigment associated with aging
- Found in the liver, kidney, heart muscle, adrenal, & ganglion cells
- Pigments that collects in cells

- **Gross Appearance**

- Brown discoloration of affected organs

- **Microscopic appearance**

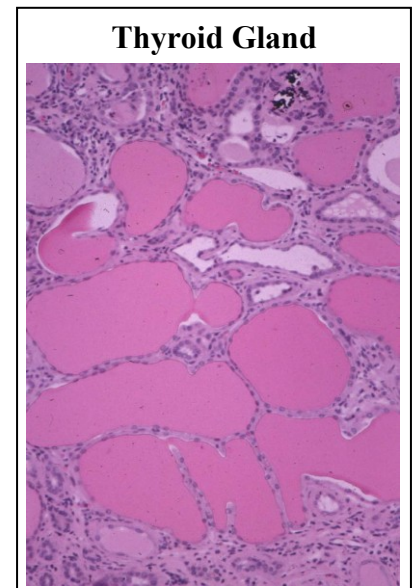
- Pigment is surrounded by the membrane (membrane-bound; autophagosomes)
- Brown coloration of pigment
- Myelin figures



- o **Ceroid**: wax-like, golden, or yellow-brown pigment found in fibrotic livers of rats & some cirrhotic human livers
 - Does NOT accept the stain

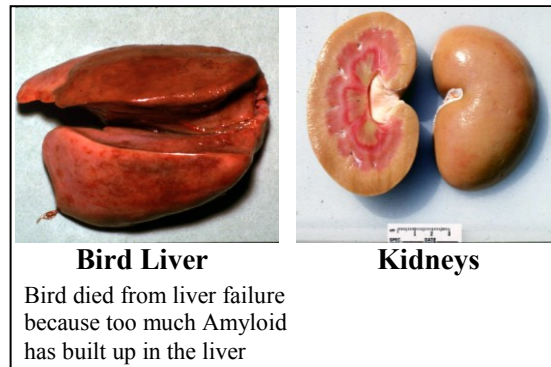
- Hyaline changes

- o Hyaline (adjective) vs. hyaline (noun)
- o Catch-all phrase for solid, glossy, semi-transparent material
- o Dense, homogenous, glossy, translucent material
- o **Types of Hyaline Changes**:
 - **Hyaline Droplets**: cytoplasm contains rounded, eosinophilic droplets, cacoles, or aggregates
 - **Hyaline Casts**: protein casts within renal tubules
 - Unabsorbed protein – morphologic expression of proteinuria
 - Often found in the kidney
 - **Connective Tissue Hyaline**: compacted collagen (scar tissue)
- o Many **causes**
 - Such as protein leakage in the kidney (this is the most common cause)



- Amyloid

- o A complex protein that accumulates within the cells
- o Homogenous, amorphous, eosinophilic matrix/substance
- o pink coloration
- o deposited along basement membranes & between cells
- o **Gross Appearance**
 - Enlarged, pale, waxy, translucent organ



Bird Liver

Kidneys

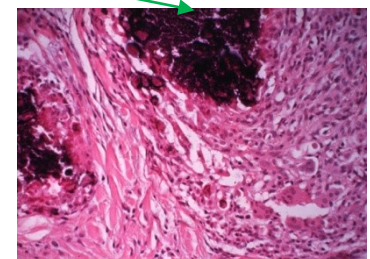
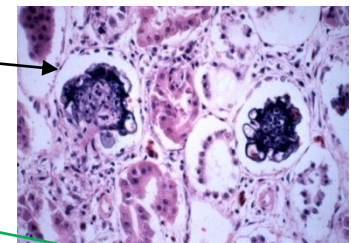
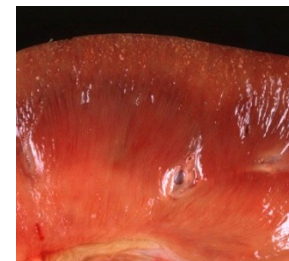
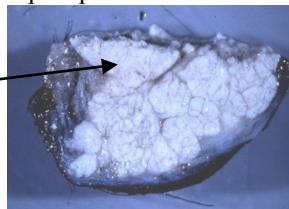
Bird died from liver failure because too much Amyloid has built up in the liver

- Mucinous changes

- o Gelatinous, semi-solid, slimy, clear, stringy
- o Serous atrophy of fat

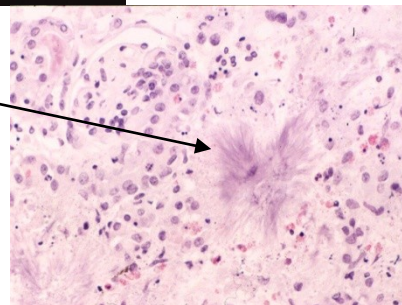
- Calcification

- o Abnormal accumulation/deposition of calcium salts in soft tissue
 - Calcium salts are usually calcium phosphate or calcium carbonate
- o **Gross Appearance**
 - Chalky, white tissue
 - Hard, gritty on cut surface
- o **Microscopic Appearance**
 - **Dark blue staining** material along the **basement membranes (BM)**
 - Stippled throughout cell
 - Large clumps
 - Often confused with yeasts by interns
- o **Calcinosis:** Widespread excessive calcification
 - **Calcinosis circumscripta:** localized deposits of calcium salts in the skin, usually surrounded by granulomatous inflammation (lesions resemble gout)
 - **Calcinosis cutis :** calcium deposits in the skin, usually follows a pre-existing inflammatory, degenerative, or neoplastic dermatosis (such as scleroderma)
- o When in cavities or lumina, the term “calculi/calculus” is used
 - **Cystic calculi:** bladder stones
- o The effect of the calcification depends on the location
 - Mechanical interference



- Gout

- o Articular crystal deposits that are associated with various acute & chronic joint disorders
- o Occurs most often in birds & reptiles
 - Because they produce urate
- o Caused by an accumulation of **urate** crystals
 - Tophus/tophi
- o Associated with renal disease due to a decrease in the excretion of urates
- o **Gross Appearance**
 - White
 - Firm
 - Crystal deposits
- o **Microscopic Appearance**
 - Granulous
 - Has radiating crystalline material
- o **Pathogenesis**
 - Disturbance of purine metabolism
 - Vitamin A deficiency
 - Kidney failure
- o **Types of gout**
 - **Visceral**: kidney failure in birds due to build-up of urates in the internal organs
 - Coats organs with a chalky white residue
 - Symptoms include anorexia & emaciation
 - **Articular**: gout attacking one or more joints
 - humans & mammals get this form
 - pathogenesis is a little different since we don't secrete urate
 - Gout is treated with iodine in humans



- Cholesterol crystals

- o Areas of previous hemorrhage or inflammation
- o

- Inclusions

- o Foreign or heterogeneous substance contained in a cell, tissue, or organ, that is not introduced by trauma
- o Viral disease (dz)
- o Intranuclear or intracytoplasmic

Subcellular Morphology of Injury

- Nuclear Change

- o Chromatin clumping
- o Condensation (**pyknosis**)
 - **Pyknosis**: a common subcellular, pathologic term meaning a thickening or reduction in the size of the cell or its nucleus (nuclear pyknosis is a stage of necrosis)
- o Dramatic nuclear change is usually indicative of necrosis

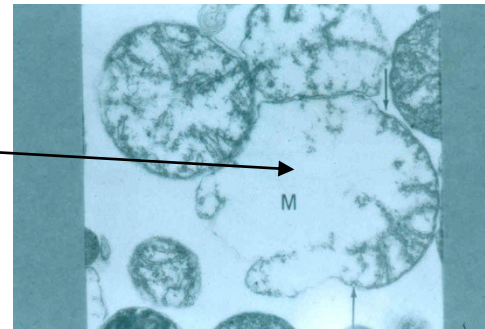
- Ultrastructural Changes

o Plasma membrane

- Loss of surface features
 - **Microvilli**: one of the minute projections in the cell membrane that greatly increases the surface area
 - **Cilia**: motile extension of the cell surface
- Desmosome breakdown
- “**bleb**” formation on the cytoplasmic membrane

o Mitochondria

- Swelling
 - may eventually rupture
 - if it ruptures the cell will most likely die
- Loss of dense granules
- Calcium deposits



o Endoplasmic Reticulum (ER)

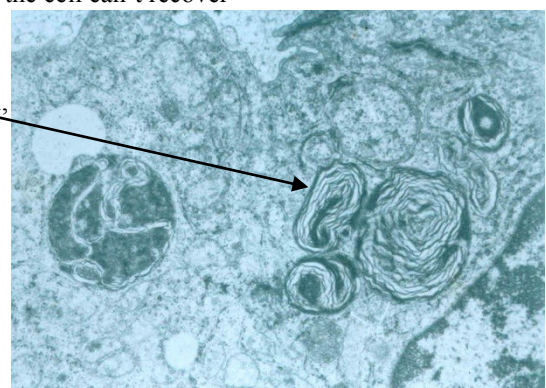
- Dilatation (contributes to vacuolar microscopic appearance)
- Dissociation of ribosomes → until they eventually fall off

o Phospholipids

- The phospholipids are from damaged organelle membranes accumulate to form “**myelin figures**”

o Lysosomes

- Dilation & rupture → pH decreases to the point where the cell can't recover
- Usually a late event/terminal event in a cell injury
- Lysosomes are packed with **concentrically laminated, peroxidized, autophagocytized** cell membranes

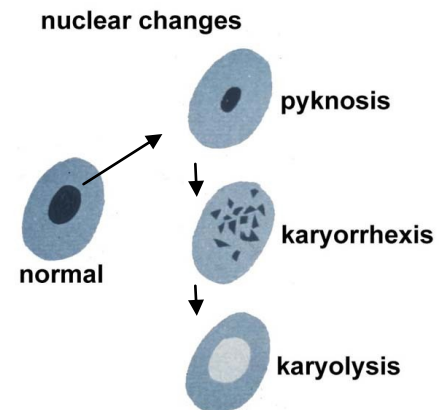


Lethal Injury & Necrosis

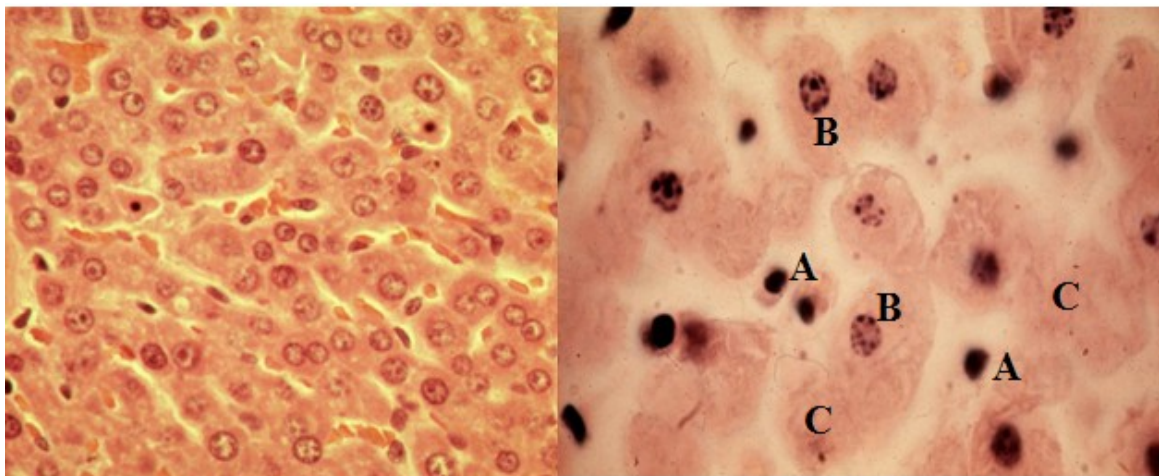
- Irreversibly injured cells can exhibit all of the previous changes
- Once cell death occurs, degradation of the cell begins
 - o Increased **eosinophilia**
 - **Eosinophilia**: altered proteins, loss ribosomes, decreased cytoplasmic RNA
 - o Moth eaten cytoplasm
 - o Loss of cellular detail

- o **Nuclear changes**

- **Pyknosis**: nucleus has condensed & is now small & dark
- **Karyorrhexis**: nucleus has fragmented
- **Karyolysis**: nucleus can't be found



- o Normal liver vs. a liver with **Necrotic hepatocytes** exhibiting **Nuclear Pyknosis(A)** & **Karyorrhexis(B)**



Normal liver

Necrotic Liver
hepatocytes exhibiting nuclear
pyknosis (A)
karyorrhexis (B)
karyolysis (C)

Pathogenesis of Cell Injury

- There are numerous causes of cell damage, such as...

1) Oxygen deprivation

- **Hypoxia**
 - o Decreased blood oxygen supply
 - Pulmonary
 - non-pulmonary
 - o Decreased blood flow
 - **Hypovolemia**: bleed out, blood pressure drops too low
 - **Vasoconstriction**: constriction makes it so that it can't get enough blood to where it is needed
 - **Cardiogenic**: can't beat fast enough to get blood where its needed
 - **Shock**: decreased blood pressure → hypovolemia
- **Ischemia**
 - o Infarction
 - o Complete or almost complete loss of blood flow

2) Physical agents

- Trauma
- Radation
- Burns

3) Chemical agents

- Huge variety
- Amount of damage done relates to the concentration, dose, length of exposure
- Variety of actions
 - o Injure cell membranes
 - o Interfere with metabolism

4) Infectious agents

- Viruses, bacteria, protozoan, fungi
- Elaborate toxins secreted by the above
- Host inflammatory responses

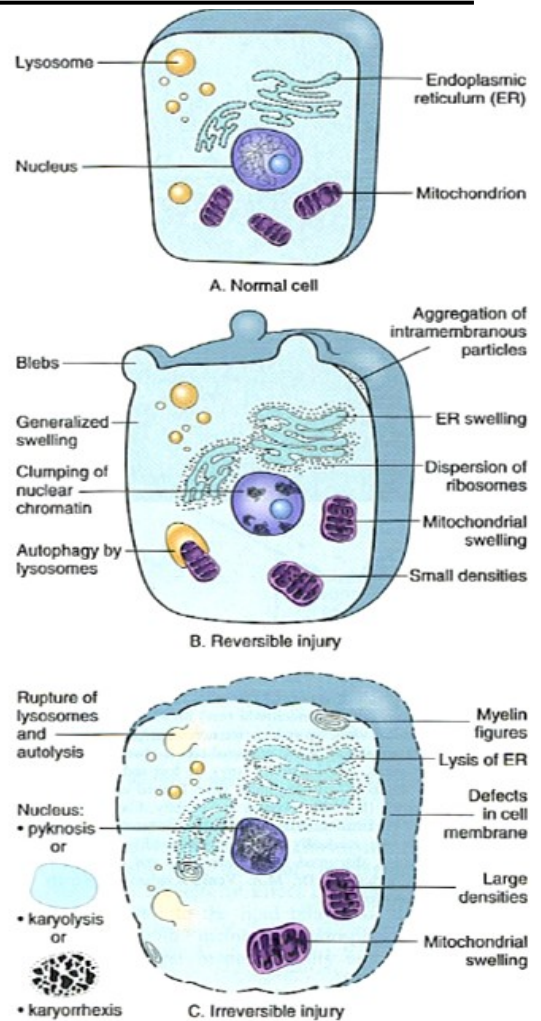
5) Nutritional imbalances

- Deficiencies
 - Excesses
- } Fats, proteins, CHOs, vitamins

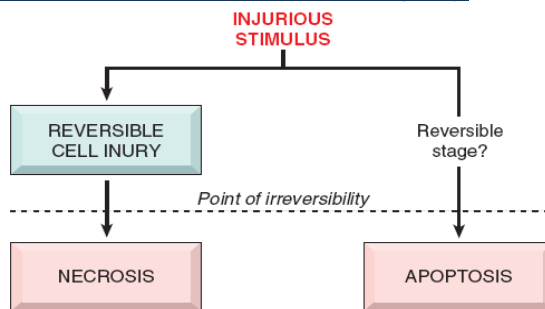
6) Genetic defects

Mechanisms of Cell Injury

- Cellular response depends upon:
 - o Type of injury
 - o Duration of injury
 - o Cell state at the time of injury
(cells are in different metabolic states)
 - o Adaptability of the injured cell
- Exact time when injury occurred may be difficult to determine
- 4 intracellular systems are particularly vulnerable:
 - o Cell membrane
 - o Aerobic respiration (mitochondria)
 - o Protein synthesis (rough ER, ribosomes)
 - o Preservation of genetic integrity within the nucleus
- Injury at any of these leads to wide ranging consequences & secondary effects

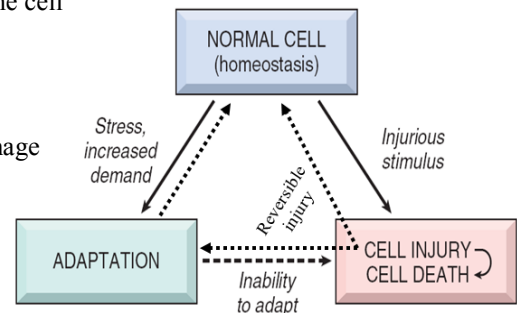
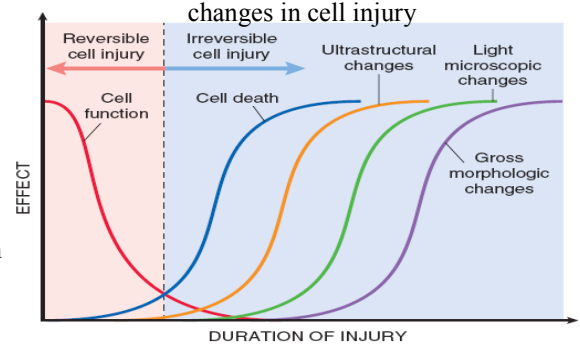


Reversible vs. Irreversible Injury



- **Apoptosis:** programmed cell death
- **Irreversible cell injury**
 - o Transition state between living & dead cell
 - o Exact "point of no return" is not possible to identify
 - o Exact point of death is not possible to identify
 - o **Morphologic hallmarks** of irreversible cell injury & death
 - Severe mitochondrial swelling
 - Large flocculent densities in mito matrix
 - Increased loss of proteins, enzymes, co-enzymes out of the cell
 - Greatly increased membrane permeability
 - **Leakage of enzymes**
 - **ALT & ALP**
enzymes that are released during liver damage
 - **CPK** is released during heart damage
 - Thus, the levels of these enzymes can be used to estimate organ damage
 - **Initiation of inflammation**

Timing of biochemical & morphologic changes in cell injury



Necrosis, Apoptosis, & Autolysis

Definitions

Necrosis: death of cells & tissues while the body is whole (still living)

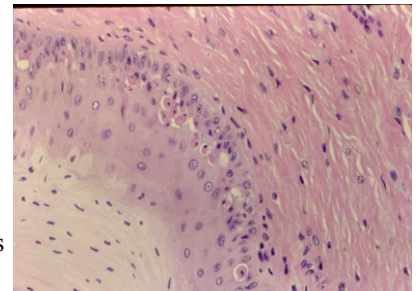
- Note it is an inflammatory response
- Some cells & tissues are dead

Necrobiosis: the natural death of cells or tissues through aging

- Not the same as necrosis or pathological death
- **Enterocytes** forming crypts in the intestines
- **Keratinocytes** in the skin (skin cells slough off) } Cells are constantly dying & being replaced

Apoptosis: programmed cell death

- **Active Process:** Requires energy & certain enzymes
- Commonly seen following DNA damage
 - Repaired → **mitosis**
 - No appropriate repair possible → **apoptosis**
- A safeguard against neoplasia following DNA damage
- The cell breaks up into small pieces surrounded by the cytoplasmic membrane (**no inflammatory response**)
- A quick, easy, unobtrusive way to get rid of cells
- **ex.: Apoptosis of the cervix**
 - Cervix of a **postparturient** dog (just had puppies)
 - Shrunk deeply **eosinophilic** cells with pyknotic nuclei which have undergone apoptosis
 - **Eosinophilic:** pink staining of tissues & cells with **eosin**
 - **Eosin:** a bright pink acidic dye used to stain basic structures
 - During pregnancy the cervix cells grow & become thick, after birth apoptosis occurs to return the cervix cells back to normal size



Autolysis: also called **self-digestion**

- destruction of tissues by certain substances (such as **enzymes**) that are produced within the organism
- cell death is a continuum...
 - single point at which death occurs &/or the single phenomenon that causes death may be difficult to determine
 - death occurs at the point at which a cell, even given the proper substrates, can no longer resume the biochemical processes necessary for normal homeostasis
- the rate of autolysis is also temperature dependent (increases in temperature → increased self-digestion rate)
- ex. mice undergo autolysis very quickly
 - very shortly after the mouse dies the enzymes begin to digest the cells, necropsy will show internal mush

Causes of Necrosis

- Acute (rapid) loss of blood supply (**ischemia**)
 - **ischemia** : restriction in blood supply, usually due to problems in the blood vessels resulting in tissue damage or dysfunction
- Loss of nerve supply (such as an atrophic muscle)
- Loss of endocrine stimulation
- Endotoxins coming from bacteria can cause wide spread cellular necrosis
- Mechanical/thermal injury
- Chemical injury
- Pressure

Injurious Agents

- Infectious agents
- Immunologic reactions
 - Immune system can sometimes cause more harm than good
 - **Anaphylaxis:**
 - **Auto antibodies:**
- Genetic derangements
 - Enzyme deficiencies
 - Storage diseases
- Nutritional imbalances
 - Protein/caloric deficiencies or excesses
 - Vitamin/mineral deficiencies or excesses

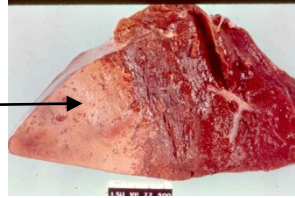
Mechanisms of Cell Injury

- Cell death dependent on type, duration, severity of insult
- Also dependent on type, state, adaptability of cell
 - o Cells can sometimes be Pre-conditioned...
 - **Chronic anemia:**
 - **Chronic hypoxia:**
 - **Hepatic enzyme induction:**

Morphologic Changes of Cells

- Gross morphologic changes

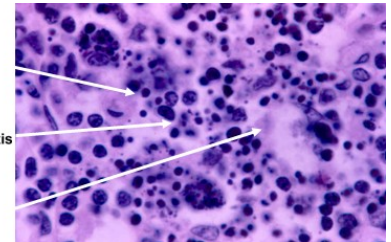
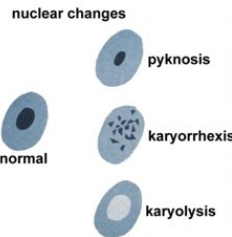
- Necrotic tissue tends to be lighter in color
 - ex. Necrotic muscle tissue (shown here)
- However, if the tissue is filled with blood it will be darker than normal
 - ex. Necrotic Intestine, the intestine is twisted → trapped blood
- Color loss is due to loss of **cytochrome oxidases**



- Microscopic morphologic changes

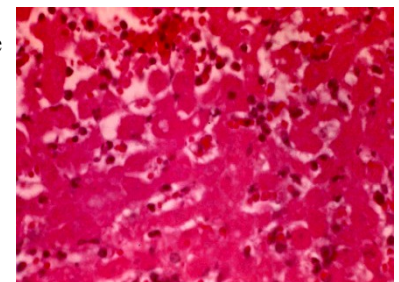
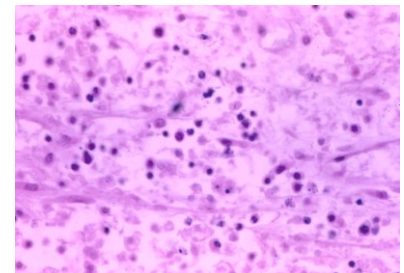
o Nuclear Changes

- **Pyknosis**: shrunken, dense nucleus
- **Karyorrhexis**: fragmentation of the nucleus
- **Karyolysis**: loss of the nucleus



o Cytoplasmic Changes

- **Increased eosinophilia**
- **Cytoplasmolysis**: cytoplasm is broken up & gone
 - the cell is basically gone
 - ex. Cytoplasmolysis & **Pyknosis**
can't see the cell outlines because all the cytoplasm has spilled into the cell
- **Coagulation**: cytoplasm is denser & stains more pink than before
 - ex. Coagulation & **Karyolysis**
much darker staining



Types of Necrosis

(1)
Coagulative necrosis

- i. Fat necrosis
- ii. Zenker's necrosis

(2)
Caseous necrosis

(3)
Liquefactive necrosis

(4)
Gangrenous necrosis

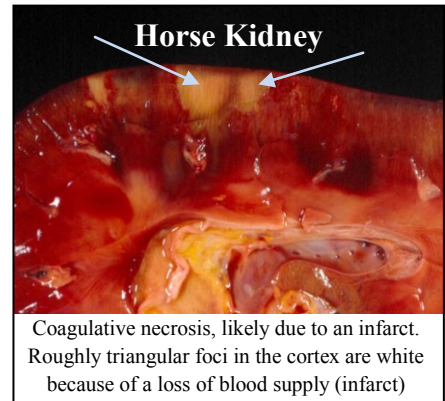
- i. Moist gangrene
- ii. Dry gangrene

(1) Coagulative necrosis

- Coagulation of proteins in the tissue (breakdown of 3° & 4° structures)
- Tissues are fixed in formalin to prevent the tissue from breaking down

- Causes

- 1) **Local heat**
- 2) **Local chemicals**
 - o Formalin
 - o Phenol
 - o alcohol
- 3) **Ischemia**
 - o Complete loss of blood supply
- 4) Certain **bacterial toxins**
 - o Black leg: ischemic, coagulative lesion in dogs
 - o *Clostridium*
 - o cattle

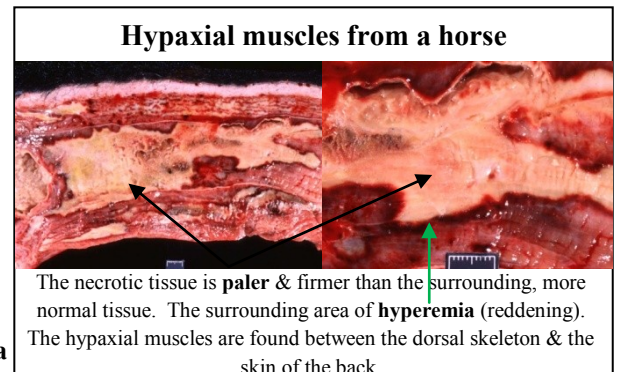


- Significance

- Specific diagnostic lesion

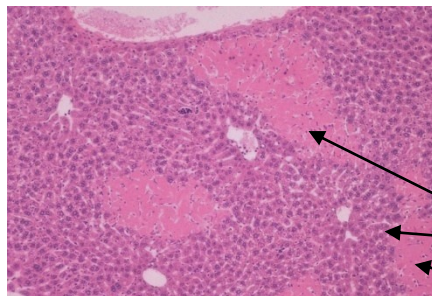
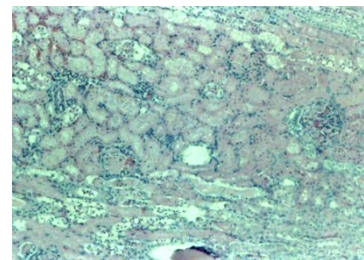
- Gross

- Tissue retains original form & coherent strength
- **Firm, pale, dry** consistency (visibly distinct from both caseous & liquifactive)
- Will eventually become **friable** (easily crumbled)
- Often surrounded by a **reddened area or hyperemia**



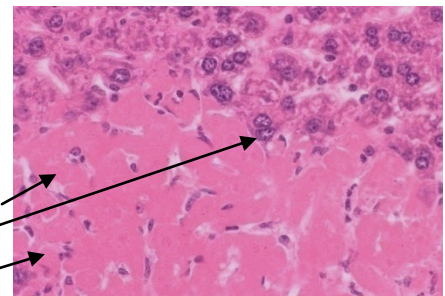
- Micro-

- Tissue organization remains able to recognize tissue as tissue, muscle as muscle, etc.
- **Cell outline remains** with loss of cellular detail
- **Nuclear changes**
- **Cytoplasmic coagulation & hyper eosinophilia**



Typical microscopic Coagulative Necrosis in a Liver

- **Hyper eosinophilia**
- **Loss of cellular detail**
- **Karyorrhexis**
- **Karyolysis**



(1) **Coagulative** necrosis (continued...)

- **Outcome:** how the body deals with Coagulative necrosis
 - Removal through slow digestion
 - Progression to liquefactive necrosis → so the body can absorb it
 - **Mineralization**
 - **Sequestration**

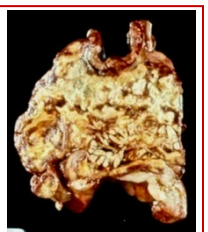
i. **Fat necrosis**

- When the fat undergoes necrosis the fat & glycerine combine with metallic ions (Na, K, Ca) to form soap (**saponification**)
- **Causes**
 - 1) **Pancreatic** fat necrosis
 - Secondary to pancreatic disease with release of lipase & other enzymes that break down fat
 - 2) **Vitamin E deficiency**
 - Manifested as **steatitis** leading to fat necrosis
 - Occurs in cats eating a diet high in rancid oxidized fats
 - 3) **Traumatic** fat necrosis
 - due to lying on a hard surface (especially in large animals)
 - presents as firm tissue beneath the skin
 - 4) **Metabolic** fat necrosis
 - **mesenteric & omental** fat become firm (necrotic) around the viscera
 - can cause obstructions (especially in the bovine abdominal cavity)

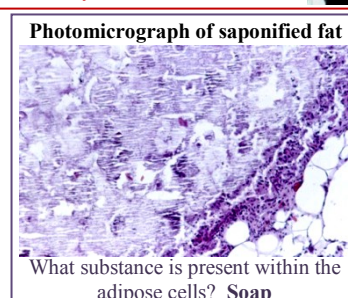
- **Gross**
 - Loss of shine
 - Dull, oblique
 - Firm, soap-like consistency



Dog Abdomen
Fat in the area of the anterior duodenum is firm, dull, & chalky. On the right the duodenum has been opened & transected at the top of the tissue. The fat is **opaque, lusterless & firm**. **What is the Pathogenesis?** **Pancreatitis** due to release of lipase & other enzymes that break down fat

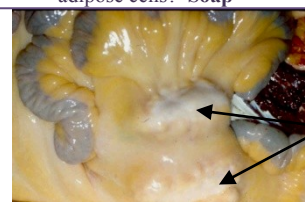


- **Micro**
 - Cell outlines remain
 - Cytoplasm is replaced by a **pale blue soap-like** material
 - Solid to stippled



Photomicrograph of saponified fat
What substance is present within the adipose cells? **Soap**

- **Outcome**
 - **Saponified fat** remains in the abdominal cavity
 - The saponified fats may have no effect
 - or they may cause **mechanical** effects (stops **peristalsis**) & cause a **functional breakdown**

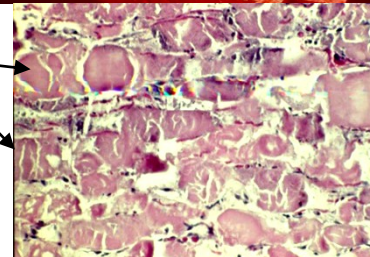
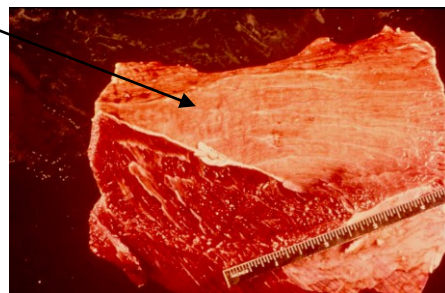


Fat from a Bovine Abdomen
Saponified fat is firm, gritty, white & opaque

(1) **Coagulative necrosis** (continued...)

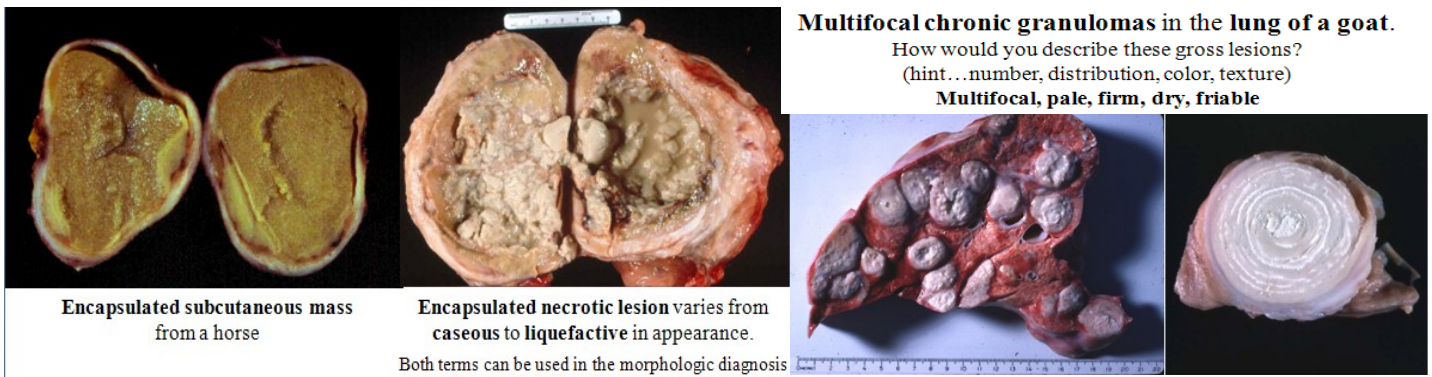
ii. **Zenker's necrosis**

- a specific type of coagulative necrosis
- it is specific to striated muscle (skeletal or cardiac)
- **Causes**
 - 1) Vitamin E deficiency
 - 2) Ischemic necrosis
 - **Mitochondrial Infarction (MI)**
 - **Myocardium**
 - 3) Certain bacterial toxins
 - Black Leg
 - *Clostridium*
- **Gross**
 - Original outline persists
 - Muscle slightly swollen
 - Waxy appearance
 - Light in color
- **Micro-**
 - Preservation of tissue organization & cell outlines
- *ex.* **Gluteal musculature of a calf**
 - One muscle fascicle is **lighter** in color
 - What type of necrosis is this?
 - Coagulative Zenker's Necrosis
 - What might have caused it?
 - Vitamin E deficiency
 - ischemic necrosis
 - *Clostridium*
 - Microscopic appearance of the muscle
 - The cytoplasm is still recognizable but they are falling apart
 - Nuclei are lost
 - How would you describe the cytoplasm & nuclei?
 - Cytoplasm = **Cytoplasmolysis**
 - Nucleus = **Karyolysis**

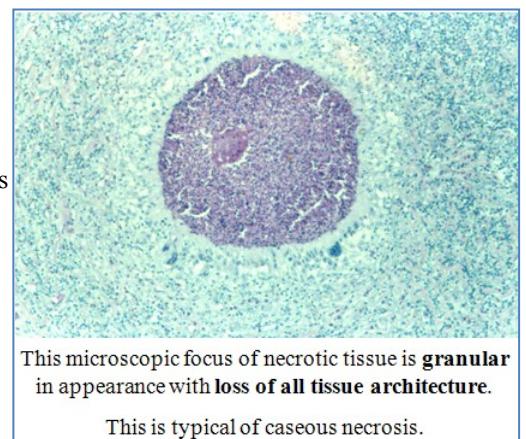


(2) Caseous necrosis

- Caseous = cheese
- Associated with **granulomatous inflammation** (seen a lot with fungal diseases)
- **Causes**
 - 1) Bacterial infection
 - o **Beacterial & Neutrophil Proteases** cause tissue breakdown
 - **Bacterial** proteases: enzymes that break down bacterial cells
 - **Neutrophil** proteases: enzymes that break down white blood cells (neutrophil)
 - 2) Some chemicals
- **Gross**
 - Dull but slightly greasy & somewhat liquefactive
 - Firm, no cohesive strength, usually pale to white (cottage cheese)
 - Easily separated with a blunt instrument (like a finger)



- **Micro**
 - Loss of all tissue outline (no discernible tissue)
 - Amorphous, granular debris, mass
 - Infiltrated with **macrophages (mΦ)**, multinucleated giant cells
 - Often surrounded by fibrous connective tissue capsules
- **Outcome**
 - Encapsulation (typical with tuberculosis)
 - Liquefaction
 - Mineralization



(3) Liquefactive necrosis

- Enzyme breakdown of tissues (tissue liquefies)
- **Causes**

1) Central Nervous System (CNS)

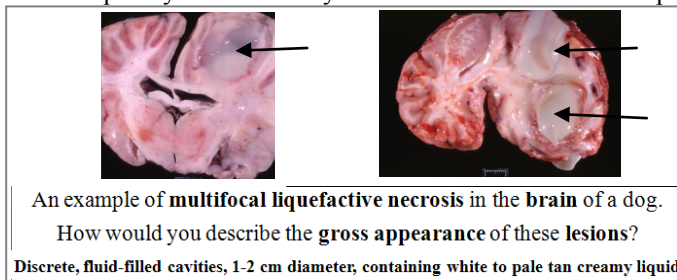
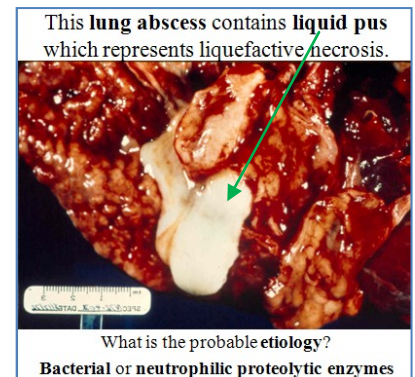
- o Necrosis in the CNS almost always results in liquefactive necrosis (**malacia**)
 - **Malacia**: liquefactive necrosis in the CNS
- o **Low** amounts of **coagulative protein**
- o **High** amounts of **lipids** (which tends to liquefy)
- o Creates a **low pH** → self perpetuating process

2) Abscess

- o A liquid center (pus)
- o **Abscess**: a focus of liquefactive necrosis that is surrounded by a connective tissue capsule
- o Abscesses are caused by bacteria & **neutrophils** release **proteolytic** enzymes that liquefy tissue

- Gross

- A fluid filled cavity in a tissue
 - o there is a thin line between liquefactive & caseous necrosis
- White to pale tan, brown, red, green colored liquid
- Cream or puddy-like consistency
- Frequently **more foul smelling** than coagulative or caseous necrosis
- Frequently surrounded by a fibrous connective tissue capsule

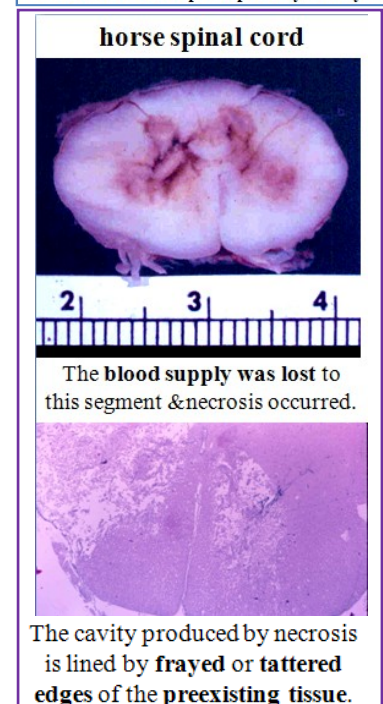


- Micro-

- Pink, proteinacious fluid
 - o or hole, if the fluid has already poured out
- Edges made up of “frayed” tissue

- Outcome

- Walled off (abscesses)
 - o Doesn't tend to be walled off in the CNS
- Remain as fluid
- Reabsorbed
- Replaced by scar tissue



(4) Gangrenous necrosis

- Archaic term applied to necrosis caused by the loss of blood supply
- Not the same as coagulative necrosis
- Necrotic tissue is invaded by **saprophytic** bacteria (**putrefactive**)

i. Moist Gangrene

- **Causes**

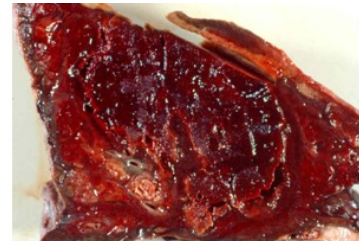
- 1) Twisted intestine (**gangrenous enteritis**)
- 2) Devitalized intestine
- 3) Lung due to aspiration (**gangrenous pneumonia**)
- 4) Anywhere else conditions are right



Loop of **discolored necrotic** small intestine in a dog.

- **Gross**

- Swollen, soft, pulpy, dark in color with **putrefactive** smell
- *In vivo* — insensitive (no viable blood supply)
— cold (no body heat)



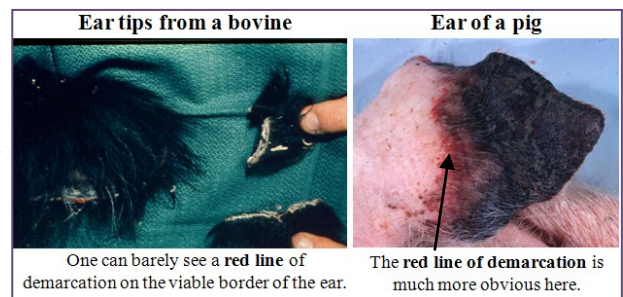
Lung from a dog.
Stomach contents were aspirated during surgery (no endotracheal tube).

This is commonly termed **gangrenous pneumonia** or **aspiration pneumonia**

ii. Dry Gangrene

- **Causes**

- 1) Seen in extremities (tail, ears, toes, etc.) due to **vascular compromise** or **ischemia** (ex. frost bite)
- 2) **Ergot** : a parasitic fungus
- 3) Not as many bacteria proliferating



- **Gross**

- Tissue is shrunken, wrinkled, leathery, often firm
- Can be pale or darker than normal
- **Marginal hyperemia**: red line of inflammatory demarcation between infected & normal tissue



Tail of an American alligator with dry necrosis

Results & Outcome of Necrosis

- **Consequences** (assuming animal survives)
 - o **Organ dysfunction**: especially of the “conducting” organs
 - **Dysrhythmias / arrhythmias** (heart)
 - **Neurologic deficits** (CNS)
 - o Necrotic tissue removed...
 - o Defect filled by fibrous connective tissue
 - Scar tissue formation
 - Scar tissue then undergoes Contracture
- **Calcification of dead tissue**
 - o Mineralization of dead tissue
 - o A way to neutralize the effects of necrotic tissue
 - o Can have mechanical effects depending on where & what is mineralized
 - *ex.* mineral tissue around joint → restricted mobility
 - o **Dystrophic** mineralization: necrotic cells attract calcium if they are not promptly destroyed & reabsorbed
- **Liquefaction & Removal**
 - o Slow & imperceptible
 - o Removed by **macrophages (mΦ)** & lymph drainage (seen in small areas)
- **Liquefaction & Encapsulation**
 - o **Abscess formation**
 - o Chronic large abscesses that the body can't deal with so it walls it off by encapsulating it
- **Replacement with Fibrous Connective Tissue**
 - o Scar tissue formation
 - o **Contracture** : shortening of a muscle or tendon in response to stress exerted on that muscle or tendon
- **Liquefaction & Migration**
 - o Migration of liquid along any plane of least resistance
 - o Pressure builds up due to an influx of inflammatory cells , which causes migration
 - o Migratory tracts
 - **draining fistulas**: leaking abnormal passage from one cell to another
 - **phlegmon**: spreading inflammation → pus or gangrene
 - o Encapsulation with sequestration
 - Isolation by encapsulation
 - Commonly seen with necrotic bone (**bone sequestra**)
 - Also seen with muscle
 - **Involucrum**: **connective tissue (ct)** capsule around a sequestrum

Metacarpophalangeal joint in a foal



There is **focal bone necrosis** proximal to the physis & early **connective tissue encapsulation**. This is a typical *Salmonella* septicemia lesion.

What is a term for the remaining necrotic bone?
Bone Sequestrum

- **Desquamation**

- o Shedding of dead tissue from a surface
- o There are 3 types of Lesions that can undergo Desquamation

1) **Erosion**

- Loss of epithelium with an intact basement membrane
- Cells will generate with an intact basement membrane
- Heals by regeneration (no scar)

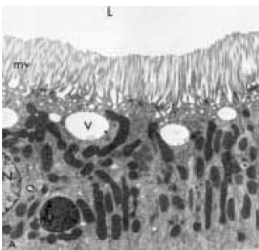
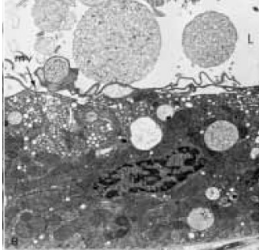
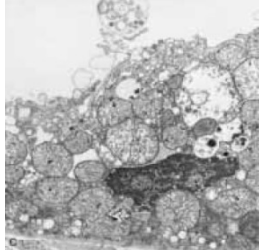
2) **Ulceration**

- Destruction of the basement membrane (deep)
- Always heals by scarring (connective tissue)

3) **Slough**

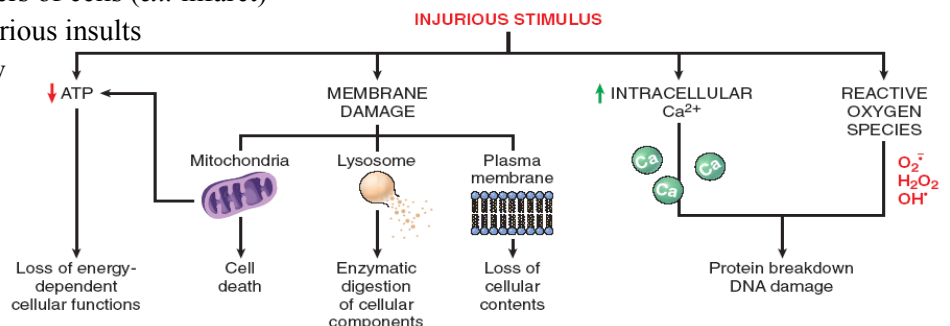
- Shedding of a large amount of tissue
- ex. 2nd & 3rd degree burns

Sub-Cellular Level Necrotic Changes

Normal Cells	Reversible Ischemic Changes	Irreversible Ischemic Changes
		
Normal epithelial cell of proximal tubule. Note microvilli (mv) lining the lumen (L) , nucleus (N) , & normal apical vacuole (V) .	<ul style="list-style-type: none"> • Microvilli are lost & have been incorporated into the apical cytoplasm • Blebs form & are extruded in the lumen • Mito are slightly dilated 	<ul style="list-style-type: none"> • Markedly swollen mito containing amorphous densities • Disrupted cell membranes • Dense, pyknotic nucleus

Mechanism of Necrosis

- **Passive** form of cell death
- Occurs in the absence of energy
- Doesn't require metabolism to complete
- Frequently affects large numbers of cells (ex. infarct)
- Generally associated with injurious insults
- **Sites of damage in cell injury**



Mechanisms of Necrosis

1) Mitochondrial ATP production Stops

- ATP depletion & decreased ATP synthesis are frequently associated with both **hypoxic & chemical (toxic)** injury
- ATP depletion to <5% to 10% of normal levels has widespread effects on many critical cellular systems
 - Small losses in ATP critically effect the cellular systems

2) Plasma membrane energy-dependent NA pumps shut down

3) $\text{Na}^+/\text{H}_2\text{O}$ enter cell

4) Cell Swelling/Membrane stretching

- This is the pathogenesis for cell swelling

5) Glycolysis allows the cell to function at a decreased level

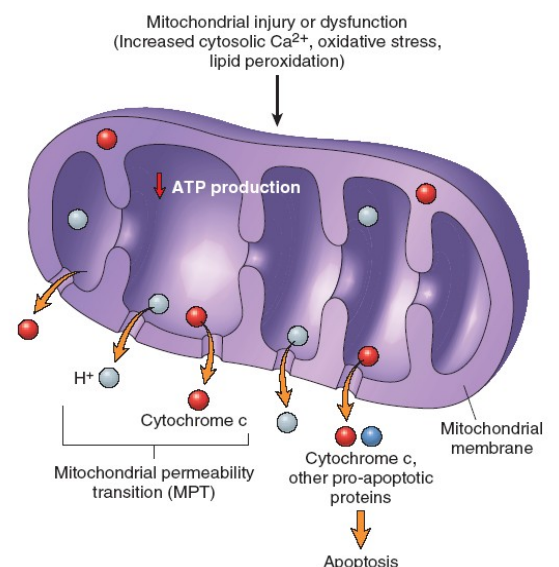
- Glycogen stores are depleted
- Lactic acid accumulates
- Cell pH drops → induction of Heat Shock Response

6) Failure of Ca^{2+} pumps → Ca^{2+} enters the cell → many effects

- Can occur simultaneously with #5
- Disruption of protein synthetic apparatus
- Detachment of ribosomes
- Decreased protein synthesis

7) Ca^{2+} activation of enzyme systems

- Too much calcium in a system can do a lot of damage all at once
 - **Phospholipases:** breakdown of phospholipids
 - **Proteases:** breakdown of proteins
 - **ATPases:** breakdown of ATP
 - **Endonucleases:**
- Mitochondria are often damaged by increases in **cytosolic Ca^{2+}**
- Inner membrane permeability is increased
- **Loss of proton motive force** = death blow for the cell
- **Leakage of cytochrome C**
 - An integral component of the electron (e^-) transport chain
 - Can trigger apoptotic death pathways in the cytoplasm



8) Unfolded Protein Response

- Attempt to prevent protein denaturation

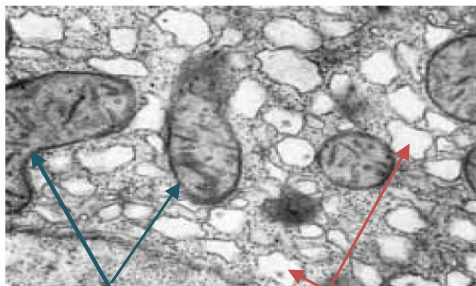
9) Protein denaturation starts

10) Damage to all membranes of all organelles

11) ER & other organelles swell

12) More changes in membrane permeability

- With massive influx of Ca^{2+}
- This will likely be the final death blow to the cell



Swelling of ER & shedding of ribosomes.

At this stage, mitochondria are unaltered

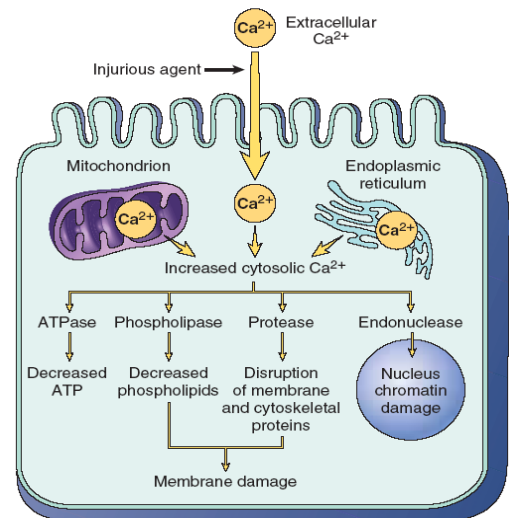
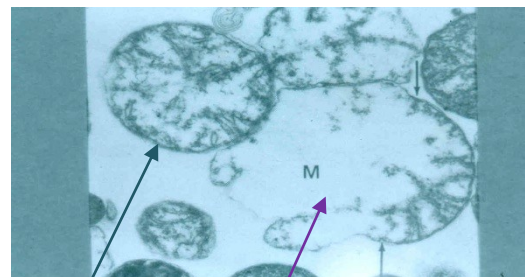


FIGURE 1-13 Sources and consequences of increased cytosolic calcium in cell injury. ATP, adenosine triphosphate.

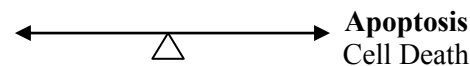


Swelling & eventual rupture of mitochondria.

Necrosis vs. Apoptosis

- Originally thought to be completely distinct from necrosis
- More recently, opinions have changed... now it is believed that there is a fairly large degree of overlap between Necrosis & Apoptosis
- Two ends of a spectrum

Necrotic
Cell Death



Apoptotic
Cell Death

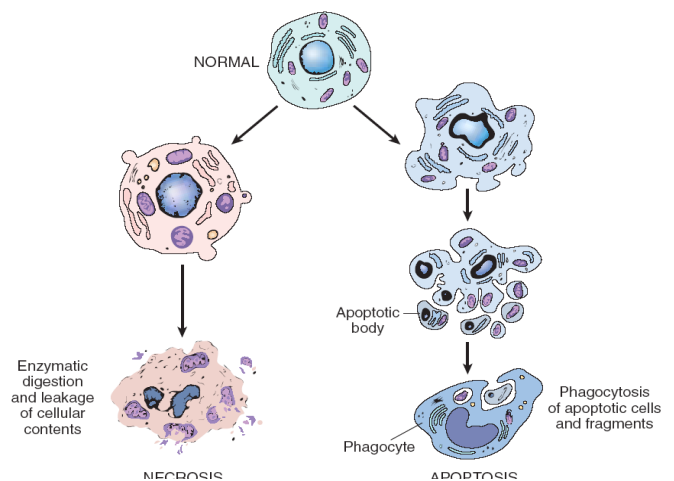


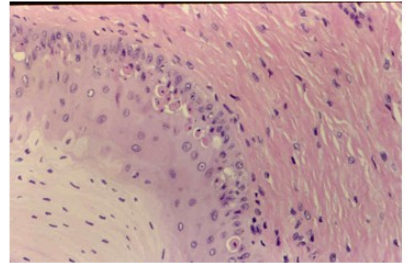
TABLE 1-2 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

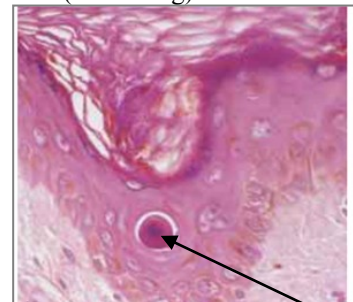
Apoptosis

- **“Programmed cell death”**
 - Deletion of un-needed cells during **embryogenesis**
 - Normal involution
 - *ex.* dog cervix after birth
 - Regression of hyperplasia
 - Deletion of genetically unstable cells
 - *ex.* Bad sun burn → cells can't fix injury → shed injured skin cells (ie. Peeling)
 - Activation of viruses
 - Activation by immune cells
- ****Does NOT elicit inflammation****
- **Active form of cell death**
 - Requires energy
 - Mediated by **caspases** (a family of proteins)
 - Does NOT elicit inflammation like typical necrosis
 - Acts at the individual cell level
 - Balance to mitosis
 - Process that is required for the survival of the individual
 - Because you need to get rid of the cells that are no longer in use
 - Active process that uses highly conserved cellular machinery
- **Features**
 - Cells shrink & round up
 - Cells become more dense
 - Cells detach from neighbors
 - Chromatin becomes very dense & separates into homogeneous masses
 - frequently **semi-lunar** or **sickle** (crescent) shaped
 - adjacent to the nuclear membrane
 - Cells will undergo **budding & blebbing**
 - Buds break off to become **apoptotic bodies**
 - Phagocytosis by surrounding cells
 - usually the **macrophages (mΦ)**
 - Characteristic DNA ladder formation

Cervix of a postparturient dog

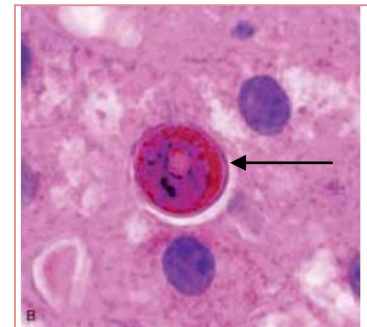


Shrunken deeply eosinophilic cells with pyknotic nuclei that have undergone apoptosis.



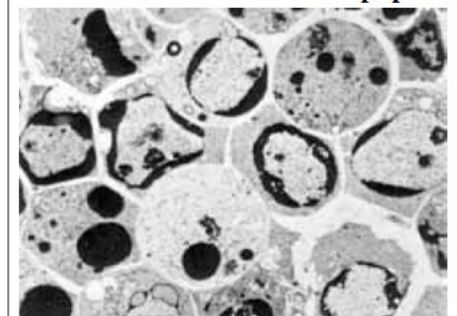
Apoptosis of epidermal cells in an immune-mediated reaction.

Note the intensely eosinophilic cytoplasm & the small, dense nuclei



Higher power of an apoptotic cell in the liver in immune-mediated hepatic cell injury.

Ultrastructural features of apoptosis



Some nuclear fragments show peripheral crescents of condensed chromatin, whereas some are uniformly dense.

Apoptosis (continued...)

- Physiologic Situations

Death by apoptosis is a normal phenomenon that serves to eliminate cells that are no longer needed

- **Embryogenesis**
 - Implantation
 - **Organogenesis** (organ formation)
 - **Developmental Involution** (getting rid of organs that are no longer needed)
 - Metamorphosis
 - “**Programmed cell death**” was coined to describe the death of **specific cell types at defined times**
- **Hormone dependent involution**
 - Post partum endometrial cell breakdown
 - Regression of the lactating mammary glands after weaning
 - Prostatic atrophy after castration
- **Cell deletion in proliferating pools**
 - Intestinal **crypt epithelium** (to maintain a constant number)
 - you must get rid of some to make room for the new healthy ones
- **Death of senile cells**
 - *ex.* **neutrophils**
 - Cells that have served their “useful purpose”
 - Often deprived of normal survival signals
- **Elimination of self reactive lymphocytes**
- **Cell death induced by cytotoxic T-cells**
 - Acts like a cellular executioner system
 - Defense mechanism against viruses & tumors
 - Same mechanism acts in rejection of transplants

- Pathologic Situations

- Cell death following an injury
 - DNA injury
 - ER stress
 - Heat
 - hypoxia
- Cell injury in some viral diseases
 - Viral hepatitis: loss of infected cells largely due to apoptotic death
- **Pathogenic atrophy** in some organs
 - Duct obstruction in kidney, pancreas, salivary gland
 - Leads to increased pressure → organ undergoes apoptosis → organ decreases in size
- Cell death in some tumors
 - Frequently during regression, but also in some actively growing tumors

Apoptosis (continued...)

- Biochemical Features

Apoptotic cells usually exhibit a distinctive constellation of biochemical modifications that underlie the structural changes in cells

• Protein cleavage

- Via activation of several members of **cysteine protease** family (*caspases*)
- Many caspases are present as pro-enzymes that must be activated to induce apoptosis
- Break up nuclear scaffold & cytoskeleton
- Also activate DNases

• DNA breakdown

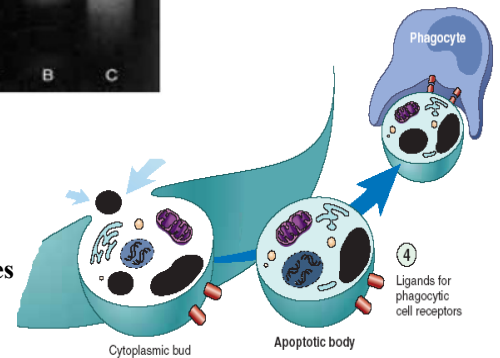
- Apoptotic cells exhibit characteristic breakdown of DNA into 50-300 kb pieces
- Subsequently there is intra-nucleosomal cleavage into multiple 180-200 bp fragments by CA^{2+} & Mg^{2+} dependent endonucleases → ladders on a gel



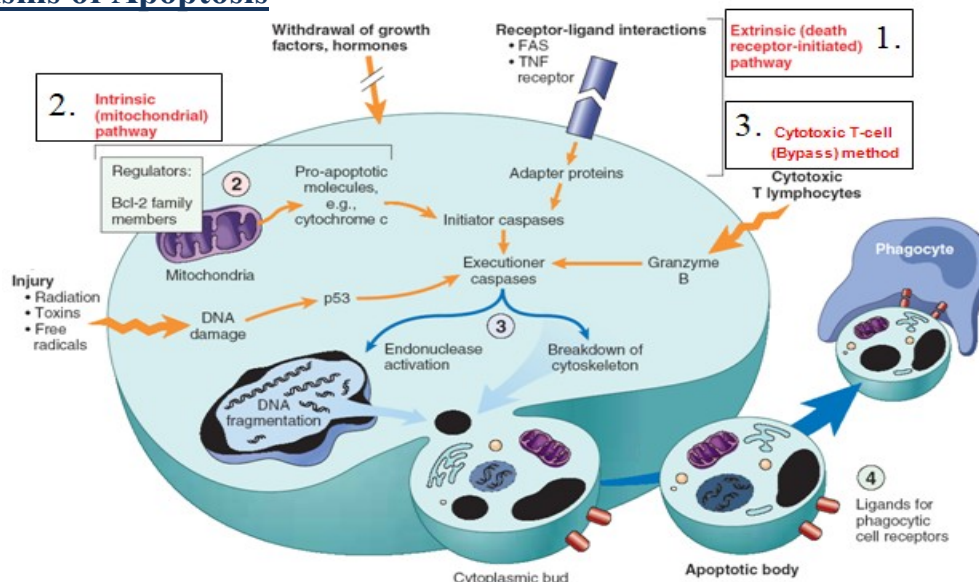
A: normal cells (control)
B: apoptotic cells (DNA ladder)
C: necrotic cells (smear)

• Phagocytic recognition

- Apoptotic cells express **phosphatidylserine** in outer layer of the membrane
- Allows for early recognition of apoptotic cells by **macrophages** ($m\Phi$) resulting in **phagocytosis** without the release of **proinflammatory** cellular components
- Apoptotic response disposes of cells with minimal compromise to the surrounding tissue



Mechanisms of Apoptosis

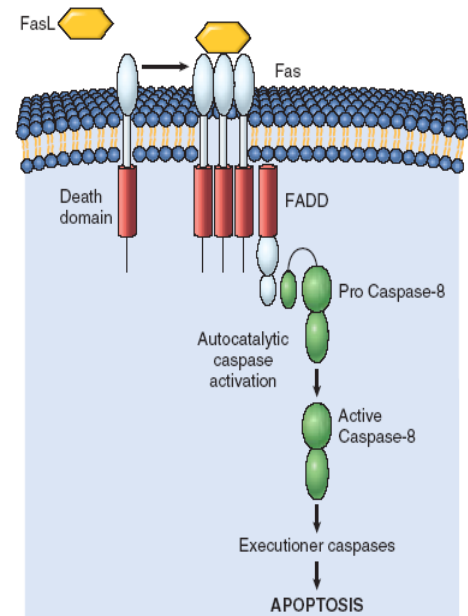


Mechanisms of Apoptosis (continued...)

- **Extrinsic (Death Receptor) pathway**

Initiated by engagement of cell surface death receptors

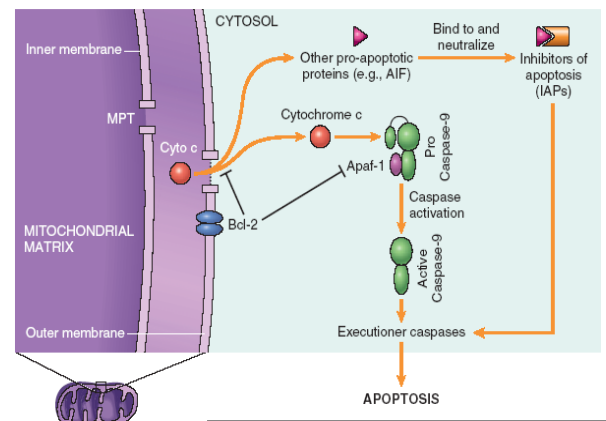
- 1) Type 1 TNF receptor (TNFR1), Fas (aka CD95)
- 2) Fas is cross-linked by a ligand (FasL)
- 3) 3 or more FasL molecules come together & their cytoplasmic death domains from a binding site for FADD
- 4) FADD then binds pro-caspase 8 (10 in humans) which cleave each other to become active
- 5) Initiation of caspase cascade
- 6) APOPTOSIS



- **Intrinsic (mitochondrial) Pathway**

Result of increased mitochondrial permeability & release of pro-apoptotic molecules into the cytoplasm

- 1) Withdrawl of growth factors or cell stress
 - Increased permeability of mitochondrial membrane
 - leakage of cytochrome C
- 2) Cytochrome C binds to Apaf-1 in the cytoplasm
- 3) Caspase 9 is activated
- 4) Caspase cascade
- 5) APOPTOSIS



Apaf-1: apoptosis activating factor-1
IAPs: inhibitors of apoptosis
AIF: apoptosis inducing factor

- **Cytotoxic T-cell (by-pass) method**

- Cytotoxic T-lymphocytes recognize foreign Ag present on infected cell membranes
- On recognition, CTLs release perforins
 - allows entry of granzyme B, a serine protease
- Granzyme B cleaves proteins at aspartate residues & activates several caspases
- Bypass mechanism for cells that refuse suicide via extrinsic or intrinsic pathways
 - Bypass upstream signaling events
 - Directly inducing the effector phase of apoptosis
- Most commonly seen with viral infections

Somatic Death

- Like cell death, often difficult to pinpoint the exact time of somatic death of entire organism
- In humans, it is considered to be the cessation of EEG activity
- Not all tissues die at the same time
 - **Neurons:** without Oxygen supply they die within **3 min**
 - **Cardiac muscle:** without Oxygen supply they die within **20 min**
 - **Parenchymal cells (liver, kidney, etc.):** without Oxygen supply they die within **1 hour**
 - **Chondrocytes:** without Oxygen supply they die within **several days**

Post-mortem (PM) Changes (after Death)

- **Algor Mortis:** cooling of the body (equilibration of temperature)
 - 10° change – 2X enzymatic activity
 - ↓ 10° to get ½ the autolysis
 - Wool, thick hair, fat are good insulators (↑ autolysis) in these cases
- **Livor Mortis:** gravitational settling of the blood before it clots (downside of discoloration)
 - Significance: laying on side, lower kidney darker than top one
this is a post mortem (PM) change, NOT a lesion
 - In forensics, can be used to tell if a body has been moved
- **Rigor Mortis:** PM contraction of muscles
 - Occurs in most used muscles first (masticulation, thorax, extremities)
 - Follows an agonal period of relaxation
 - Onset 2-4 hours PM
 - Duration 24-48 hours
 } will go away & not come back if muscles are stretched,
due to ion release
 - Occurs when glycogen & creatine phosphate are depleted
 - ATP depletion
 - With the muscle tissue causing it to freeze up
 - Examples:
 - Dog dead of strychnine poisoning:
 - Animal died in convulsions
 - no glycogen or creatine phosphate left
 - → RAPID onset of rigor
 - Feedlot steer that is well fed & rested:
 - Muscles full of glycogen & CrPO4
 - Muscles degenerate before rigor sets in
 - → DELAYED (or slow) onset, that may not even occur

Autolysis

- Changes that occur after death
- Post Mortem (PM) degenerative changes
- Due to lysosomal proteases that are released as the cells die & are dissolved (self digestion)
- Autolytic changes can occur at the cellular, organ, & organism levels
- **Gross:**
 - Changes in color (organs look lighter or darker)
 - Changes in texture
 - Muscles contract initially, then relax
 - Tissues tend to be softer, due to loss of strength
- **Micro-**
 - Same changes as seen with necrosis (dead cell = dead cell)
 - Nuclear changes are the same
 - Cytoplasmic changes are the same
- Other changes with somatic death
 - **Leakage of pigments**
 - **Hemoglobin imbibition:** blood leakage → red stained tissue
 - **Bile imbibition:** bile leakage → green stained tissue
 - **Pseudomelanosis**
 - Hydrogen sulfide + hemoglobin = FE sulfide (black)
 - Seen in & around intestine
 - **Gas formation**
 - Can cause organs to move
 - Can cause diaphragmatic herniation or rupture
 - Can cause gut to twist
 - Sometimes hard to differentiate from **Anti Mortem (AM)** lesions
 - **Anti Mortem (AM)** = Before death

- **Putrefaction**
- **Skeletalization**

A very dead goat.

Skeletalization

when bones are exposed by advanced decomposition



Necrosis vs. Autolysis

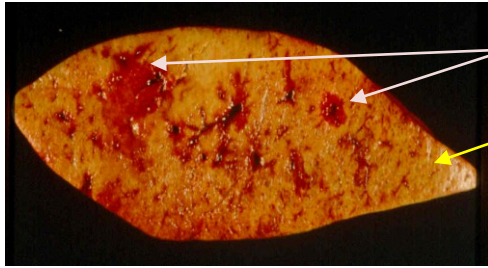
- Inflammatory responses to dead tissue within the same section
 - Which means that the tissue died while the animal was still alive → its Necrosis & not autolysis

- Relative rates of degeneration following somatic death
 - Biliary epithelium (digested very quickly)
 - Gut mucosa (goes quickly due to bacteria & enzymes)
 - Adrenal medulla
 - Nervous tissue
 - pancreas

- Presence of living & dead tissue in the same section → suggests necrosis before death

- Condition of **Red Blood Cells (RBC)** within vessels → tend to lyse with autolysis

Post Mortem Changes



Pony Liver

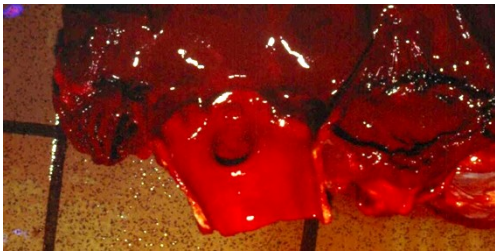
- **Red staining** around the large vessels in the liver
- Staining can NOT be washed way
- The liver is **pale & yellow** in coloration
- It has a greasy feel

Q. What postmortem change is this?

- Fatty Liver?

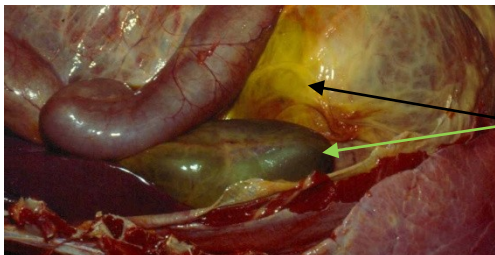
Q. What antemortem lesion is present in the liver?

- hemoglobin imbibition ?



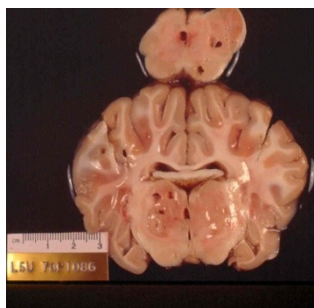
Bovine aortic valves & aorta

- the red stain could not be washed way
- this staining is typical of **hemoglobin imbibition**



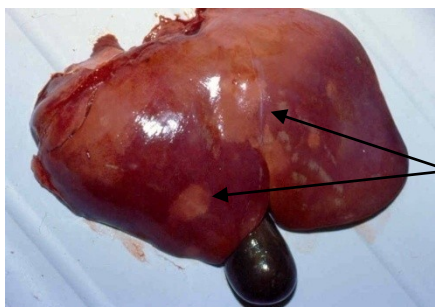
Intestines

- **yellow-green staining** after death
- typical of **bile imbibition**



Bovine Brain

- Postmortem gas formation
- → formation of cavities in the brain



Cow Liver

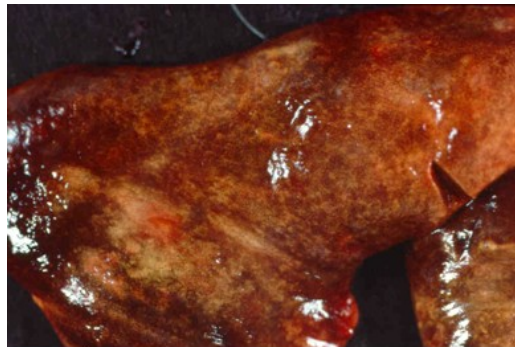
- Irregular autolytic changes
- **Abnormally pale areas** that are very **soft to the touch**
- **Irregular pale staining** is typical of autolysis
- Livers generally autolyze rapidly after death

Pigments

- Inherent color without any kind of staining upon gross examination
- There are 2 types of pigments: Exogenous & Endogeneous

Exogenous Pigments

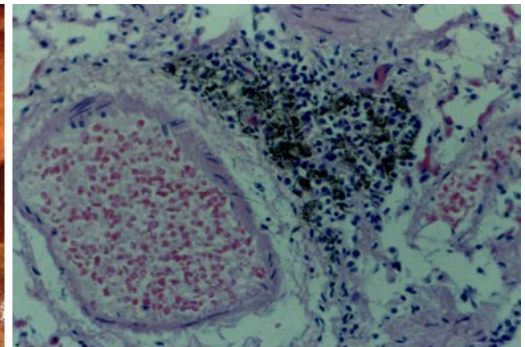
- Pigments produced outside the body, & taken in a pre-formed state
- **Pneumoniosis:** Pigmented material that presents in the lungs (most often they are pigments that have been inhaled)
 - **Asbestosis:** asbestos dust
 - **Bagassosis:** cane pulp dust
 - **Byssinosis:** cotton fiber dust
 - **Silicosis:** silicone dust
 - **Siderosis:** iron dust
 - Commonly seen in the lungs during heart failure
 - **Anthracois:** carbon or coal dust
 - Traditionally from coal mines
 - Now seen in dogs & cats from smoking households
 - Can be presented in tissues other than just those in the lungs



Lung from a dog

Diffuse black pigmentation is present.

Dog lived in a heavy tobacco-smoke home



Microscopic picture of **carbon** dust in macrophages in the lung from the previous slide.

What is the term for inhaled dust in the lung?

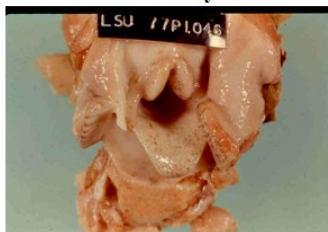
Anthracois

- Tattooed animals can also have pigments that settle out in the lungs

Endogenous pigments

- Pigments that form inside the body
- **Melanin**: black pigment formed by **melanocytes**
 - **Benign melanosis**
 - **Aberrant melanocytes** producing pigments in odd places such as the...
 - **Meninges**: system of membranes in the central nervous system
 - **mucous membranes**:
 - **subserosal surfaces**: layer of connective tissue
 - Very common in sheep

Lamb Larynx



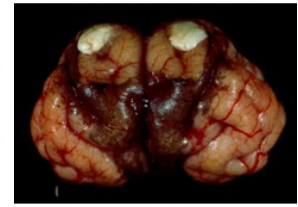
Black foci represent benign melanosis

Heart valves from a lamb



Black foci represent benign melanosis

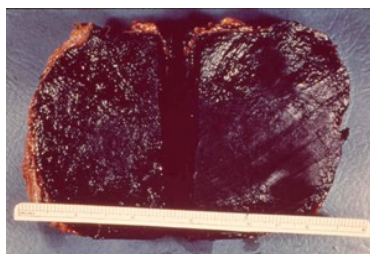
meninges in a calf



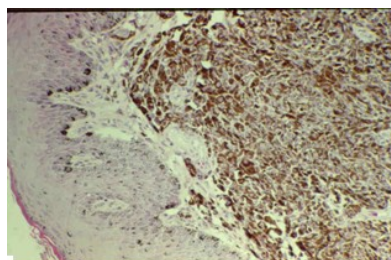
Benign melanosis

- **Tumors of melanocytes**

- **Melanomas**: pigmented **malignant** tumor of the melanocytes found mostly in the skin
- **Melanocytomas**: pigmented **benign** tumor of the melanocytes found mostly in the skin
- Characteristic tumors that are heavily pigmented



This is a **subcutaneous tumor** from an equine.



Photomicrograph of a **melanoma**

Pigmented melanocytes are present in the **dermis**.

A quick impression of a cut surface onto white cloth or white paper will leave an **inky black residue** in the case of **melanomas**, or a **red residue** from **old blood (hematoma)**.

- **Chronic inflammation of the skin**

- Often seen in birds, amphibians, & fish as an integral part of the inflammatory process
- Also associated with chronic flea bite dermatitis in mammals (otherwise rare in mammals)
- Can increase the pigments in the skin or decrease the skin pigments (e.g. after a trauma)

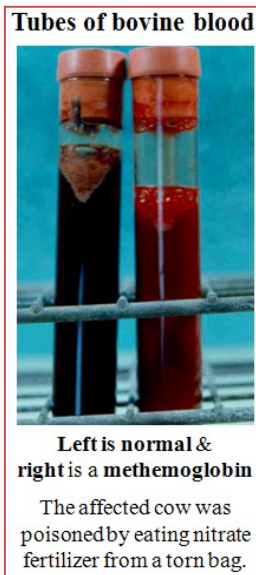
Endogenous pigments (continued...)

- **Hemoglobin (Hgb)**: red respiratory protein used to transport oxygen from the lungs to various tissues

Note: Hgb is the only way to get oxygen to the brain

- **Oxygenated Hgb**: **arterial** hemoglobin that is **redder** in color
- **Reduced Hgb**: hemoglobin in found in **veins**, it is **less red** though not blue
 - veins appearing blue is an optical illusion

- **Methemoglobin**: oxidized hemoglobin



- Oxidized hemoglobin turns Iron from the Ferrus (Fe^{2+}) to Ferric (Fe^{3+}) state
- Poor affinity for oxygen
- Appears **brown to salmon pink** colored
- Usually found in bovine (cows) & some cats
- Blood remains this color for 4 to 6 hours
 - necropsy can miss it if not performed within 6 hours of death
- Caused by...
 - o **Nitrates (nitrite toxicity)**: fertilizers give the soil a salty taste
 - cows like the salty taste & seek it out
 - cows eat too much & die from Methemoglobin
 - o **Chlorate toxicity**: defoliants used by railroads to clear the area around the railways
 - o **Acetaminophen toxicity**: in cats → Heinz body formation

- **Carboxyhemoglobin**: hemoglobin combined with **Carbon Monoxide (CO)**

- Hemoglobin is a **bright cherry red** colored
- Hemoglobin remains this color for 1 to 2 hours
- Carbon monoxide preferentially binds to the hemoglobin
 - CO has a high affinity for Oxygen
 - but it is bound so tightly to that it wont allow the O_2 to leave & go where its needed
 - animal becomes hypoxic because it can't get enough oxygen (suffocates)
- Light areas of the animal appear red
- Not seen very often in veterinary medicine

- **Cyanide Toxicity**: differential diagnosis (**Ddx**) for carboxyhemoglobin

- Blood is saturated with oxygen (bright red colored) → can look like carboxygemoglobin
- Ties up cytochrome oxidase in the cells so that the cells can't accept any O_2 from the blood
- Nothing is wrong with the blood, the problem is with the cells
- Causes an ↑ in heart & lung function (blood is super oxygenated, but the cells can't use it)

Endogenous pigments (continued...)

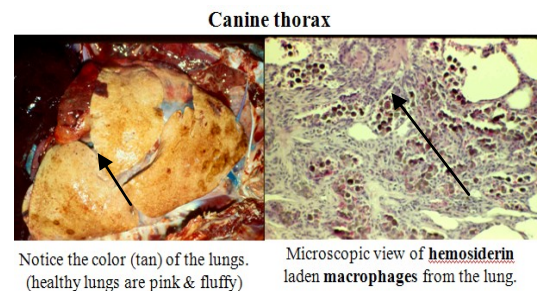
- **Hemosiderin**: golden brown pigment in the lungs or kidneys
 - “siderin” = **iron** in the blood (blood iron)
 - Hemoglobin derivative
 - Brown pigment due to lysosomal breakdown of Hgb in the cytoplasm of macrophages
 - Iron (Fe) + **apoferritin** → **pathogenic ferritin (hemosiderin)**
 - **Micro-** : **cytoplasmic spherules** (lysosomes are full of hemosiderin)
 - May need special stains to differentiate (iron stains)

Significance:

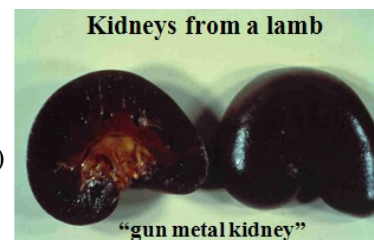
- Old areas of hemorrhage turn **brown** due to breakdown of the red blood cells (RBCs)
- **Chronic passive congestion**:
 - Hemosiderin is backed up in the **liver** → **Right** heart failure
 - Hemosiderin is backed up in the **lungs** → **Left** heart failure
- **Extravascular hemolysis**: break down of red blood cells (RBCs) **outside** of the vessels, **within the mΦ**
 - Seen in a hemolytic crisis
 - Occurs mostly in the spleen, intestines, bone marrow
 - Affected areas are enlarged & FULL of hemosiderin
 - **Anaplasmosis**:

What pigment should be suspected with brown lungs of heart failure? **Hemosiderin**

Would these stain positive for iron? **Yes**



- **Intravascular hemolysis**: red blood cells (RBCs) break down **within the blood vessels**
 - Hemoglobin is free in the blood
 - Break down of RBCs = Hgb → porphyrins + Fe
 - **Dark blood** goes through the kidneys & into the urine
→ **urine** becomes **red/black** colored (“**port wine urine**”)
 - **Kidneys** become **dark red/black** (“**gun metal kidneys**”)
 - **Icterus** is also present
 - Animal appears yellow in color
 - Seen in **Leptospirosis**



What substance discolors the urine?

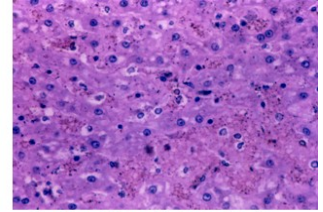
Hemoglobin

Endogenous pigments (continued...)

- **Hematin:** brown pigment occurring where there is acid action on the hemoglobin

- **Acid formalin hematin:** Artifact, NOT a lesion

- Brown pigment that is distributed throughout the tissue'
- Occurs when there's a low pH interacting with the Hgb
 - low pH → brown pigment to be distributed throughout tissue
 - necropsy is hard b/c tissues are now very difficult to interpret
- Use a buffered (or neutral) formalin to avoid this problem

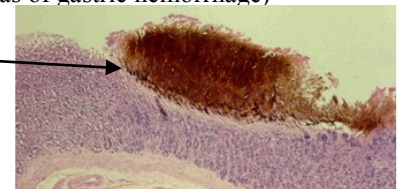


Portion of liver that was fixed in non-buffered formalin solution. The brown pigment is hematin.

Will this pigment stain positive for iron?
No, b/c the brown is caused by a low pH

- **Hydrochloric Acid (HCL) hematin:** occurs around gastric ulcers (areas of gastric hemorrhage)

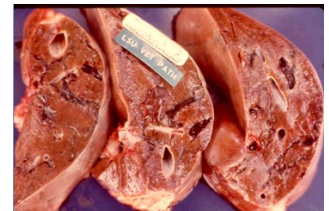
- Brown line delineates the ulcer
- Margins of gastric ulcers are sometimes accentuated by formation of acid hematin
- There is blood associated with this lesion but it doesn't stain positive for iron



Margins of gastric ulcers are sometimes accentuated by formation of acid hematin

- **Parasitic hematin :** hemoglobin is ingested & then digested by parasites

- **Black pigmented parasite feces**
- Liver flukes in ruminants
- Use the presence to ID the parasites
- Parasitic hematin is often associated with **liver-fluke infestations**



Parasitic hematin is often associated with liver-fluke infestations

- **Hematoidin:** "oid" = "looks like"

- Found in areas of old hemorrhage
- **Yellow** (color of an old bruise)
- **Bilirubin-porphyrin** compound
- **Super-saturated bilirubin**

- o **Bilirubin:** Yellow pigment that causes icterus

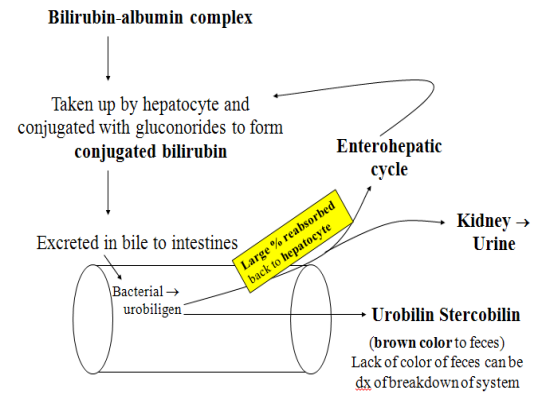
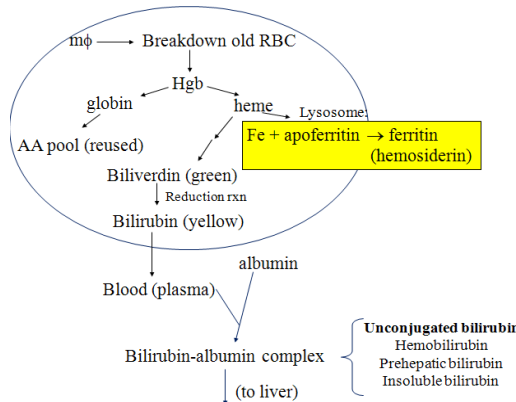
- **Icterus:** a condition where there is **increased bilirubin**
- Normally white tissues are colored yellow, such as...
 - **Sclera** of eyes (white part of eye ball)
 - Intima of large vessels (aorta)
 - Mesenteric fat
 - Fascial planes between muscles
- The **species of animal** is important to consider during the interpretation of the tissue
 - **Fat is normally yellow in:** Horses, Guernsey & Jersey cows, & monkeys
 - **Fat is normally white in :** Holstein, Angus, & Hereford cows



o **Bilirubin/ Icterus** (continued...)

- **Light source** is important when diagnosing icterus
 - Sunlight is best >> incandescent is okay >> fluorescent is not good
- **Microscopically:** can't see icterus because it is soluble & will not be present after fixing

Causes of Icterus		
Type of Icterus	Serum Unconjugated Bilirubin	Serum Conjugated Bilirubin
Pre-hepatic (hemolytic crisis)	↑	
Post-hepatic (obstructive crisis)		↑
Hepatic (toxic crisis)	↑	↑



There are **3 types** of icterus:

1) **Hemolytic (Pre-hepatic) Icterus:** causative problem occurs before bilirubin gets to the liver

Tissues from a cat

Intravascular or extravascular?
Extravascular

What form of bilirubin caused the yellow discoloration?

Unconjugated bilirubin
(b/c it hasn't gone through the liver yet)



The **spleen was large & brown** in color while urine & kidneys were normal

- There is too much bilirubin presented to the liver
 - liver can't conjugate all of it
 - increase in serum **unconjugated** bilirubin
- More RBCs coming to the liver than can be conjugated
 - so pre-hepatic bilirubin builds up in the blood b/c the liver is over-loaded
- Excess breakdown of red blood cells (RBCs) = **hemolysis**

- o **Intra-vascular hemolysis:** hemoglobin is found in the urine
- o **Extra-vascular hemolysis:** urine is normal (hemoglobin is not found)

2) **Obstructive (Post-hepatic) Icterus:** Bile duct is obstructed (by a tumor or gallstone)

- biliary system backs up
- leaks conjugated bilirubin into the liver's sinusoids

- **Conjugated** bilirubin backs up into the blood
- **Increased** serum conjugated bilirubin
- Animal still appears yellow in color

3) **Toxic (hepatic) Icterus:**

- o **Sick liver:** can't conjugate all the bilirubin
 - increased serum **unconjugated** bilirubin
 - the problem is with the hepatocytes themselves
- o **Swollen hepatocytes** obstruct **canniculi** so conjugated bilirubin can't flow out into the gall bladder
 - **Canniculi:** the pathways bile goes through on its way to the liver)

- **Photosensitizing pigments:**

- **Photosensitization:** immune mediated phenomenon
- Due to presence of a **photodynamic pigments** in the skin]
 - Derivatives of **porphyrins**
 - o Hemoglobin
 - o Chlorophyll
 - Pigments receive light at 1 wavelength, ultraviolet (uV) & give off another wavelength , infrared (ir), + heat
 - This causes damage to the cells & eventually causes cell death
- Does not occur in the skin protected by a heavy hair coat or dark pigmentation (white part of Holsteins)
- There are **3 types** of **Photosensitization**

1) **Primary photosensitization (Type I)**

- Ingestion of a preformed photodynamic agent
- Pigments circulate in the blood to the skin where the sun hits
- Compounds known to cause photosensitization include...
 - St John's wort
 - Antibiotics (tetracycline, sulfa drugs, etc)
 - Phenothiazine (anthelmintic)
 - Saccharine
 - Buckwheat (in sheep)

2) **Congenital porphyria (Type II)**



- **Inborn error** of the metabolism → certain enzymes are altered
→ resulting in abnormal porphyrins
- The porphyrins can't be incorporated into the hemoglobin so they build up & are eventually deposited throughout the body (skeleton) & in the skin
- Photodynamic in bovines
- Herefords: porphyrins cause **pink to red** coloration of the **teeth, bones, & urine**

3) **Hepatotoxic photosensitization (type III)**

- Occurs when a herbivore with liver disease eats chlorophyll
- In a healthy herbivore ...
 - The consumed chlorophyll is then converted to phyloerythrin by gut flora
 - The phyloerythrin is then conjugated by the liver & excreted in the bile
- In a herbivore with liver disease
 - The phyloerythrin builds up in the body & is deposited in the skin making it photosensitive
 - The skin then reacts to the sun → the damaged skin sloughs off
- This happens in Holsteins when they have liver problems, the Photosensitization causes...



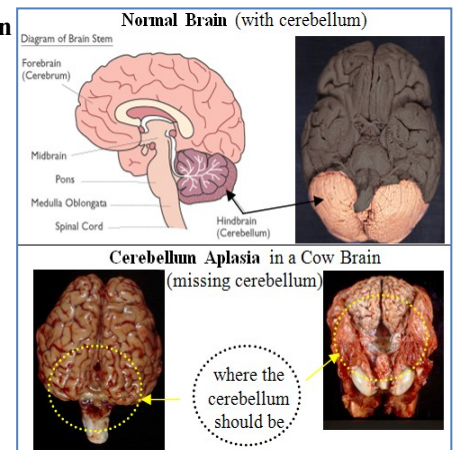
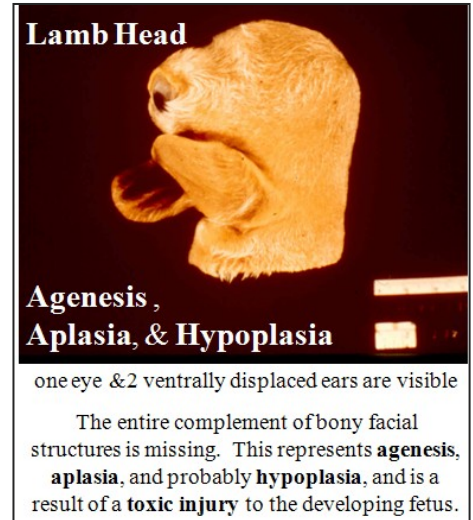
- Edema
- Inflammation
- Necrosis
- Sloughing of skin: they slough off the white sections of their fur
- This is much more severe than a sunburn

Disturbances of Cell Growth

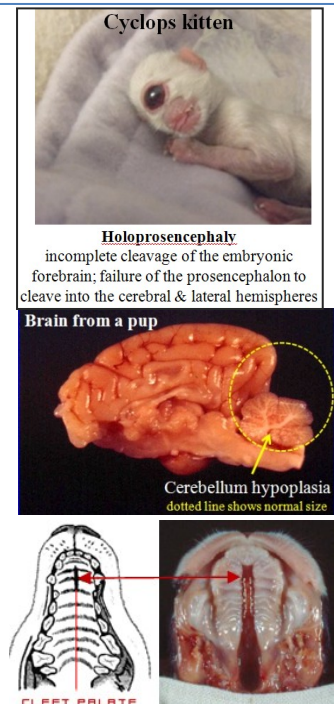
Tissues are **smaller** than normal (4 types)

- 1) **Agenesis** – “absence of the beginning”
 - There is nothing there
 - no primordium, vestage, or anlage have formed
 - There's a total lack of development
 - The organ has **no function**, because there is nothing present to represent the organ
 - Fairly rare, but it does happen

- 2) **Aplasia** – “absence of form”
 - A **primordium** is formed, but there is **no cellular differentiation**
 - **Primordium**: An organ or tissue in its earliest recognizable stage of development
 - The organ has **no function** b/c there is no cellular differentiation
 - Often seen in the kidneys of kittens & pigs
 - ex. **Aplastic Cerebellum in a Calf Brain**
 - The cerebellum is missing
 - This was most likely caused by a fetal viral infection, such as the **Bovine Viral Diarrhea (BVD) virus**
 - Viruses tend to attack rapidly dividing cells like those seen in the brain

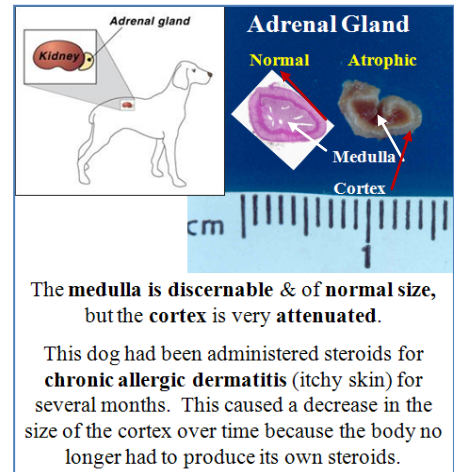


- 3) **Hypoplasia** – “small form”
 - Partial formation of an organ
 - Organ fails to achieve normal size (**too small**)
 - Correct organ cellular differentiation (can tell what the organ is)
 - The organ may have **limited function**
 - ex. 1: **Bain from a pup with hypoplasia of the cerebellum**
 - the cerebellum is present, but too small
 - the **arbor vitae** appearance is obvious, this indicates that there was **tissue differentiation & limited function**
 - possibly caused by a fetal canine parvovirus infection
 - ex. 2: **Maxillary palate from a pup**
 - The mandible was removed for viewing
 - The palate normally forms from fusion of shelves that grow in from each side, these shelves **stopped growing**
 - *What is the medical term for this condition is?*
Palatoschisis (cleft palate)



Tissues are **smaller than normal (4 types)** (continued...)

- 4) **Atrophy** – “absence of size” (a = absence of + troph = size)
- **Reduction** or shrinkage of previously normal organ or part
 - Involves **cell necrosis & loss (apoptosis)**
 - **Lipofuscin** is commonly associated with atrophy
 - Can be caused by **Disuse**
 - o ex. muscle atrophy while injured limb is in a cast



Hypoplasia vs. Atrophy

- **Similar Causes**
 - Loss of **blood supply**
 - Loss of **nerve supply**
 - Loss of **endocrine stimulation**
 - **Mechanical** injury
 - **Thermal** injury
 - **Toxins**
 - **Pressure necrosis**
- **Medical History** of the part is crucial to differentiating between Hypoplasia & Atrophy
 - Was the part once normal size? Did it ever function?
- **Examine Lesions for past injury**
 - If the part appears to have undergone **necrosis, fibrosis, scarring**, etc. than the small size is more likely due to **Atrophy** (shrinkage caused by injury) than **Hypoplasia** (never reached full size because it stopped growing)
- Know what is common in that particular species
 - Hypoplasia is fairly common in the kidneys of pigs & kittens, but would be extremely rare in a dog
-

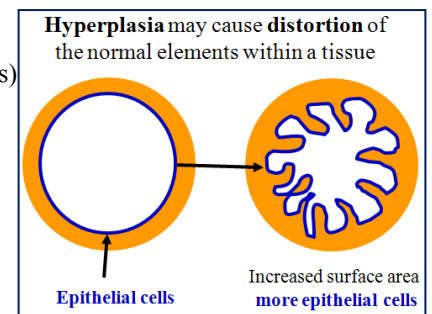
Tissues are larger than normal (2 types)

1) **Hypertrophy** – “larger than normal size”

- **Enlargement** of organ or part without cell division
- No increase in mitosis
- Organs becoming larger because **cells are becoming larger**
- Caused by an **increase in macronutrients & organelles**
 - NOT caused by water & fat (Fatty Liver)
- New steady state adaption
- Mostly restricted to **muscles (skeletal & heart)**
 - Compensatory hypertrophy: gets larger due to increased work (*ex.* building muscles)
- Generally beneficial, but not always true as there are certain limits (if the part enlarges past this amount growth becomes pathogenic)
 - Heart: enlarged heart shadow is bad
distortion of chambers & valves, valves become insufficient)
 - Conditioned (more efficient) heart ≠ heavier heart
heavier is not necessarily a conditioned (healthy) heart, it can also be an unhealthy heart
 - Increased heart weight is bad
 - Heart has a constant blood supply with no way to increase

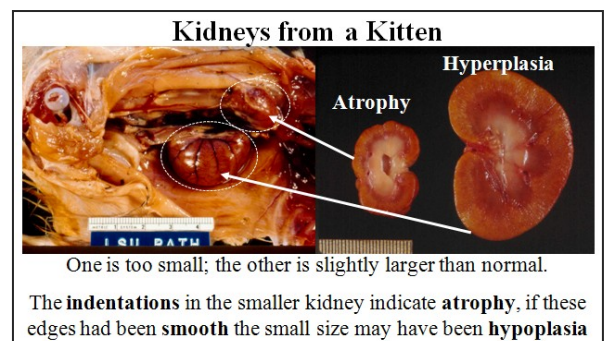
2) **Hyperplasia** – “increase in number”

- Enlargement caused by **increased number of cells**
- If severe, it can be difficult to differentiated from **neoplasia**
- **Caused by...**
 - **increased demand** for function (**compensatory process**)
 - **response to an altered steady state**
- May cause a **distortion** of the normal elements in the tissue
 - This can make histologic differentiation more difficult
- Involves **epithelial** organs (*e.g.* **endocrine glands**)
- Also found in the spleen (*e.g.* **splenic nodular hyperplasia**)



Hypertrophy vs. Hyperplasia

- **Kidney Misnomer**
 - Often one kidney is hypoplastic, which causes the other to undergo hypertrophy to compensate
 - However, this isn't actually hypertrophy (thought it is often called that)
 - **new nephrons** are **produced** which makes the kidney enlargement **hyperplasia** not hypoplastic

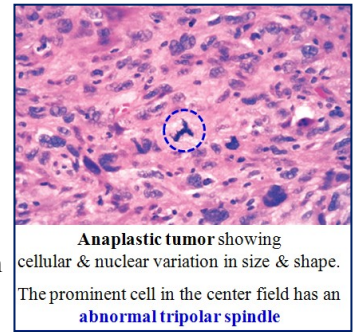


Disturbances in cell Differentiation

Changes in Cell Differentiation (6 types)

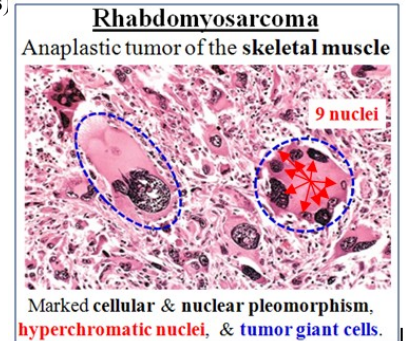
1) **Anaplasia** – “backward form”

- Backward development (**reversion**) of **differentiated cell** population to a more undifferentiated, primitive, or embryotic cell type
- Typically seen in **rapidly proliferating** cell populations (**tumors**)
- Always indicates a **neoplastic process**
- Anaplasia correlates to the **degree of cellular malignancy**



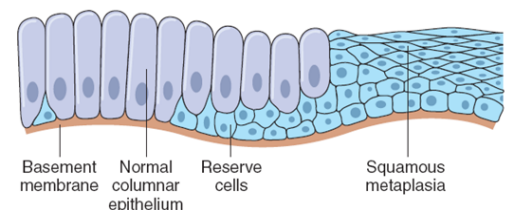
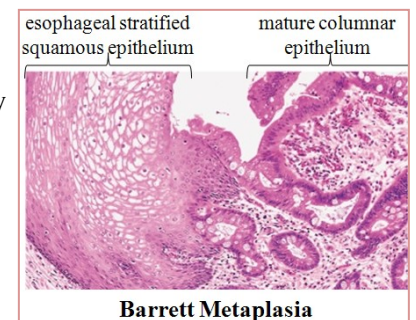
2) **Atypia** – “away from normal”

- a loss of normal polarity & orientation
- **strictly a microscopic change**
- always a **pre-neoplastic change**
- cells tend to slough off & may be seen in tissue smears
 - **ex. Pap smear:** looks for cellular atypia diagnostic of cancerous lesions



3) **Metaplasia** – “next form”

- Indicated a change from one **terminally differentiated** population of cells to another terminally differentiated population
- **Caused by of chronic inflammation**
 - the body is trying to protect the organ from further injury
- *ex. 1: “side bones” in horses*
 - **ossification** of **lateral cartilage** to **bone**
 - **caused by overwork** or **abnormal pressure**
 - the **tendons & ligaments** can also ossify
- *ex. 2: Barrett metaplasia:*
Metastatic transformation of one type of epithelial cells to another type of epithelial cells
- *ex. 3: respiratory epithelium* becomes **stratified squamous epithelium**
 - can no longer undergo oxygen exchange



Schematic diagram of **columnar** to **squamous** metaplasia

Changes in Cell Differentiation (6 types) continued...

4) **Dystrophy** --

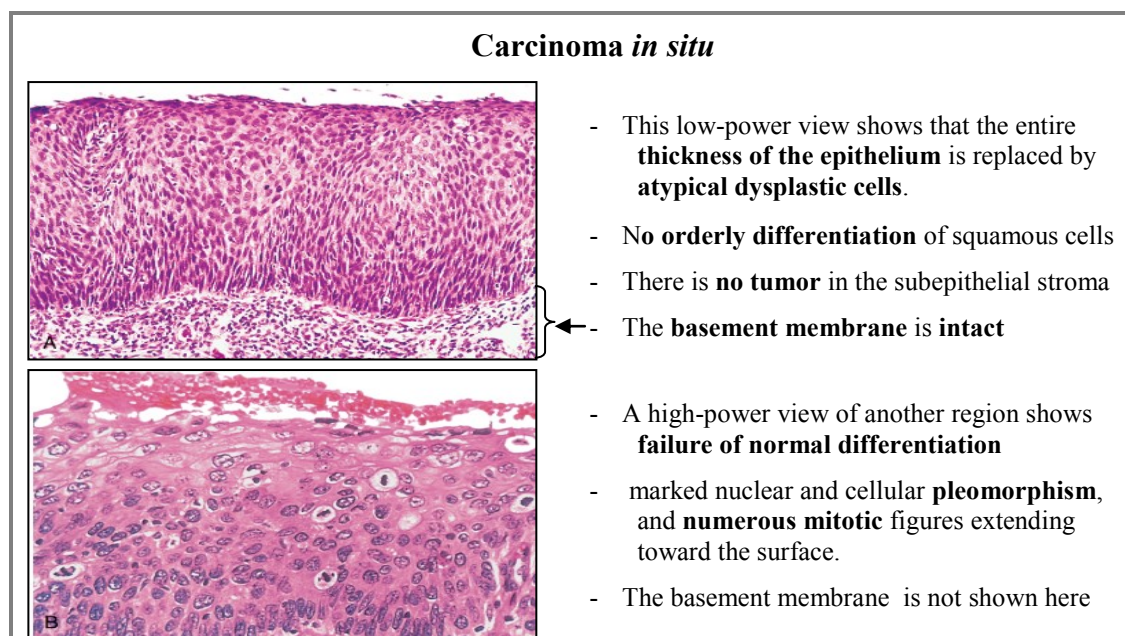
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5) **Dysplasia** – “sick form”

- Malformation during maturation such that there is...
 - a loss of normal tissue relationships & arrangements of tissue elements
- Typically occurs during embryogenesis
 - especially in joint development (*ex.* hip dysplasia)
- The part is **never** normal because the malformation occurs during the part's development
- Can be used grossly or microscopically

6) **Carcinoma *in situ***

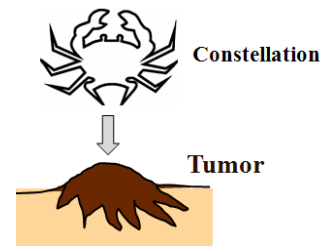
- Within place, site of origin
- A population of **neoplastic cells** that have **not yet spread** (still in place)
- **a little nest of neoplastic cells**
- Have **not broken through the basement membrane**
 - therefore, a malignant tumor that is easily removed
- Want to diagnose neoplasia at this stage (first recognition of malignant process)



Neoplasia (tumor)

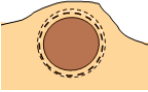
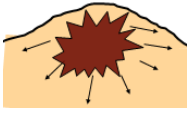



- “new form” of tissue
- **Oncology**: the study of swelling = the **study of neoplasia**
- **Tumor**: originally meant “swelling,” now it is synonymous with **neoplasm**
- **Characteristics** of neoplasm (5)
 - 1) **Abnormal mass** of cells or tissue
 - 2) Growth rate exceeds normal; **rapid mitotic activity**
 - 3) Growth is uncoordinated with the body’s needs &/or other tissues
Autonomous: self-controlled growth
 - 4) Growth continues after the inciting cause is removed
 - 5) Progressive such that each generation of cells is further from normal until death

- **“Cancer”** Greek term describing tumors growing on the skin
 - **squamous cell carcinomas** (most common skin tumors)
resembles a crab-like shape (Cancer = crab sign)
 - over time the term came to mean “malignant tumor of the skin”
 - now “cancer” means uncontrolled growth, mainly malignant



- **Classification**

- Each neoplasm is derived from a **particular type of cell** (all tumors come from one cell)
 - The only way to classify and identify is with microscopic exam (judgment of the pathologist)
 - Assume the tumor is still close enough to the “parent” to identify it
 - Histogenic classification (an imprecise science)
 - **Named** based on the **cell type of origin (parent cell)**
 - **Hallmarks of malignant** growth (2):
 - Metastasis
 - Infiltrative growth
 - **In tumors**:
 - Stroma :
 - **Vasculature** : the more vascularized the tumor, the more blood the tumor is pulling in
 - Inflammation:
- **Benign**: “favorable for recovery,” from benignant
 - **Malignant**: having a bad prognosis, generally leading to death if not controlled

Gross/Clinical Characteristics	Benign	Malignant
Growth rate	- Slower	- Faster
Growth progression	- Limited Growth - STOP or REGRESS - most will quit growing once a certain size is reached	- Unlimited growth - Progressive & grows until death - Each generation may grow faster
Interface with normal & adjacent tissue**	- Expansive growth - usually easy to remove - Sharp demarcation - often encapsulated 	- Infiltrative growth - Difficult to remove - may have isolated podia & islands of cells away from main body*** 
Growth on surface**	- Grows outward - Grows on a stalk - Has a with restricted base - becomes pedunculated 	- Sessile - broad base- growth - un-restricted base 
Recurrence	- Not expected	- Expected
Vascularization	- adequate blood supply (~ normal) - no necrosis -	- Inadequate blood supply - necrosis due to anoxia - infarction b/c tumor grows into itself - tumor outgrows supply
Metastasis	- No	- Yes
Anaplasia	- No anaplasia - normal, uniform population	- Yes – more anaplasia - more malignant
Nuclear chromatin	- Near normal	- Hyperchromatic - Polyploidy (several X #)
Nuclear/cytoplasmic ratio	- Small (normal)	- Large (b/c large nuclei)
Nucleoli	- normal	- Large - prominent - exaggerated - triploid - bizarre 
Mitotic figures	- Few or absent	- Numerous - Bizarre - abnormal looking
Overall cell size	- Normal and uniform	- Pleomorphic (many shapes & sizes) - irregular
Invasion of vessels	- none	- yes
Tissue structure (architecture)	- Nearly normal	- Loss of normal tissue structure - more malignant - more non- normal

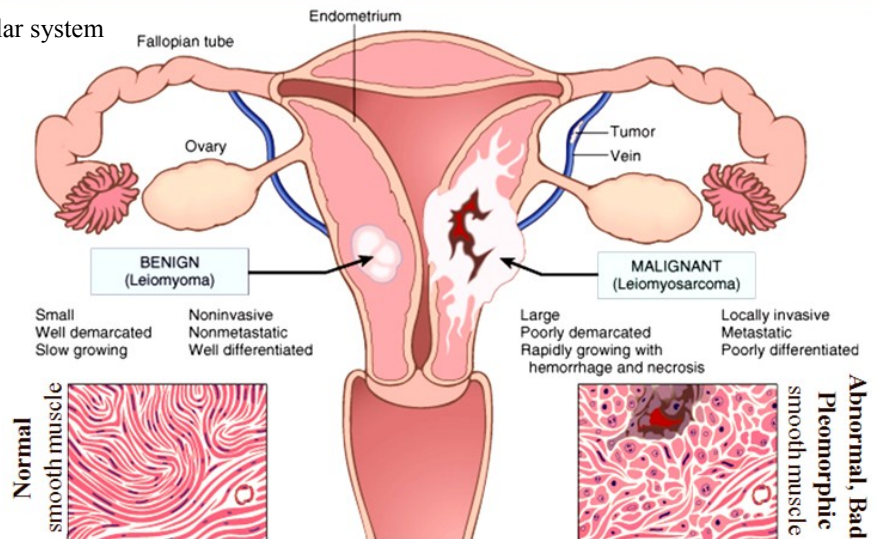
Neoplasia (tumor) continued...

Nomenclature

- **Sarcoma** nomenclature

- o Neoplasia of **Mesenchymal** origin
- o **Mesenchymal = Support tissues**
 - Fibroblasts
 - Muscle
 - Bone
 - Cartilage
 - Endothelial cells of vascular system

Sarcoma Nomenclature			
Mesenchymal (Support Tissue) Origin			
	Prefix (cell of origin)	Benign (Suffix = oma)	Malignant (Suffix = sarcoma)
Fibroblasts	Fibr-	Fibroma	Fibrosarcoma
Bone	Oste-	Osteoma	Osteosarcoma
Cartilage	Chondr-	Chondroma	Chondrosarcoma
Striated muscle	Rhabdomy-	Rhabdomyoma	Rhabdomyosarcoma
Mast cell		--	Mast cell sarcoma
Lymphocytes	Lymph-		Lymphosarcoma or Lymphoma



Comparison between a **benign** tumor of the **myometrium (leiomyoma)** and a **malignant** tumor of similar origin (**leiomyosarcoma**).

- **Carcinoma** Nomenclature

- o Neoplasia of **Epithelial** origin
- o **Epithelial = glandular**
- o A covering that sits on a basement membrane
 - **Epidermis**
 - Squamous cells
 - Basal cells
 - **Urothelium** epithelium
 - Transitional

Carcinoma Nomenclature		
Epithelial (glandular) Origin		
Prefix	Benign (Suffix = oma)	Malignant (Suffix = carcinoma)
Simple epithelium (Prefix = gland)		
Stratified squamous	Squamous papilloma	Squamous cell carcinoma
Urothelium	Transitional papilloma	Transitional cell carcinoma
Basal Cell	epithelioma	Basal cell carcinoma
Glandular epithelium (Prefix = gland + adeno)		
Mammary	Mammary adenoma	Mammary adenocarcinoma
Thyroid	Thyroid adenoma	Thyroid adenocarcinoma

- Leukemia Nomenclature

- “white blood” (“leuk” = white; “eme” = blood)
- **Neoplasms that circulate** (come from cells that circulate), although origin does not have to circulate
- **Bone marrow origin** (“sarcomas”)

Breakdown of the type of white blood cells the Leukemia is effecting

- **Granulocytes**
 - neutrophils
 - eosinophils
 - basophils
- **Erythrocytic series** → **Erythroid** leukemia
- **Mast cells** → **Mast Cell** Leukemia (but...are they embolic cells or are they actually leukemia?)
- **Aleukemic** leukemia – **non-circulating** leukemia (just seen in the bone marrow)

- Mixed Mammary Tumors

- Common in the mammary glands of dogs (80-90% are benign in dogs)
- Mixed because they have both **mesenchymal** (sarcoma) & **epithelial** (carcinoma) components
- They're called “mixed mammary tumors” regardless of whether they are benign or malignant

- Collision Tumors

- Collision Tumors are Rare
- They are a mass of cells of part **mesenchymal** (sarcoma) & the rest of **epithelial** (carcinoma) origin
- These two tumors then collide & grow together

- **Breaking the nomenclature rules**

- Adding malignant
 - **Lymphosarcoma** = malignant lymphoma
- “cyt” vs. “blast”
 - If a tumor has “cyt” in its name, it is not as malignant as one with “blast”
 - **Astrocyte** vs. **astroblast** (malignant astrocytoma << malignant astroblastoma)
- **Melanocytic tumors**
 - **Benign** = melanocytoma
 - **Malignant** = melanoma

Metastasis (METS)

- **Metastasize** (verb)
- **Metastasis** (noun, singular)
- **Metastases** (noun, plural)

- **Metastasis** – the **spread of a disease process throughout the body** by way of the **circulatory system** (blood and/or lymphatics)

- The “**deadly**” characteristic about **malignant tumors** is that they **move**
- Involves an **embolism** : **occlusion of a blood vessel by an embolus**
 - **Embolus** = a **loose clot** or **air bubble** or other particle

****rules of thumb****

- **Sarcomas:**
 - **metastasize** by way of **venules (blood system)**
 - Look in the lung for secondary metastases
 - *e.g.* **Osteosarcoma**

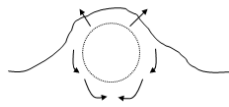
- **Carcinomas:**
 - **Metastasize** by way of the **lymphatics**
 - Look for **secondary METS** in the (**draining**) **lymph nodes**
 - Look for **tertiary METS** in the **lung**
 - *e.g.* **Mammary adenocarcinoma**

Other Routes of Tumor Spread

- Direct invasion

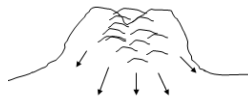
- The tumor **grows** in a linear fashion **into adjacent tissues**

- **Benign** tumors



- freely moveable (**non-anchored**)
- No invasion of neighboring tissues
- Adjacent tissue can slide over the tumor

- **Malignant** tumors



- “**dimple effect**” (**anchored**)
- Adjacent tissues not fully moveable because tumor is attached
- Tumor will invade adjacent structures

- Transplantation

- **Fine needle aspirate** –

- When tumor cells (or entire tumor) are being extracted & a tumor cell on its way out of the body, this dropped cell begins to proliferate, introducing the tumor to a new region of the body
- Certain types of tumors are more prone to dropping cells
- Fairly common
- Usually occur in a few days
- BAD sign...(malignant tumor)

- **Organ transplantations** (must carefully examine organs for tumor cells before they are transplanted)

- Implantation

- Transfer of tumor from one adjacent surface to another by **physical contact**
- Especially important in **thoracic & abdominal cavities**, where organs rub together (spread over **serosal surface**)
- Tumors that are prone to spread through Implantation are:
 - **Carcinomatosis** - the entire peritoneal cavity is covered with tumors
 - **Ovarian cancer**
 - **Mesophilioma**
 - **Lung tumors** - rub off to pleural surface and spread to the thoracic wall

- Transmissible Venereal Tumor (TVT)

- A “tumor” **caused by a virus**, spread by **mating dogs**
- The infected cells are “transplanted” from one individual to another where they stick to mucous membranes
- Usually regress, but sometimes metastasize (metastatic sites can also regress)

- Spread along preformed ducts

- **Milk ducts in mammary gland**
- **Salpinx**
- **Seminiferous tubules (Sertoli cell tumors)**

Paraneoplastic syndrome

- **Syndrome:** a set of **clinical signs** that occur with enough regularity to be recognized as a **distinct entity**
 - o Sign= objective, quantitative, visible
 - o **Symptoms:** subjective, qualitative, internal (associated with humans not animals)
- **Not a disease *per se***, because a **disease has a particular...etiology, clinical course, treatment**
- **Paraneoplastic syndrome:** sets of **clinical signs** that are a **side effect of neoplasia**
- Usually due to secretion of hormones, metabolites, or other mediators that have an action on other organs
- o **ex. Feminization of male dogs with Sertoli Cell Tumors**
 - Sertoli cells usually produce sperm, but here they start **secreting estrogens** instead
 - With tumors, see **hyperestrogenemia** (increased estrogen production)
 - rarely metastasize
 - Frequently see with **cryptorchid testicles**
 - Bilateral alopecia over back and rump
 - Enlargement of mammary glands
 - Pendulous prepuce (can even drag the ground)
 - Pendulous testis (one normal)
 - Male dogs become “attractive” to other male dogs
 - **Treatment (Tx):** remove the tumor by neutering the dog
- o **ex. Lymphosarcoma:**
 - Lymphocytes inappropriately secrete IL-1 and parathyroid hormone-related peptides (PTHrP)
 - Cause mobilization of calcium from bone (pulls calcium out of bone & deposits it into the blood stream)
 - ➔ Leads to **hypercalcemia** (too much calcium in the blood)
 - Common presenting clinical signs
 - Mineralization of soft tissues (**metastatic mineralization**)
 - Vomiting
 - Irregular heartbeat

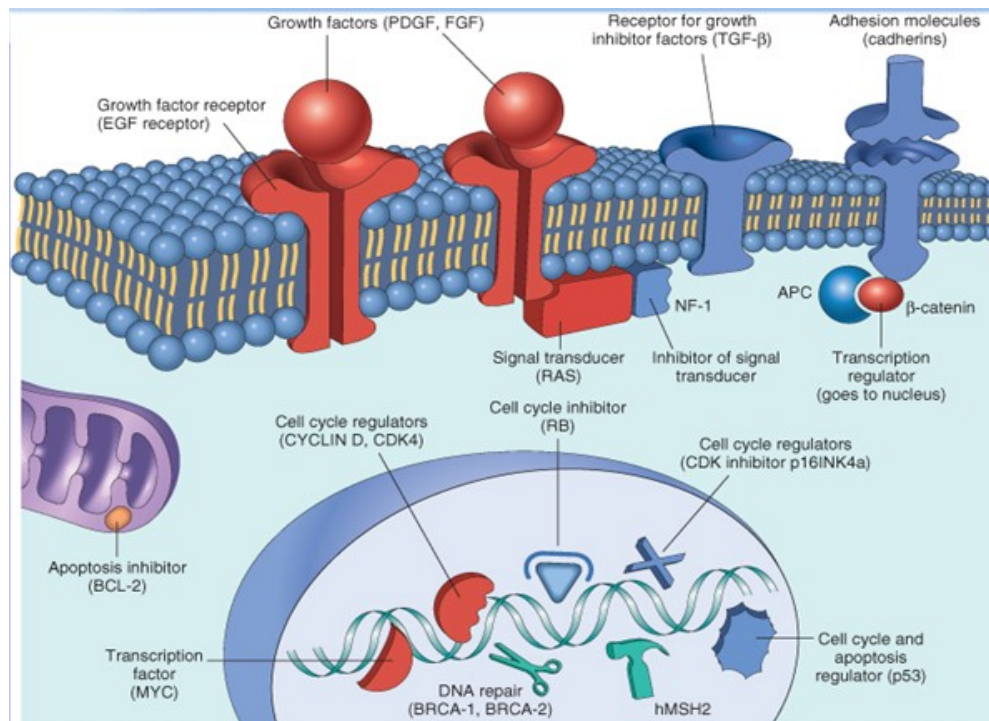
Dystrophic vs. Metastatic Mineralization

- o **Dystrophic mineralization:** occurs following cellular necrosis/degeneration of tissue
 - Vitamin E deficiency
 - Saponification of fat
 - Chronic irritation or cellulitis
- o **Metastatic mineralization:**
 - occurs when there are **metabolic derangements** leading to dietary or nutritional **imbalances**
 - **dietary imbalances: calcium, phosphorous or vitamin D**
 - **nutritional imbalances: hyperparathyroidism** = secretes too much **parathyroid hormone (PTH)**
 - **Renal disease:** secondary renal **hyperparathyroidism**
 - PTH or PTH-like hormone producing lesions
 - Parathyroid and other neoplastic processes.
- o Hard to tell which type of process leads to soft tissue mineralization, sometimes both are present

Molecular Basis of Cancer

- Cancer is a **genetic disease**
- Damage to the cellular genome is a common feature for virtually all neoplasia, regardless of the tissue it is found in
- Many diverse agents can result in this damage
 - Viruses
 - Mutagenic chemicals
 - Radiation
- The genetic damage is believed to be random & many mutations may be inconsequential
- Classes of **regulatory genes** that can be **affected** in the **development of abnormal cell growth**, eventually **resulting in neoplasia**
 - 1) **Oncogenes**
 - **growth-promoting** regulatory genes
 - 2) **Tumor suppressor genes**
 - **growth-inhibiting** regulatory genes
 - 3) **Apoptotic genes**
 - regulate “**programmed cell growth**”
 - 4) **DNA repair genes**
 - often considered to be another class of tumor suppressor genes

Go back through old notes & figure out how a disruption of the Apoptotic genes can cause neoplasm formations



Subcellular localization and functions of major classes of cancer-associated genes. The **proto-oncogenes are colored red**, **tumor suppressor genes blue**, **DNA repair genes green**, and **genes that regulate apoptosis orange**

1) **Oncogenes** (growth-promoting)

- **Derived from a proto-oncogene**

- A cellular gene that **promotes cellular growth & cell differentiation**
- When mutated such that it becomes constitutively and uncontrollably activated, it becomes an oncogene
 - Once it is turned on, they can't be turned off (**fail to respond to regulatory signals**)
→ **uncontrollable cell growth**
- Translational products known as oncoproteins
 - Devoid of regulatory elements
 - Production in transformed cells may proceed regardless of any (normally regulatory) external signals

- **Gain of function mutations:**

- Point mutations - can result in constitutively acting products
- Gene amplifications – overexpression of encoded proteins
- Chromosomal rearrangements – bring growth
 - regulatory genes under the control of inappropriate promoters
 - resulting in **erroneous expression patterns** (things are turned on at inappropriate time & place)

- **2 major effects of gene mutations:**

1) **Gene Structure** may be altered

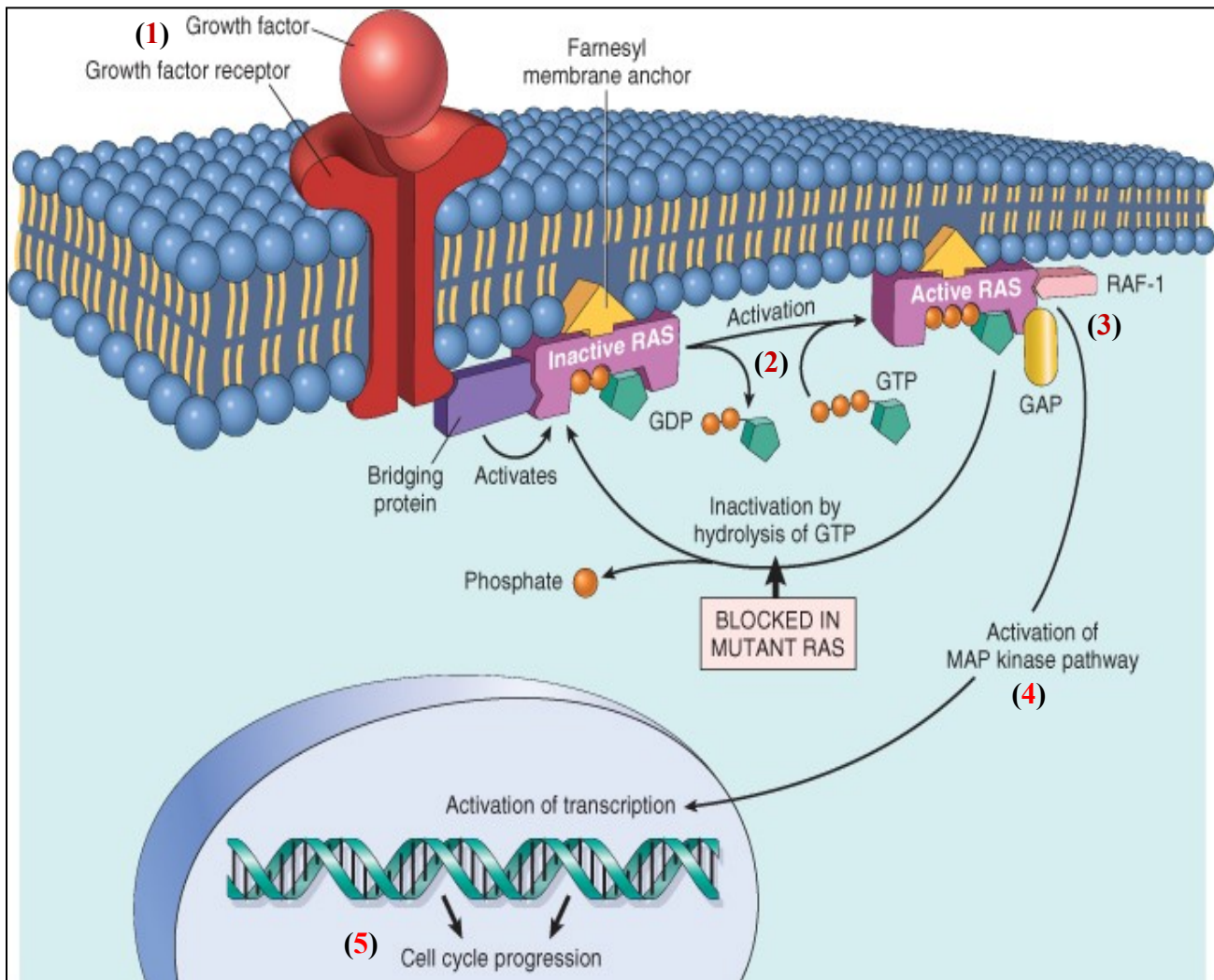
- resulting in an abnormal gene product (oncoprotein) with an abnormal function
- *i.e.* oncogenes make oncoproteins

2) **Gene Expression** may be affected

- result in enhanced or inappropriate production of a structurally normal growth-promoting protein

- *ex.* **RAS Family (GTPase superfamily)**

- **Most common abnormality of dominant oncogenes**
- Mutated in 10-20% of all human tumors
- Located in the **inner surface** of the **plasma membrane**
 - near the cytoplasmic domains of **Growth Factor (GF)** receptors
 - Well situated to receive signals from outside the cell (activation of GF receptors)
 - Transmit signals (via cascade of 2 messengers) to the nucleus where they ultimately change the cells gene expression profile and its cell-cycle status



Model for Action of RAS genes.

- 1) A normal cell is **stimulated** by a GF receptor
- 2) this **activates** the **inactive (GDP-bound) RAS** to **GTP-bound** state
(so it has become **transiently activated** by **receptor-ligand interactions** causing it to exchange **GDP** for **GTP**)
- 3) This energy exchange **Activates RAS** by binding to **RAF-1**
- 4) This binding stimulates the **MAP-kinase pathway** to **transmit growth-promoting signals** to the nucleus
- 5) The **mutant RAS protein** is **permanently activated** because of inability to hydrolyze GTP
→ leading to **continuous stimulation** of cells **without any external trigger** (no longer need the growth factor)

The anchoring of RAS to the cell membrane by the farnesyl moiety is essential for its action

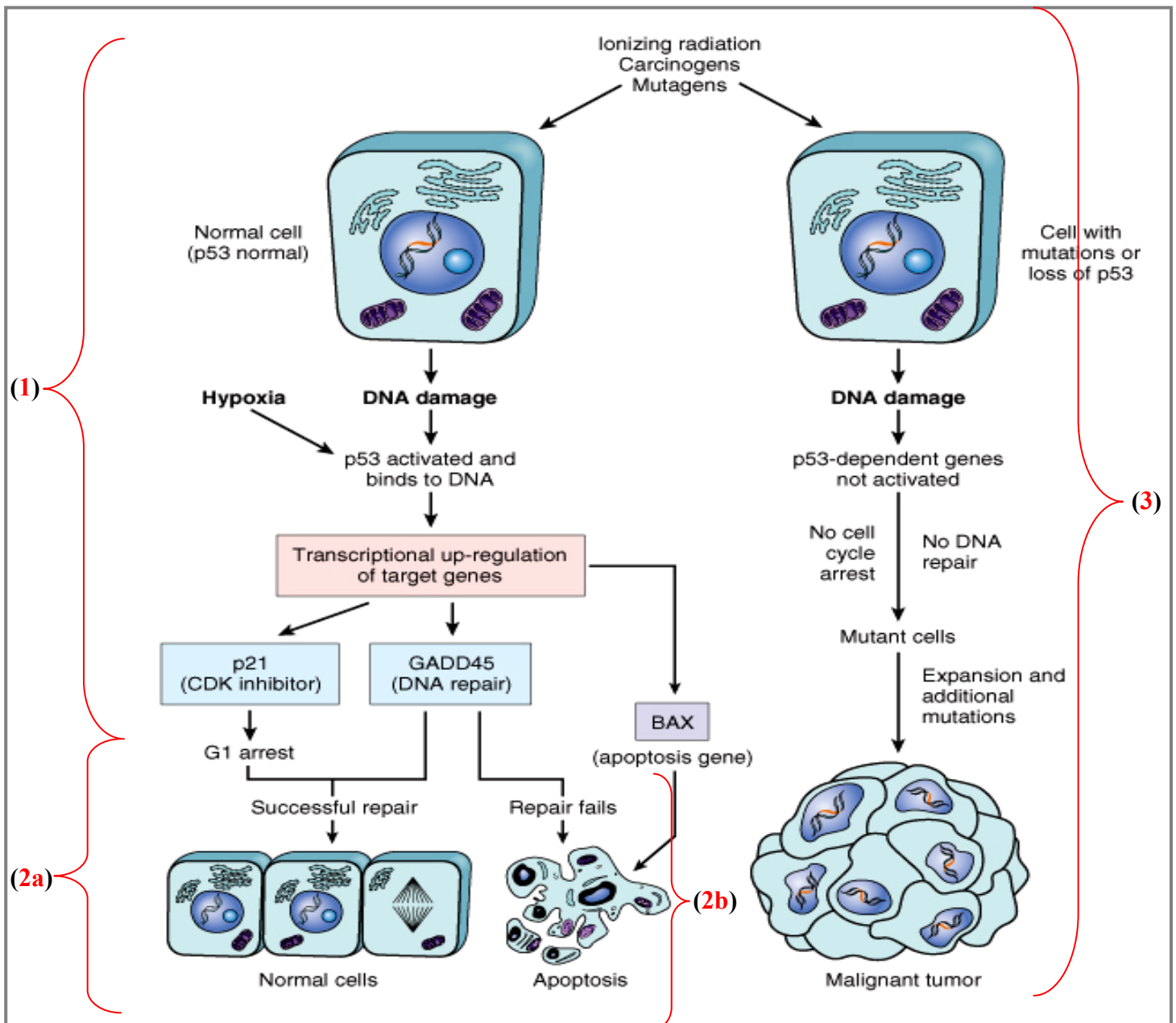
2) **Tumor suppressor genes** (growth-inhibiting)

- Most common cause of Neoplasia
 - Widely believed that inactivated tumor suppressor genes are commonplace in almost all types of neoplasia
- **Loss of function mutation**, with a “double hit” necessary for development of tumors
 - Implies a “recessive” mutation
 - Both copies of the gene must be mutated before neoplasia can ensue
 - Loss of **heterozygosity**
 - if you still have one copy of the Tumor Suppressor Gene you are still heterozygous
 - once you lose both copies of the gene you are no longer heterozygous
- **Hereditary disease occurs when...**
 - One genetic change (the first hit) is inherited from an affected parent
 - The second occurs in one of the many cells already harboring the first mutationor
 - **In a sporadic form**
 - both mutations occur somatically within a single cell whose progeny then form a tumor.

1) *ex.* The **most well studied** tumor suppressor gene is “**p53**”

- Known as the “protector” or “policeman” of the genome
- Functions to arrest the cell cycle at the G₁ phase in the attempt to prevent propagation of the genetically damaged cells
- Most common target for genetic alteration in human neoplasia
- Homozygous losses reported in 50% of all tumors, regardless of the cell of origin

Note: there are other Tumor Suppressing Genes that are just as important as p53



The role of p53 in maintaining the integrity of the genome

- 1) Activation of normal *p53* by DNA-damaging agents or by hypoxia leads to cell-cycle arrest in G₁ & induction of DNA repair, by transcriptional up-regulation of the cyclin-dependent kinase inhibitor *p21*, & the *GADD45* genes, respectively
- 2a) Successful repair of DNA allows cells to proceed with the cell cycle
- or
- 2b) if DNA repair fails, p53-induced activation of the *BAX* gene promotes apoptosis.
- 3) In cells with loss or mutations of *p53*, DNA damage does not induce cell-cycle arrest or DNA repair, and hence genetically damaged cells proliferate, giving rise eventually to malignant neoplasms.

Hemodynamics

Hemodynamics: The study of the dynamics of blood circulation

- The health of cells & organs depends on **uninterrupted circulation** to **deliver oxygen & nutrients & remove waste**
- Tissue well-being also requires a **normal “fluid balance”**
- Abnormalities in vascular permeability or hemostasis can result in injury, even with an intact blood supply.
- **Normal fluid homeostasis** encompasses **maintenance of ...**
 - **vessel wall integrity**
 - **intravascular pressure**
 - **osmolarity** within certain physiologic ranges
- Changes in vascular volume, pressure, or protein content (or alterations in endothelial function) all affect the net movement of water across the vascular wall.

- **Blood Circulation Problems:**

1) Edema: swelling caused by fluid in tissues

- i. **Increased Hydrostatic Pressure**
- ii. **Decreased Plasma Colloidal Osmotic Pressure**
- iii. **Increased Vascular Permeability**
- iv. **Lymphatic Obstruction**
- v. **Heart Failure / Sodium Retention**

2) Local Increased Volume & Pressure of Blood in a given Tissue

- i. **Hyperemia**
- ii. **Congestion**

3) Clot Forming processes

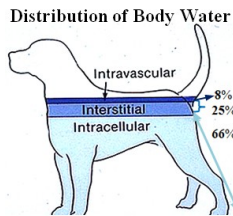
- i. **Hemostasis**
- ii. **Hemorrhage**
- iii. **Thrombosis**

4) Ischemia: restriction in blood supply, generally due to factors in the blood vessels

- i. **Emboli**
- ii. **Infarctions**

5) Shock: life-threatening condition in which the body is not getting enough blood flow

1) Edema



Approximately 60% of lean body weight is water

- 66% is intracellular
- 25% is extracellular
- 8% of total body water is in blood plasma (intravascular)

Edema: increased fluid extravasation into interstitial/extracellular spaces (including body cavities)

- Most easily **recognized grossly**
- May occur in any tissues
- Most commonly seen in **Subaqueous (SQ)** tissue, brain, and lungs
- **Microscopically**
 - Edema can Not be easily seen microscopically
 - This is because edema generally manifests only as **subtle cell swelling**, with clearing and separation of the intracellular matrix elements
- **Sites** where edema can occur:
 - Can occur as **localized process** or **may be systemic**
 - Often occurs in the **Brain** or **Lungs**
- **Site-based Nomenclature:**
 - 1) Prefix '**hydro**' added to anatomic site to indicate edema:
 - **Hydrothorax** – fluid in pleural cavity
 - **Hydropericardium** – fluid in pericardial sac
 - **Hydrosalpinx** – fluid in uterine tube
 - **Hydrocephalus** – accumulation of fluid in the brain
 - **Hydrocoele** – fluid-filled cyst anywhere in body
 - **Hydroperitoneum (ascites)** – edema in the peritoneal cavity
 - **Anasarca** – severe and **generalized edema**, with profound **SQ** tissue swelling
 - 2) "**Hydrops**" – sometimes used similarly to prefix "hydro"
 - **Hydrops of gall bladder**
 - **Hydrops allantois** – accumulation of fluid in the placenta
 - **Dropsy** – accumulation of fluid in a body cavity
- **Significance & Effect**
 - Edema is considered to be a **space displacing lesion** (exerts pressure in a closed area)
 - Edemas are generally **easily resorbed** if cause is removed


- **General Causes**

- **Intracellular edema**
 - **Depression of metabolic systems** of the tissues or lack of adequate nutrition to cells
 - **Depressed ionic pumps** → **Sodium (Na) & water leak in**
 - **Inflammation**
 - **Increased permeability of cell membranes** → **Sodium (Na) & water leak in**

- **Extracellular edema**
 - **Abnormal leakage of fluid from blood capillaries**
 - **Failure of lymphatic system** to return fluid from interstitium
 - **Renal retention** of salt and water

- **Non-inflammatory edema (Transudate)**
 - **Low protein levels**
 - **Fluid accumulation** due to **hydrostatic imbalances** between intravascular & extravascular compartments **DESPITE normal vascular permeability**
 - **Clear**, colorless, or slightly yellow

- **Inflammatory edema (Exudate)**
 - Related to **increased endothelial permeability**
 - **High protein levels**
 - Caused by **leakage of plasma proteins (albumin) & leukocytes (white blood cells)**
 - Usually **opaque**

	Transudate Edema (Non-Inflammatory)		Exudate Edema (Inflammatory)
Specific gravity	≤ 1.015		>1.017
Protein content	< 2.5 gm/dL		> 3 gm/dL
# Nucleated Cells Present	< 1000		> 1000
Fibrin clots	none		Yes – fibrin is escaping
Clarity	Clear		turbid
Color	None (clear)	Transudate Exudate	Yellow-orange

By analyzing the leaked fluid, you can better determine what type of edema it is → better treatment

- There is also a **Modified Transudate Edema**, which is between the transudate & exudate (**FIP**)

- Generalized Edema & Species Differences

Different species develop edema in different places, regardless of the cause

- **Cats:**
 - **Hydrothorax**
- **Dog**
 - **ascites**
- **Horse**
 - Ventral abdomen
 - Ventral thorax
 - If severe – distal extremities (“stocking”)
- **Bovine**
 - **Intermandibular space**
 - **Brisket area (thoracic inlet)**

- Gross Appearance of Edema

- **Acute (rapid) onset**
- **Swollen, distended**, tends to **gravitate ventrally (sagging tissues)**
- Tissue pits on pressure & indentations remain after pressure is removed
- **Tissue is cool** to touch (unless inflammation is also present)
- Tissue is **not red or painful**

○ SQ edema

- Different distributions, depending on the cause
- Can be diffuse or may be more conspicuous at sites of highest hydrostatic pressures
- In this case, distribution is frequently gravity dependent

○ Ascites edema

At necropsy, edema is recognized by...

- presence of **clear, yellow-tinged fluid**
- Fluid distends **loose connective tissues**
or
- Fluid **accumulates in body cavities**
 - Peritoneal
 - Pleural
 - pericardial

Bovine Edema



Cat with FIP Ascites Edema



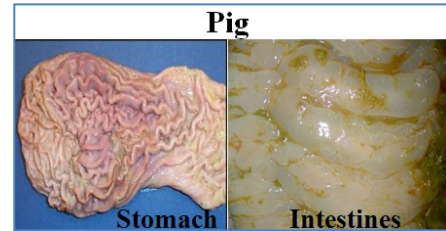
Note: this cat is icteric (yellow stained intestines)

- **Gross Appearance of Edema** (continued...)

o Animals with **Septicemia & Edema**

- *ex.1:* **Pig** suffering from edema disease

- Due to **septicemia** with certain strains of *E. coli*
- These **bacteria produce a toxin**
- The **toxin acts on endothelial cells**
→ **allowing fluid to leak out**
- Pigs also frequently exhibit **conjunctival edema** (cannot open eyes)



- *ex.2:* This **frog** had **Septicemia** (systemic bacterial infection)

- Bacteria or bacterial toxins caused vascular leakage of protein
→ resulting in **total body edema**
- This accumulation of fluid is called **generalized edema** or **Anasarca**



- **Micro appearance of edema**

o **Separation of tissues** by clear or colored **spaces** in **hematoxylin and eosin (H&E)** stained slides

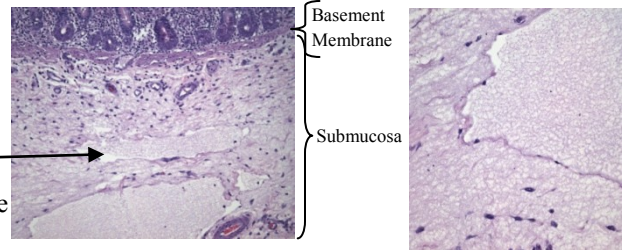
- **clear** (if edema is **protein-poor**)
- **pink** (if edema fluid is **protein-rich**)

o Dilation of **lymphatic vessels**

- *Note:* Lymphatic vessels are the **natural channel** for **removal of excess fluid**

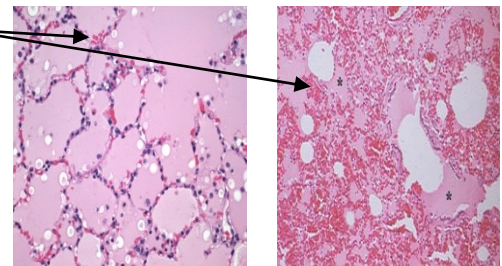
▪ *ex.1:* **Submucosa of small intestines**

- Markedly **distended by fluid**
- **Lymphatic vessel greatly dilated**
- **nutrients can not be absorbed** from the intestine



▪ *ex.2:* **Pulmonary edema**

- **Protein-rich pink fluid** has leaked out of vessels
- Pink Fluid has filled **alveoli** and **bronchioles**
- **Gas exchange can not take place in alveoli**
- **Very serious** for animal because they lose their oxygen exchange mechanisms
- Commonly found in animals that are about to dye
- Here the pulmonary edema was pathogenic (caused by a disease)



Factors affecting Fluid Balance Across Capillary Walls

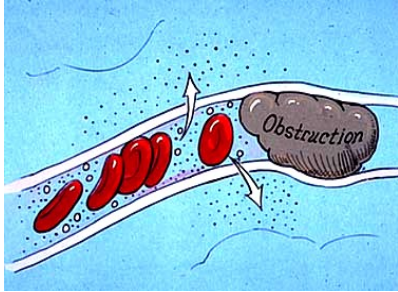
- 1) **Capillary hydrostatic & osmotic forces are normally balanced**
 - so that there is **no net loss or gain of fluid** across the capillary bed
- 2) **↑ hydrostatic pressure** or **↓ plasma osmotic pressure**
 - leads to a **net accumulation of extravascular fluid** (edema)
- 3) As the **interstitial fluid pressure increases**
 - **tissue lymphatics remove much of the excess volume**
 - eventually **returning it to the circulation via the thoracic duct**
- 4) If the **lymphatics' ability to drain tissue** is exceeded → **persistent tissue edema**

Fluid Balance in the Body

<p>Forces driving fluid OUT of a blood vessel</p> <p>Hydrostatic pressure (blood pressure) → OUT</p> <ul style="list-style-type: none"> • 37 mm Hg at arterial end of capillary • 17 mmHg at venous end <p>Interstitial fluid colloidal osmotic pressure → IN</p> <ul style="list-style-type: none"> • Interstitium normally ↓ proteins • Little impact on formation of edema 		<p>Forces drawing fluid INTO a blood vessel</p> <p>Intravascular colloidal osmotic pressure → IN</p> <ul style="list-style-type: none"> • ~ 25 mmHg • due to plasma protein in vessel lumen <p>Hydrostatic Pressure (Tissue Tension) → OUT</p> <ul style="list-style-type: none"> • ~ 1-4 mm Hg • Important in distribution of edema • Lax areas of the body are more prone to edema fluid accumulation than are the Tense areas
<p>Hydrostatic pressure vs. Osmotic pressure</p> <p>(due to Blood Pressure) vs. (due to proteins)</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>High hydrostatic Low osmotic</p> <p>↓</p> <p>Lose fluid out of vessels</p> </div> <div style="text-align: center;"> <p>(leads to)</p> <p>↗</p> </div> <div style="text-align: center;"> <p>High osmotic Low hydrostatic</p> <p>↓</p> <p>Fluid out proteins more concentrated</p> </div> </div>		
<p><i>Note:</i> These forces are normally kept in a delicate balance so that body fluid movement occurs without edema</p>		

Pathogenesis of Edema (5 causes)

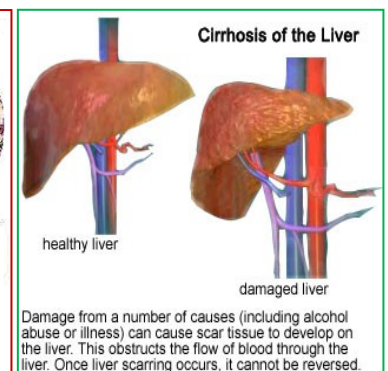
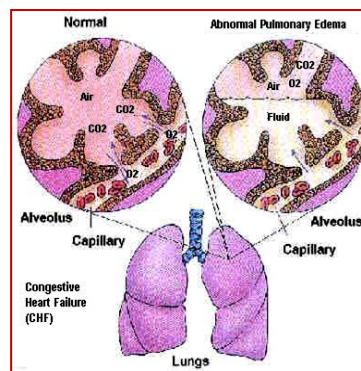
(1) Increased Hydrostatic Pressure



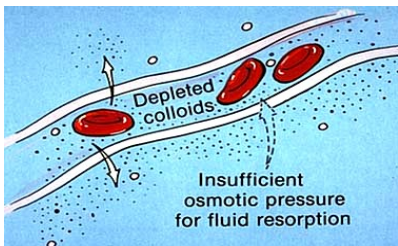
- ↑ **Intravascular Pressure** (↑ blood pressure)
- **Venous obstruction or impaired venous outflow**
 - Results in ↑ hydrostatic pressure as **blood backs up** in the venous system
 - Causes **leakage of sodium & fluid** into the **interstitial tissue**
 - No significant leakage of colloids

- **Diseases** that can cause ↑ hydrostatic pressure:
 - **Congestive heart failure** (left)
 - **Cirrhosis of the liver** (right)

- These diseases cause **obstruction or narrowing** of the veins & ultimately results in **impaired venous return & congestion**, which will eventually cause **leakage & edema**



(2) Decreased Plasma Colloidal Osmotic Pressure



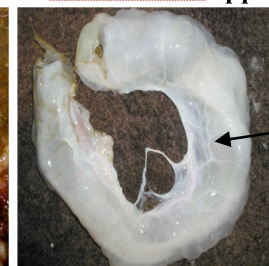
- ↓ **proteins & solutes** in the blood
- **Capillary blood** contains a ↓ **quantity of colloids** due to:
 - ↓ **hepatic synthesis** of proteins
 - ↑ **protein loss** through the **kidney or GI tract**

- **Diseases** that cause ↓ oncotic pressure of plasma (**hypoproteinemia**)
 - **Cirrhosis of the liver/liver failure** (**hypoalbuminemia**: not enough albumin in the blood)
 - **Kidney disease**
 - **Malnutrition/starvation**
 - Protein-losing **gastroenteropathies**
 - **Gastrointestinal parasitism** (shown on the right)

- As a result of **hypoproteinemia**, **fluid & sodium** are **not reabsorbed** at the **venous end** of the **capillary**

- **Fluid accumulated** in the **interstitium** as **edema**

Edema in Goat Due to *Haemonchus* spp



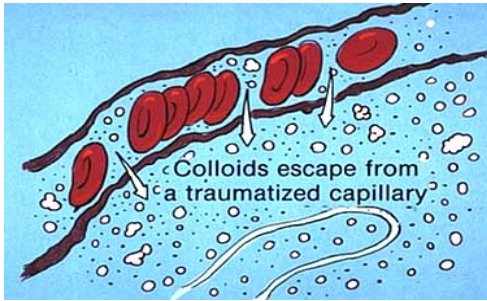
White, glossy substance is Edema

These parasites attach to **abomasal mucosal surface** in order to **suck blood & proteins**

The animal **does not have enough intravascular proteins** to maintain **colloidal osmotic pressure**

(These animals die of hypoxia because they have such bad systemic anemia)

(3) Increased Vascular Permeability



- Endothelial cell damage results in
→ ↑ capillary permeability to fluids, salts, & colloids
- An ↑ in colloids within the interstitium
→ ↓ re-absorption of fluid at the venous end of the capillary
- These colloids may eventually be drained away by lymphatics

- Diseases that cause ↑ vascular permeability

Edema in Baby Pig with Cytomegalovirus (CMV) Infection



Hemorrhage

The virus damages endothelium leading to ↑ vascular permeability

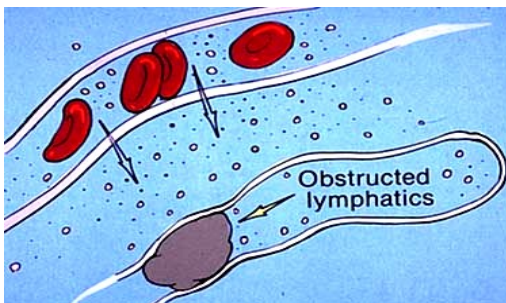
The structure is spiral colon.

What is between the spirals of colon?

Edema Fluid

(white & glistening substance)

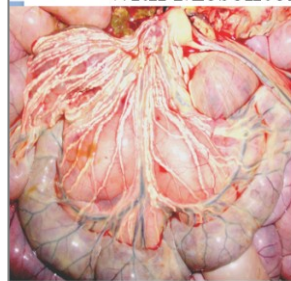
(4) Lymphatic obstruction



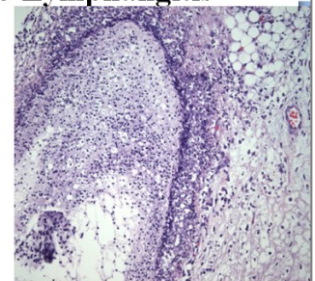
- Normally, small quantities of fluids, salts, & colloids escape from capillaries & are drained from the interstitium by lymphatics
- In lymphatic obstruction, these materials accumulate

- Diseases that cause lymphatic obstruction
 - Inflammation (shown on the right)
 - Neoplasia
 - Post-surgical blockage by lymphatic ducts
 - Post-irradiation of a tumor → lymph damage or blockage
- Common following lymph node disease, at least until collateral circulation can be established

Two Day-Old Foal with Mesenteric Lymphangitis



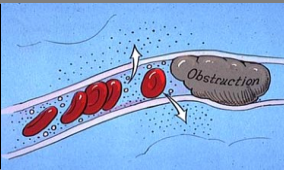
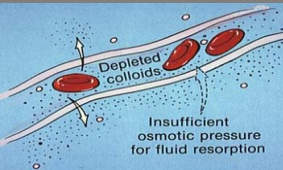
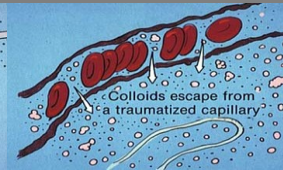
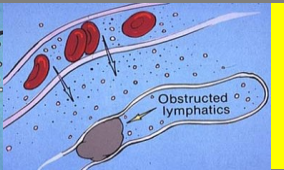
Lymphatic vessels are dilated & filled with inflammatory cells – which act as lymphatic obstruction



Intestine fills with fluid & mesentery accumulates edema fluid mixed with inflammatory cells

(5) Heart Failure / Sodium Retention

- Can't consume enough salt to cause Na retention edema...
- Mechanism: ↑ tubular re-absorption of sodium
 - Common pathway in congestive heart failure & edema due to hypoproteinemia
 - Reduced renal perfusion due to Congestive (Chronic) Heart Failure (CHF)
 - Increased renin-angiotensin-aldosterone secretion
- Diseases / conditions that cause sodium retention & → increased plasma volume
 - Heart failure → Hypoperfusion of the kidneys
 - Renin – released from juxtaglomerular apparatus
 - Angiotensin – causes secretion of aldosterone
 - Aldosterone – causes increased absorption of Na in the kidneys
 - With Na comes H₂O (causing **anasarca**)
 - Kidney disease
 - Na not excreted
 - Results in Na retention

Edema Pathogenesis Review					
	(1)	(2)	(3)	(4)	(5)
	↑ Hydrostatic Pressure	↓ Plasma Colloidal Pressure	↑ Vascular Permeability	Lymphatic Obstruction	Heart Failure / Sodium Retention
Depiction					
Description	<ul style="list-style-type: none"> - Venous obstruction or impaired outflow → ↑ hydrostatic pressure as blood backs up → sodium & fluid leak into the interstitial tissue 	<ul style="list-style-type: none"> - ↓ Hepatic protein synthesis - ↑ Protein loss through kidneys → ↓ colloids in capillary blood - Hyperproteinemia → fluid & sodium are not re-absorbed - interstitium fluid accumulation 	<ul style="list-style-type: none"> - Endothelial cell damage → ↑ capillary permeability to fluids, salts, & colloids ↑ colloids in the interstitium → re-absorption of fluid - lymphatics may drain colloids 	<ul style="list-style-type: none"> - Lymphatic obstruction → Accumulation of fluids, salts, & colloids in the capillaries 	<ul style="list-style-type: none"> - Can't consume enough salt to cause sodium (Na) retention - ↑ Tubular re-absorption of sodium
Diseases that cause	<ul style="list-style-type: none"> - Congestive Heart Failure - Cirrhosis of the Liver 	<ul style="list-style-type: none"> - Hypoalbuminemia (liver failure) - Cirrhosis of the Liver - Kidney disease - Malnutrition / starvation - Protein-losing gastroenteropathies - Gastrointestinal parasitism 		<ul style="list-style-type: none"> - Inflammation - Neoplasia - Post-surgical - Post-irradiation 	<ul style="list-style-type: none"> - Congestive Heart Failure - Kidney disease

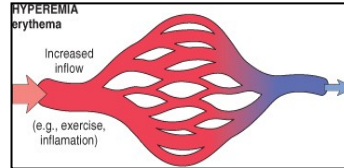
2) Local Increased Volume & Pressure of Blood in a given Tissue (Hyperemia & Congestion)

- 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.

i. **Hyperemia**: presence of an increased amount of blood flow in a part of an organ

- **Active Process** resulting in **increased tissue blood flow** due to **arteriolar dilation**

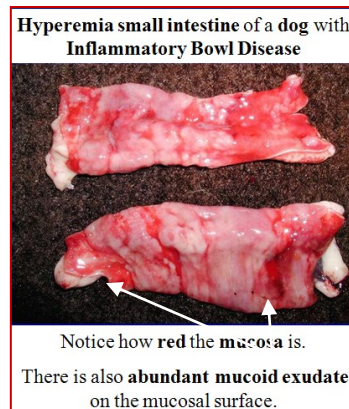
- o Excess blood of arterial origin
 - Skeletal muscles during exercise
 - At sites of inflammation



- o Effected area is red because of engorgement with oxygenated blood
- o increased inflow leads to engorgement with oxygenated blood, resulting in erythema

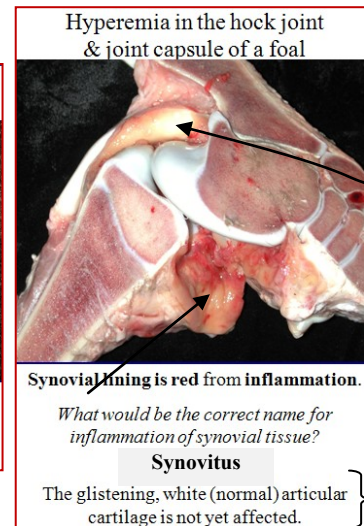
- **Causes** of hyperemia

- o Normal physiologic process
 - GIT gets blood for digestion
Gastro Intestinal Tract = (GIT)
- o Hallmark of inflammatory response



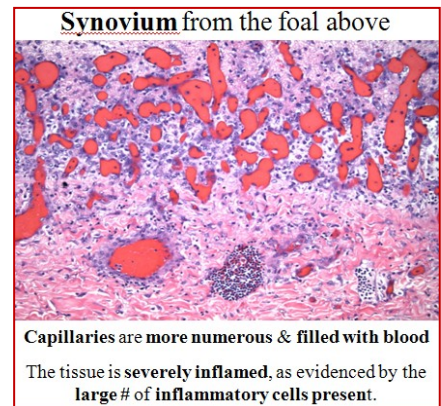
- **Gross Appearance** of Hyperemia

- o Tissue is **bright red**
- o **warm** to touch
- o often **pulsating**




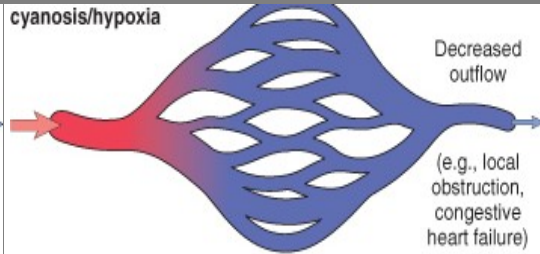

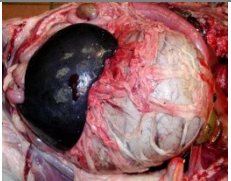
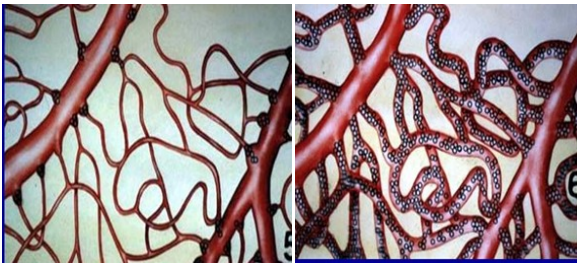
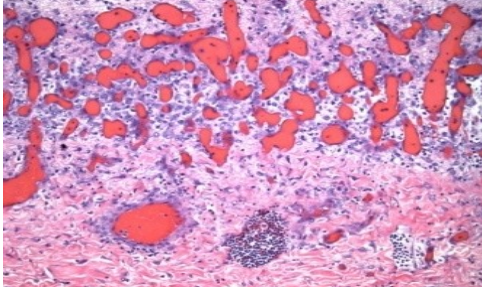
- **Microscopic Appearance** of Hyperemia

- o Arterioles & capillaries are dilated and filled with blood
 - may appear more numerous
- o If the cause is inflammatory (usually is), other morphologic features of inflammation may also be present
 - **Inflammatory cells**
 - **Necrotic cells**



ii. Congestion: Presence of an abnormal amount of fluid in the vessels or passages of a part of an organ

- **Passive Process** resulting from impaired outflow from a tissue
 - o Interference with venous drainage
 - May be systemic as in heart failure
 - May be local due to isolated venous obstruction
 - o Tissue has a **red-blue color (cyanosis)** due to the accumulation of deoxygenated blood
 - o diminished outflow leads to a capillary bed swollen with deoxygenated venous blood and resulting in cyanosis.
- The diagram illustrates a capillary bed where the outflow is obstructed, leading to congestion. The text 'CONGESTION cyanosis/hypoxia' is written above the capillary bed. An arrow labeled 'Decreased outflow' points away from the capillary bed. Below the diagram, it says '(e.g., local obstruction, congestive heart failure)'.
- **Causes of Congestion**
 - o **Heart failure** (generalized slowing of blood everywhere)
 - Left heart failure – blood backs up in the **lung** 1st → lung most affected (**chronic pulmonary congestion**)
 - Right heart failure – blood backs up in the **liver** 1st (**chronic passive congestion**)
 - o **Venous occlusion** (localized) – thrombus, pressure, twisting
 - o **Hypostasis** – hypostatic congestion (where blood pools on the downside of an animal)
 - **Gross Appearance of Congestion**
 - o Tissue is **bluish** in color (blood is stagnant), slightly **swollen**, cool to the touch
 - o ex. **Acute gastric dilatation and volvulus** in a **Great Dane** dog.
 - **Overeating** → **gastric dilation**
→ **accumulation of gas** in the **stomach**
 - The stomach has rotated clockwise and taken the spleen with it.
 - Venous return to both organs is occluded, but some blood continues to flow in, allowing the spleen to fill with blood
- The photograph shows a surgical view of a dog's abdomen. A large, dark, distended stomach is visible, along with a spleen that appears to be rotated and filled with blood. The caption reads: 'Acute gastric dilatation and volvulus in a Great Dane dog. The stomach is filled with air, & the spleen is filled with blood.'
- **Significance & effect of Chronic Congestion**
 - o **Anoxic injury** (stasis of blood with no new blood coming in)
 - Atrophy (cell death and shrinking)
 - Fibrosis or Scarring
 - o **Thrombosis** – expected because of decreased blood flow (clots)
 - o **Edema**
 - o **Hemosiderin deposition**
 - **Types of Congestion**
 - o **Hypostatic** congestion:
 - blood pooling in organs & tissues on the lower side of a recumbent animal
ex. sitting for a while → blood pools in lower half → stand up fast → dizzy b/c not enough blood flow
 - contrast to livor mortis which is a post-mortem change
 - o **Chronic passive** congestion:
 - Caused by any disease that results in **right heart failure (RHF)**
 - o **Chronic pulmonary** congestion:
 - Caused by any disease that results in **left heart failure (LHF)**

	Hyperemia (too much blood flow in)	Congestion (not enough blood flow out)
Commonality	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.	
Depiction	<p>erythema</p>  <p>Increased inflow (e.g., exercise, inflammation)</p>	<p>cyanosis/hypoxia</p>  <p>Decreased outflow (e.g., local obstruction, congestive heart failure)</p>
Description	<p>↑ inflow</p> <p>→ engorgement with oxygenated blood (engorgement is usually associated with an acute inflammatory process)</p> <p>→ resulting in erythema</p>	<p>↓ outflow</p> <p>→ a capillary bed swollen with de-oxygenated venous blood</p> <p>→ resulting in cyanosis.</p>
Gross	 <ul style="list-style-type: none"> - Tissue bright red - warm to the touch - often pulsating 	 <ul style="list-style-type: none"> - Tissue is bluish in color (blood is stagnant) - cool to the touch - slightly swollen
Histology	 <p>difficult to distinguish; vessels FULL of blood in both</p>	
Microscopic	 <p>(Blue dots are the inflammatory cells)</p>	

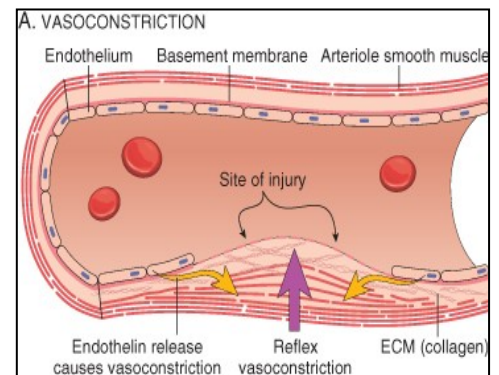
3) Clot forming Processes (Hemostasis, Hemorrhage, & Thrombosis)

i. Hemostasis: physiologic process stopping the movement of blood

- **Normal hemostasis:**
 - o The **circulatory system** must be **self-healing** to prevent life-threatening injury
 - o **Bleeding is rapidly stopped** by a process called **hemostasis**
 - o Hemostasis occurs via a complex interaction of **endothelium, platelets,** and the **coagulation cascade**
 - These processes maintain blood in a fluid, clot-free state in normal blood vessels
 - They can also induce a rapid and localized “**hemostatic plug**” at the site of vascular injury
 - **Anticoagulant** activities also occur to **limit the extent** of the “plug”...process of **fibrinolysis**
- **Pathogenic hemostasis**
 - o **Thrombosis** : The **pathologic opposite** to **hemostasis**
 - o Considered to be an **inappropriate activation** of normal hemostatic processes
 - o Formation of a **blood clot (thrombus)** in **uninjured vasculature**
 - o **Thrombotic occlusion** of a vessel after relatively minor injury
- **Sequence of events with Vascular Injury**

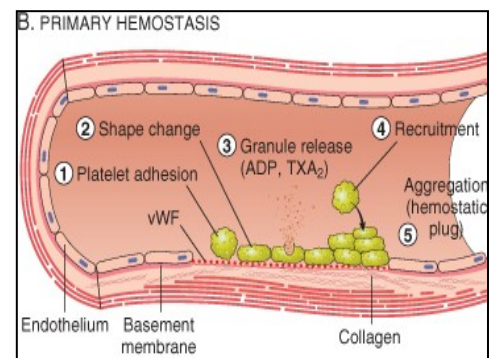
1. Vasoconstriction

- **Transient arteriolar vasoconstriction** after initial endothelial injury that **exposes collagen** of the subendothelial matrix (ECM)
- Vasoconstriction due to **local nerve reflex & release of endothelin** by endothelial cells
- Vasoconstriction helps immediately **limit escape of RBCs & proteins** from damaged areas
- Basement membrane is not completely intact (if it were then the collagen couldn't escape)



2. Primary hemostasis

- (1) **Platelets adhere** to **exposed ECM** via von Willebrand factor
- (2) **Platelets** undergo **activation** (change shape)
- (3) **Platelets** release **secretory granules**
 - Granules contain ADP & thromboxane₂
 - **vasoconstriction** & promote further platelet aggregation
- (4) Form **primary hemostatic plug**
- (5) vWF is released immediately from adjacent endothelial cells
 - aids platelet binding to collagen that is exposed below



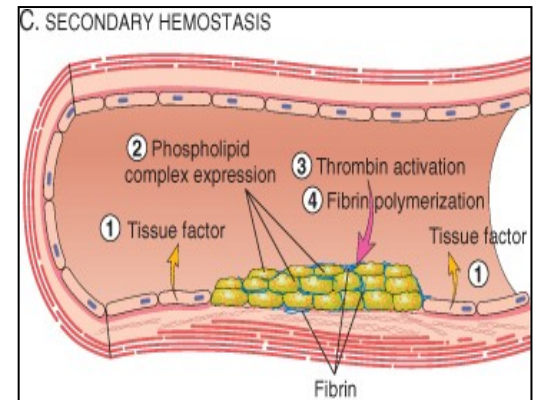
- **Sequence of events with Vascular Injury** (continued...)

3. Secondary hemostasis

- Local activation of the coagulation cascade
 - o **Tissue factor (thromboplastin)** is secreted by adjacent endothelial cells
 - o Thromboplastin initiates the clotting cascade

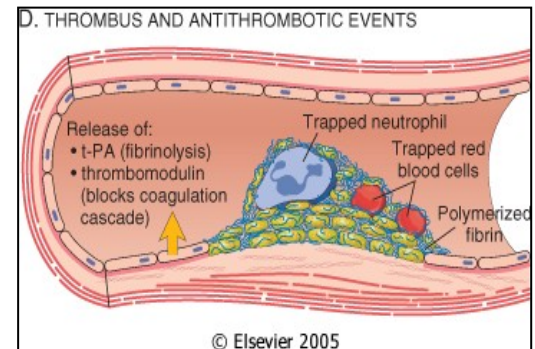
4. Reorganization and formation of a permanent “plug”

- Secondary hemostasis results in **fibrin polymerization** & “**cementing**” platelets into a definitive secondary plug



5. Counter-regulatory mechanisms

- Must know when to stop clotting
- Release compounds that limit the hemostatic process to the site of the injury
 - o **Fibrinolytic** tissue type plasminogen activator (**t-PA**)
 - o **thrombomodulin** interferes with the clotting cascade & actually stops the clotting cascade when it gets to a certain point

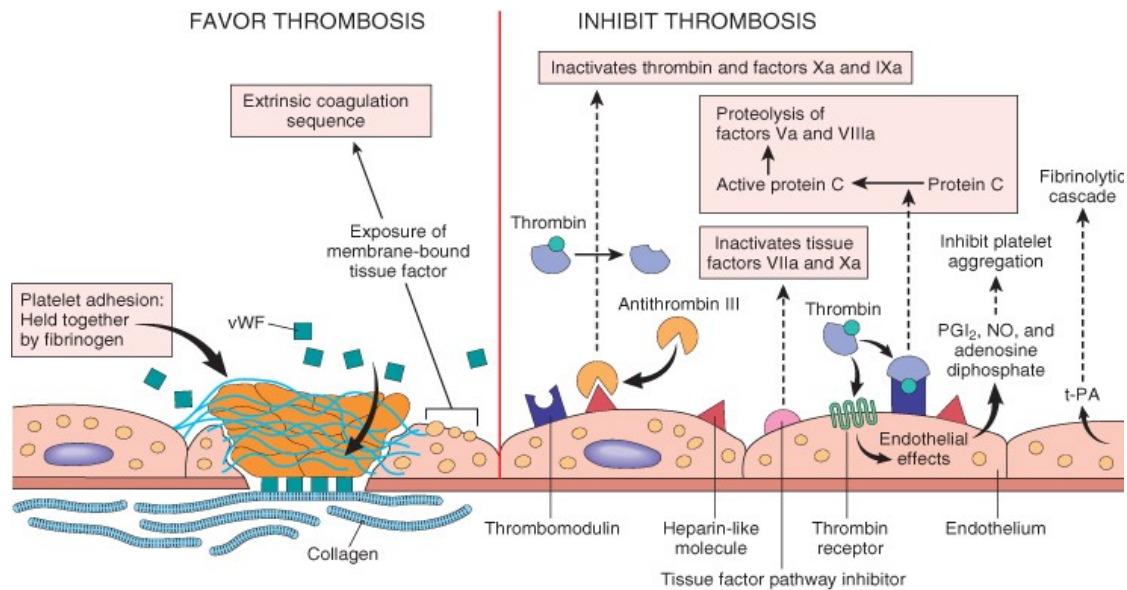


- **Thrombosis**

- o **Formation of a blood clot (hemostatic plug)** due to either inappropriate activation of normal hemostasis or formation of a clot in a vessel after injury
- o Can also be due to other abnormal processes that can block a blood vessel & lead to death
- o **Fibrinolysis** is the process of limiting the hemostatic process at the site of injury
 - Includes the release of tissue plasminogen activator (t-PA) & thrombomodulin by adjacent endothelium

- **Properties of Endothelium**

- o **Endothelium** = cells that line blood vessels
- o **Antithrombotic properties**
 - Normally acts as a barrier between blood and subendothelial collagen
 - Block platelet aggregation
 - Interfere with coagulation cascade
 - Actively lyse clots
- o **Prothrombotic properties**
 - Injury or activation of endothelial cells can → procoagulant phenotypes that augment local clot formation



- Antithrombotic Properties of Endothelium

o Antiplatelet effects

- **Inhibit platelet aggregation**
- Intact endothelium prevents platelets & coagulation factors from meeting the highly thrombogenic subendothelial ECM
- Non-active platelets do not adhere to the uninjured endothelium
- Activated platelets are inhibited from adhering to surrounding uninjured endothelium by endothelial prostacyclin (PGI₂) & nitric oxide (NO)
 - Potent vasodilators and inhibitors of platelet aggregation
- Endothelial cells also express **ADPases** (ADP is needed for platelet aggregation)

o Anticoagulant effects

- Inhibit blood coagulation
- Heparin-like molecules (**cofactors**) from endothelium act indirectly with & inactivate several coagulation factors (thrombin, factors IXa, Xa, XIa, and XIIa)
- Thrombomodulin from endothelium also acts indirectly, binding to thrombin & converting it from a procoagulant to an anticoagulant
- Major source for tissue factor pathway inhibitor
 - a cell surface protein that complexes with & inhibits several proteins of the clotting cascade (tissue factors VIIa and Xa)
 - Makes sure that clots form & stay in the damaged area where they are needed

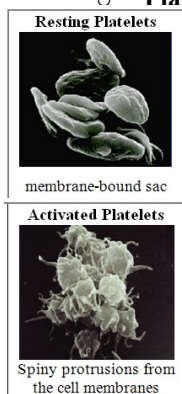
o Fibrinolytic effects

- Endothelial cells synthesize tissue-type plasminogen activator (t-PA)
 - Promotes fibrinolytic activity
 - Clears fibrin deposits from endothelial surfaces

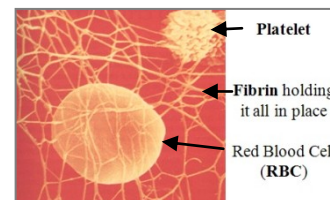
- Properties of Platelets

- Play a central role in **normal hemostasis**
- Smallest components of mammalian blood (diameter 2-4 μm)
- They are not cells; Membrane-bound smooth discs with no nucleus (when non-activated)
- Originate from bone marrow megakaryocytes as the end products of cytoplasmic and membrane protrusions
- Their surface has several glycoprotein receptors called integrins that bind to exposed collagen
 - vWF acts as a bridge between integrins and exposed collagen \rightarrow process called adhesion
- **After vascular injury**, platelets encounter ECM constituents normally sequestered beneath an intact endothelium
 - Collagen (most important)
 - Proteoglycans
 - Fibronectin
 - Other adhesive glycoproteins
- On contact with ECM, platelets undergo 3 **general reactions**:
 - Adhesion and shape change
 - Secretion (release reaction)
 - Aggregation
- Contain two types of granules
 - **Alpha granules**
 - Express the adhesion molecule P-selectin
 - contain fibrinogen, fibronectin, factor V, factor VIII, vWF, PDGF, TGF- β
 - **Dense bodies**
 - A.k.a. delta (δ) granules
 - contain ADP, ATP, ionized Ca, histamine, serotonin, epinephrine

○ **Platelet Activation**



- Activated platelets undergo change in shape (exact process remains unknown)
- Secrete **granule contents** (release reaction) and express surface phospholipid complex
- Aggregate (with help of thromboxane A_2) and form reversible primary hemostatic plug
 - Thrombin (from coagulation cascade) binds to surface receptors & binds fibrinogen to integrins on surface
- Contract irreversibly to form secondary hemostatic plug
 - Thrombin converts fibrinogen to fibrin
 - Fibrin “mortars” in place



○ **Thrombocytopenia**

- Lack of platelets (Thrombo=platelet, Penia = deficiency of)

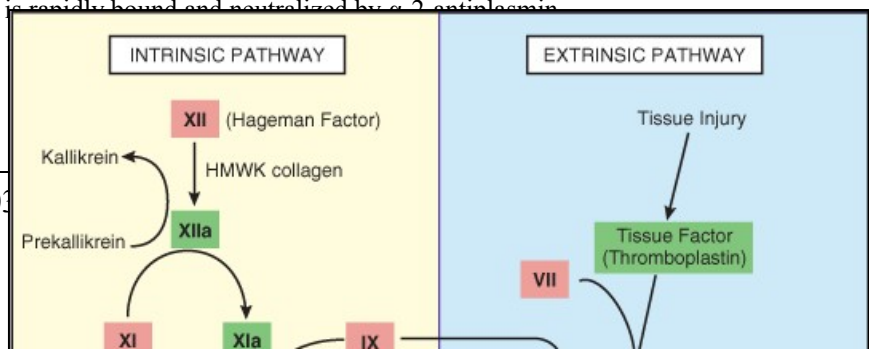
- **Coagulation (Clotting) Cascade**

- **Secondary hemostasis** (3rd component of the hemostatic process)

- Intrinsic & Extrinsic come together to form the Common Pathway
- **Intrinsic** – initiated *in vitro* by **activation of the Hageman factor (factor XII)**
- **Extrinsic** – initiated by **tissue factor** (a cellular lipoprotein exposed at site of tissue injury)
- Artificial *in vitro* divisions
- Note the common link between the pathways at the level of factor IX activation
- A blood clot (**thrombus**) forms through the action of a cascade of proteolytic reactions involving almost 20 different substances
- Most are **liver-synthesized plasma glycoproteins**
- **Major contributor to thrombosis**
- Cascade of enzymatic conversions that turn inactive proenzymes into activated enzymes
- Culminates in the **formation of thrombin**
- Thrombin then converts the soluble plasma protein fibrinogen precursor into the insoluble fibrous protein fibrin
- Each reaction in the pathway results from the assembly of a complex composed of:
 - An **enzyme (activated coagulation factor)**
 - A **substrate (proenzyme form of coagulation factor)**
 - A **cofactor (reaction accelerator)**
- These components are assembled on a phospholipid complex & held together by Calcium ions
 - Calcium must be present for this to occur
 - Clotting tends to remain localized to sites where such assembly can occur
 - e.g. on the surface of activated platelets or endothelium

- Fibrinolysis

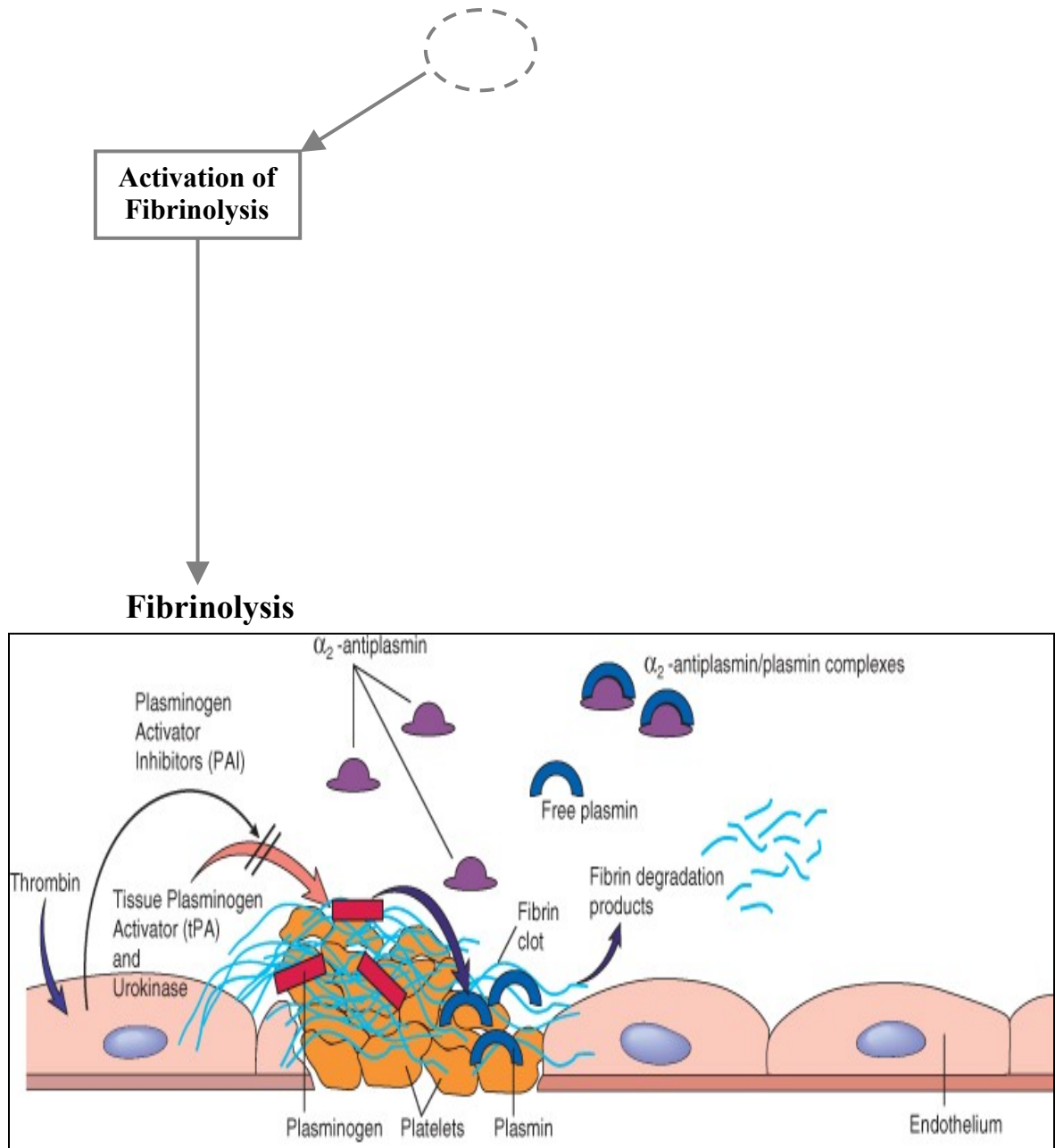
- Besides inducing coagulation, activation of the clotting cascade also initiates the **fibrinolytic cascade** that limits the final size of the clot
- Plasminogen is in circulation and is cleaved to plasmin by tissue plasminogen activator (t-PA)
 - Tissue type-PA is synthesized by endothelial cells
 - Most active when attached to fibrin meshwork
 - Activity is blocked by PA inhibitor (PAI)
- Plasmin breaks down fibrin & interferes w/its polymerization
- The resultant fibrin split products (fibrin degradation products) can also act as weak anticoagulants
 - Elevated levels of these products are measured in clinical labs as fibrin d-dimers
 - Helpful in diagnosis of DIC (disseminated intravascular coagulopathy)
 - Can also degrade fibrinogen
- Any free plasmin in circulation is rapidly bound and neutralized by α₂-antiplasmin



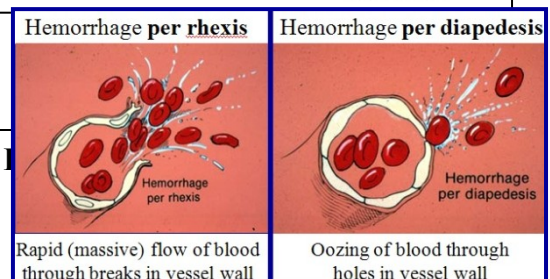
Coagulation Cascade

a.k.a. Clotting Cascade

or Secondary Hemostasis

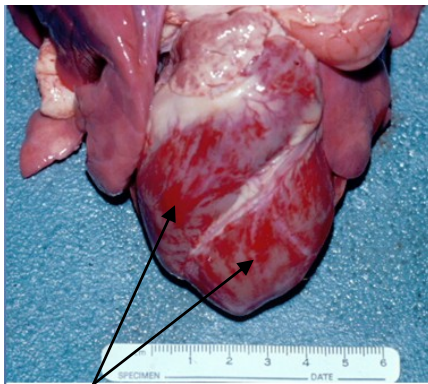


ii. **Hemorrhage**: a large accumulation of blood in a body cavity



- Why are we clotting? To Avoid hemorrhaging
- **Extravasation**: escape of blood from blood vessels
- Hemorrhages are Always **antemortem** (occur before death)
- **Types of Hemorrhages**
 - o **Hematoma**: enclosed accumulation of blood in a tissue (bulging, rounded area of hemorrhage)
 - Can be insignificant (**bruise**)
 - Can cause death (**intracranial hematoma**)
 - o **Petechiae**: 1-2 mm hemorrhage in the skin, mucous membranes, or serosal surface of an organ
 - Associated with locally increased intravascular pressure, thrombocytopenia, defective platelet function, of clotting factor deficits
 - o **Ecchymoses**: 2mm-1cm SQ hemorrhage
 - Associated with same as above, esp. trauma
 - o **Purpura**: >1cm hemorrhage in the skin, mucous membrane, or serosal surfaces of organs
 - Associated with same as petechiation
 - Also trauma, local vasculitis, increased vascular fragility
 - o **Suffusive (Paintbrush)**: hemorrhage along a natural plane
- **Nomenclature of Hemorrhages**
 - **Hemothorax** – blood in thorax
 - **Hemopericardium** – pericardial sac
 - **Hemoperitoneum** – peritoneal cavity
 - **Hemarthrosis** – joint or synovial cavity
- **Fate of hemorrhage**
 - o RBCs are **phagocytized & enzymatically degraded** by **mφ**
 - o **Porphyrin** release from **hemoglobin** produces **color**
Hemoglobin (red-blue) → **Bilirubin (blue-green)** → **Hemosiderin (gold-brown)**
 - o **Clot** – contracts which causes separation of serum from coagulum
 - **Coagulum**
 - Lysed & removed (if small)
 - Can become organized by connective tissue
 - **Serum**
 - Resorbed & removed
 - Form **seroma** (large area of fluid in a tissue)
 - Seromas can be excellent growth media for bacteria
 - need to drain the seroma to avoid the development of a nasty infection
- **Significance, Outcome, & Effect of Hemorrhage**
 - o Depends on the **Rate & Amount** of the hemorrhage

- Slow blood loss → **compensatory** changes
 - If < 1/3 blood volume lost quickly → **possible compensation & survival**
 - **Exsanguination**: rapid loss of a lot (>1/3) of blood lost quickly (min. to hrs) → **Hypovolemic Shock**
- Depends on the **Location** of hemorrhage
 - Brain, pericardium, lungs → **interference** with organ normal function
 - If blood lost slowly, as much as ½ blood volume can be lost over weeks to months & animal is able to compensate
 - **Respiratory Rate (RR)** may increase to help oxygenate better
 - **Hematopoiesis** (making more blood) in bone marrow
 - **Extramedullary hematopoiesis** (making more blood outside the bone marrow)
 - Animals will limit exercise to keep O₂ consumption low
 - May die acutely if over exerted
- **Gross & Microscopic Appearance of hemorrhages**



Multifocal to coalescing petechial to ecchymotic hemorrhages on the epicardial surface of the heart.



- Adrenal glands from a 50 hour old foal
- **Diffuse hemorrhage** throughout an organ
- **Bilateral hemorrhage** throughout both cortices & medullas
- Due to Klebsiella spp.

Urinary bladder from a male cat with urethral blockage

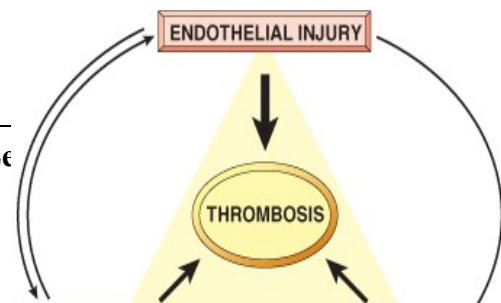


- **Blood** is being **aspirated** from the **bladder** (left)
- Stain from cross-section **won't wash off** (center)
- Hematuria is secondary (2°) to **hemorrhagic cystitis** (which caused the cat's death)

iii. **Thrombosis** : Pathological or inappropriate clotting

- Pathological formation of a clot (**thrombus**) within the cv system

PBS 7003 (VMED 7003 or SVM 3511) | Dr. Lε

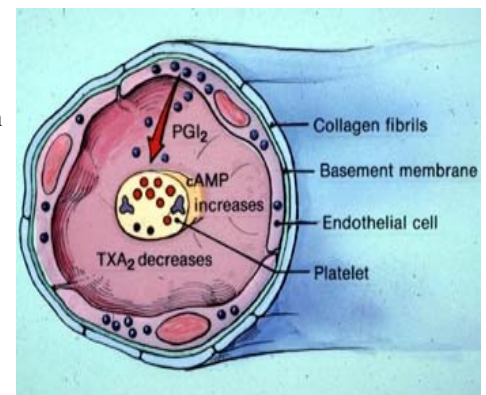


- **May lead to** (or be caused by) interference with blood flow
 - o Turbulence
 - o Stasis

- **Causes of Thrombosis**
 - o **Blood flow slows down**
 - o Change in **blood viscosity**
 - ex. Plasma Blood Tumor
 - o **Loss of vascular endothelial smoothness**
 - ex. cholesterol plaques accumulate → bumpiness
 - o **Hyper reactive states of platelets**
 - Parturition, Sepsis, Surgery, & massive trauma
 - o Proteinuria (renal dz)

- o **Endothelial injury**

- Primary etiology (**primary cause** of most Thromboses)
- Endothelial cell damage & exposure of subendothelial collagen
 - **Vasoconstriction**
 - **platelet adhesion**
 - **aggregation**
 - **activation of the clotting cascade**
- A **platelet plug** is formed
- This plug is often held together by **polymerized fibrin**



- o **Stasis or turbulence of blood flow**

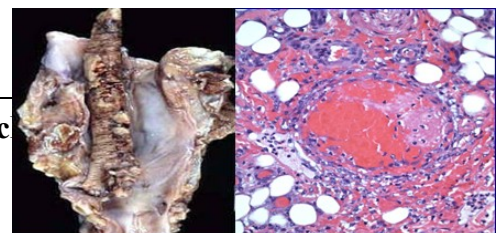
- Turbulence contributes to **arterial & cardiac thrombosis** by causing **endothelial injury** & by forming countercurrent & local areas of stasis
- Stasis is a major factor in the development of venous thrombi
- Stasis & turbulence **disrupt laminar flow** & bring **platelets** into **contact** with **endothelium**
 - Prevents dilution of clotting factors by fresh flowing blood
 - Retards inflow of clotting factor inhibitors

- o **Blood hypercoagulability** (least common)

- In human medicine, defined as any alteration in coagulation pathways that predisposes to thrombosis
- Primary (1°) genetic mutation in factor V gene (not described in vetmed)
 - Affects 2-15% of Caucasian population as recurrent deep venous thrombosis
- 2° (acquired): seen in all species
 - DIC
 - Disseminated cancers – release of procoagulant tumor products
 - Certain glomerular diseases (loss of anti-thrombin III)

- **Types of Thrombosis**

- o **Venous thrombus**



- Located in **jugular vein** of a horse that had received repeated injections in the jugular vein
- Usually occurs at sites with **blood stasis**
- **Extends** in the direction of blood flow (**toward the heart**)

○ **Arterial thrombus**

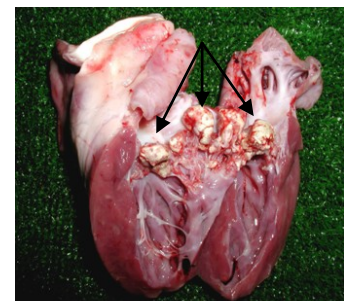
- **Saddle thrombus** in a cat with **cardiomyopathy**
- **Iliac arteries blocked**
→ lead to **lameness** in rear legs; **cold to touch**
- Tend to **grow in retrograde** direction from the point of attachment
- Begin at site of endothelial injury or turbulence (i.e. **vessel bifurcation**)



HCM or dilated left ventricle creates turbulence
→ produces **microthrombi**
→ **saddle thrombi** at vessel bifurcation site

○ **Vegetative thrombus**

- Most common on **mitral** (left AV) valve of the heart
 - Tend to travel in general circulation (**kidneys**)
- Also occur on semilunar and R AV valves
 - Tend to travel to lungs or general circulation
- Mouth bacteria tend to seed in the heart, which is why you may be pre-medicated with antibiotics prior to dental surgery



Mitral vegetative valvular endocarditis in a nursery pig with *Streptococcus suis* bacteremia

○ **Verminous thrombus**

- Caused by parasites
- **Strongylus vulgaris** in the anterior mesenteric artery of a horse
- Leads to loss of blood supply to large intestine (**colic**)
- Decrease in occurrence due to ivermectin administration



○ **Mural thrombus**

- attached to the endocardium

○ **Septic thrombus**

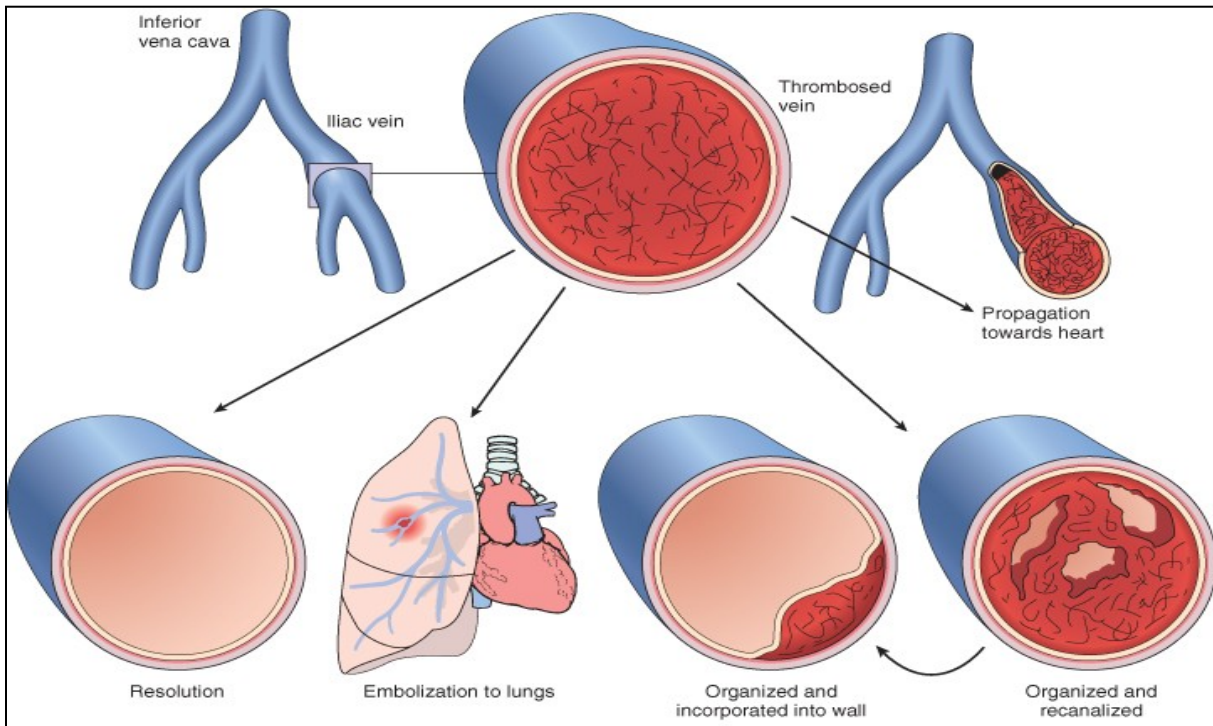
- bacterial colonization of a thrombus
- causes or is a result of bacteremia

- **Outcomes** of Thrombosis (what happens to a thrombosis after it forms)

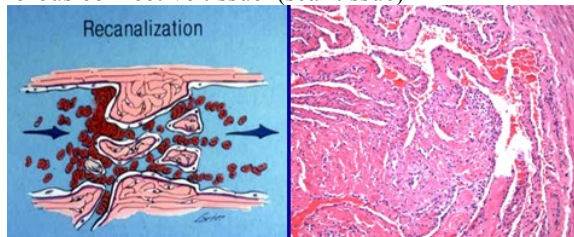
May result in...

- **infarction**
- **passive congestion**

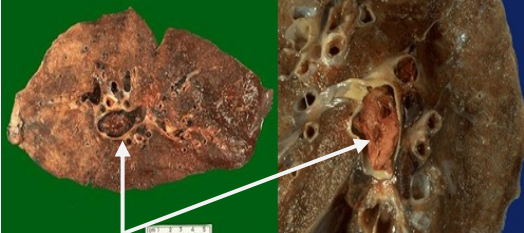
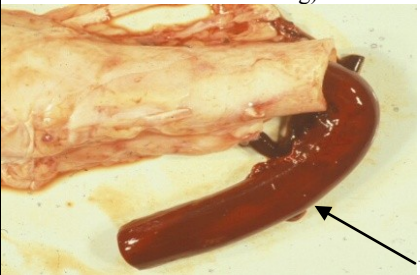
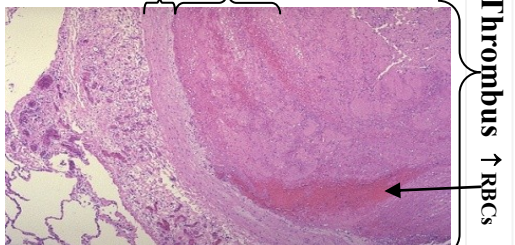
- **embolism** (fragment of thrombus that breaks off & lodges somewhere distal)



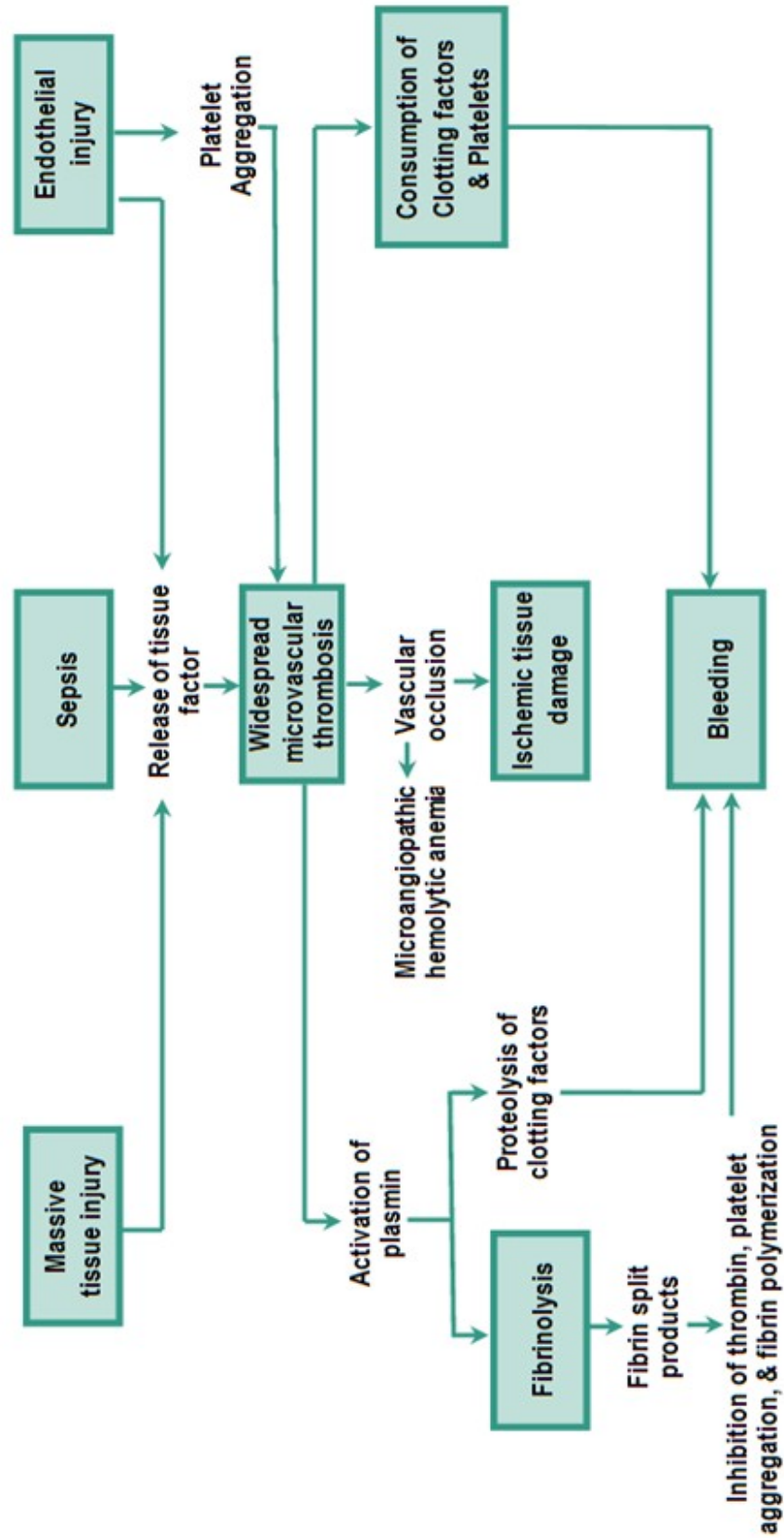
- **Propagation:** thrombus may accumulate more platelets & fibrin leading to vessel obstruction
- **Embolization:** thrombus may dislodge & travel to other sites, forming **thromboemboli**
- **Dissolution/resolution:** thrombi may be removed by **fibrinolytic activity** (drugs available for this)
- **Organization & Recanalization:**
 - May induce inflammation & fibrosis (organization)
 - May eventually become recanalized (re-establish blood flow or be incorporated into a thickened vascular wall)
 - Possible formation of collateral circulation
 - **Recanalization**
 - Thrombus converted to fibrous connective tissue (scar tissue)
 - May contract over time



	Thrombosis	Postmortem (PM) Clots
--	-------------------	------------------------------

Description		when an animal dies, blood clots in vessels & forms a mold in the shape of the vessel (or the heart chamber)
Surface	<ul style="list-style-type: none"> - Dull - Rough, stringy on surface - may not fit vessel 	<ul style="list-style-type: none"> - Shiny - Smooth - molded to vessel
Cut Surface	<ul style="list-style-type: none"> - Granular - Layered - laminations 	<ul style="list-style-type: none"> - Homogenous - Uniform - Shiny & smooth
Consistency	<ul style="list-style-type: none"> - Brittle (crumbly) - Friable 	<ul style="list-style-type: none"> - Resilient - Elastic
Color	<ul style="list-style-type: none"> - Stippled - irregular color - yellow to gray to red - layered with each part different colors 	<ul style="list-style-type: none"> - Current jelly clot – homogenous red - Chicken fat clot – homogenous yellow (plasma)
Attachment	Attached somewhere because it originates from a platelet sticking to vessel wall	Not attached to vessel although may form around valves
Gross	<ul style="list-style-type: none"> - Rough surface - attached to vessel wall - Difficult to remove - Usually pale color (early thrombi may be red) - Due to protein & fibrin  <p>Thrombus (close-up of left image) The surrounding tissue has died</p>	<ul style="list-style-type: none"> - Shiny & gelatinous - Fills entire chamber - Easily Removed - Usually red, but may have yellow plasma near the surface and be red at the base (as RBCs settle before clotting)  <p>PM clot</p>
Microscopic	<ul style="list-style-type: none"> - Attached to vessel wall - Laminations – alternating pale layers of platelets admixed with some fibrin & darker layers (↑ RBC)  <p>wall laminated layers</p> <p>Thrombus ↑ RBCs</p>	

Pathophysiology of Disseminated Intravascular Coagulation (DIC)



4) Ischemia (Emboli & Infarctions)

- **Ischemia**: Loss of blood supply from **impeded arterial flow** or **venous drainage** from a tissue
- Ischemia compromises the supply not only of **oxygen**, but also **metabolic substrates**
 - o **** Glucose** (normally provided by flowing blood)**
- As a result, ischemic tissues are injured more rapidly & severely than hypoxic tissues
 - o because with Hypoxia it is the lack of O₂ that causes cell injury; while ischemia has blocked O₂ & blood flow
- **Causes of Ischemia**
 - o Pressure
 - o Vascular constriction
 - o Thrombi
 - o Thromboemboli
- **Outcome of Ischemia**
 - o Inevitably **all emboli lodge** in **vessels** too small to permit further passage
 - result in partial or complete **vascular occlusion**
 - Typically leads to **infarction** with **ischemic necrosis**

i. Emboli

- **Embolism**: A **detached intravascular** solid, liquid, or gaseous **mass** that is carried by the blood to a site distant

- from its point of origin
- Can be hemic or lymphatic
 - Almost all **emboli** represent some **part** of a **dislodged thrombus** (a.k.a. **thromboembolus**)
 - Unless otherwise specified, an embolism should be considered to be **thrombotic in origin**
- **Types of Emboli**
- o **Rare forms of Emboli (not necessarily thrombotic)**
 - Droplets of fat
 - Bubbles of air or nitrogen (**Benz** disease: when going from areas of higher pressure to areas of lower pressure)
 - Atherosclerotic debris (cholesterol emboli)
 - Bits of bone marrow
 - Foreign bodies such as bullets
 - Tumor fragments (METS; Lung, kidney, liver, brain)
 - Septic emboli (colonies of bacteria flowing in blood cells)
 - Miscellaneous (usually incidental; found in lung; hair, skin, liver cells)
 - o **Common types of Embolism & Thromboembolism in vetmed**
 - **Neoplastic emboli**
(Tumor cells grow into a vessel and flow through blood to a new site where they can develop into a MET)
 - **Fibrocartilagenous emboli** – ruptured intervertebral discs
 - Bacterial (septic) emboli
 - Pulmonary thromboembolism – **venous emboli** (end up in the lung)
 - Systemic thromboembolism – **arterial emboli** (end stage capillaries in an organ)
 - **Lymphatic emboli**
 - draining regional lymph node that can stay local
 - or if it goes to the thoracic duct, ends up in venous system & goes to the lung
 - o **Less Common Types**
 - **Air** – injected via syringe; can be deadly if injected into veins
 - **Fat** – when a bone if fractures, adipose from bone marrow can enter blood stream & cause embolism
 - Fat Emboli arise as a complication of bone fracture, prolonged surgery, or osteomyelitis
 - Seldom cause infarction
 - Gross lesions usually not obvious
 - Microscopically, capillaries in lungs contain small masses of fat
 - Emboli can also lodge in the renal glomerulus (Lipid glomerulopathy, fairly rare in dogs)

Gross & Microscopic depictions of Emboli & Thromboemboli

Venus embolism

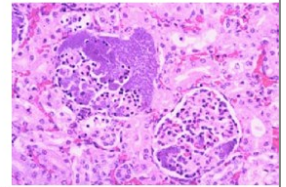
(Pulmonary thromboembolism)

- Embolus is carried to the right heart from the periphery
- Pushed into the pulmonary tree (Heart has pushed embolism out of the lung)
- Obstructs blood flow to the lungs (surrounding lung tissue is dead)
- Results in acute death



Bacterial (Septic) Emboli

- Septic emboli are clusters of bacteria & platelets that are carried by blood and lodge in very small vessels or capillaries
- Kidney glomeruli are a common site
- Usually arise from vegetative valvular left heart lesion

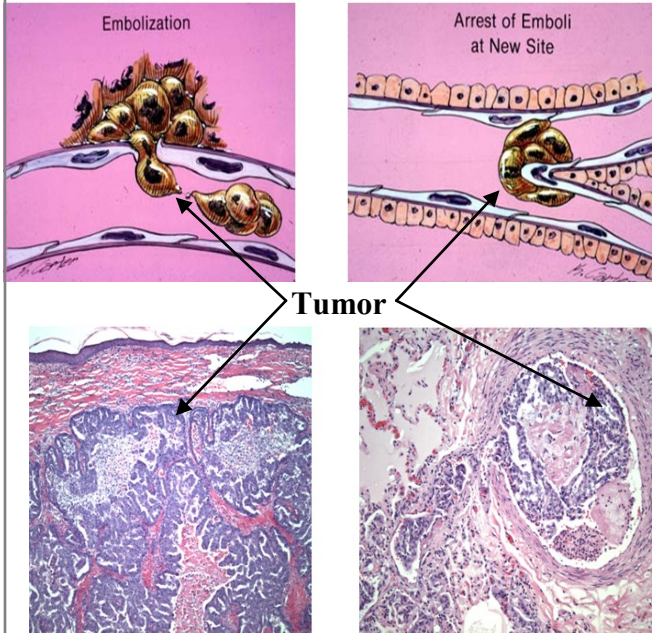


Necrotic foci



Neoplastic Emboli

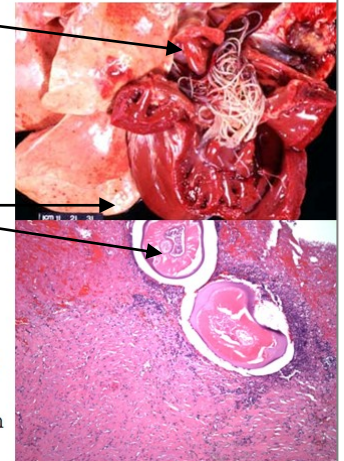
Primary Tumor → metastasizes → Tumor in a new area



Mammary adenocarcinoma from a dog

Parasitic emboli

- Parasitic emboli are pieces of **intravascular nematodes** that break off & lodge at a distant site
- This is a common complication in dogs after therapy for heartworm disease
- Inflammatory cells
- The result would be **verminous pulmonary embolism**
(verminous pulmonary thromboembolism has pieces of a clot in it)

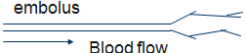



Fibrocartilagenous Emboli

- Emboli frequently from ruptured IV discs
Material from nucleus pulposus may herniate directly into venous sinus or enter small arteries
- Cause spinal cord infarcts
- Seen in dogs, cats, horses
- Emboli wedged in aa or vv of meninges & **spinal cord** causing necrosis of tissue (**necrotizing myelopathy** = necrosis of spinal cord)



ii. Infarction

- Ischemic necrosis of tissue caused by occlusion of either the arterial supply or the venous drainage in a particular tissue
- Most infarcts result from thrombotic or embolic events in arteries 
- Although venous thrombosis may cause infarction, it usually results in venous obstruction and congestion 
 - o Infarcts caused by venous thrombosis are more likely in organs with single venous outflow (e.g. Testis & Ovary)
- **Infarct:** a localized area of anoxic necrosis

- Consequences of infarction

- o All infarcts heal by scarring because all tissue is dead (including the stroma) & there is nothing left to heal
- o Consequences of **ischemia/necrosis**
 - Earliest change is **cell swelling & disintegration of mitochondria**
 - **Loss of energy → cell membrane damage**
 - Allows water, electrolytes, & plasma proteins to leak into cells
 - Increases intracellular Ca → irreversible cytopathic changes & necrosis
 - Cellular enzymes are released into interstitial fluid as the cell dies & starts to kill surrounding cells

- Classification of Infarcts

Infarcts are classified on the basis of their color (which has to do with the amount of hemorrhage)

- o **Red** infarcts – venous occlusion in loose tissue (lung) which allows blood to collect in the infarcted zone & in tissue with dual circulation (small intestine)
- o **White** infarcts– arterial occlusion, solid organs such as heart or kidney
density of tissue limits the amount of blood that can seep into an area of ischemic necrosis
- o **Septic** infarcts– occur when emboli fragment from bacterial vegetation on a heart valve
these infarcts cause inflammation and can spread infection to other tissues

Red Infarct	White Infarct
--------------------	----------------------

- **Venous blockage**
- ↑ **blood** in a tissue
- **thrombus**
- Pervious (loose) tissue
- Lungs
- New
- tends to be red for a few hours

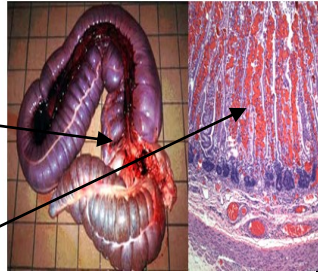
• Caused by obstructed veins



• Necrosis 2° to hypoxia

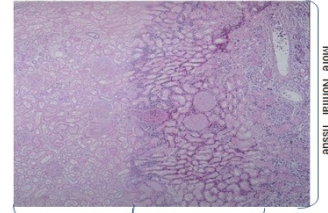
• **Twisted intestine** (colonic torsion) collapses the veins but the more muscular aa allow some blood to be pumped into the area

• Congested red intestines



- **Arterial blockage**
- **no blood** in tissue
- **embolism**
- Dense tissue (heart, kidney)
- not much blood can get in
- Old
- white due to RBC breakdown

Microscopic renal infarct

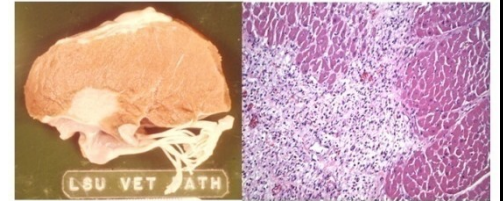
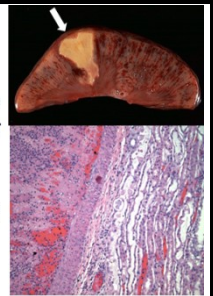


Dead tissue homogenous no tissue architecture

Inflammatory cell hemorrhage

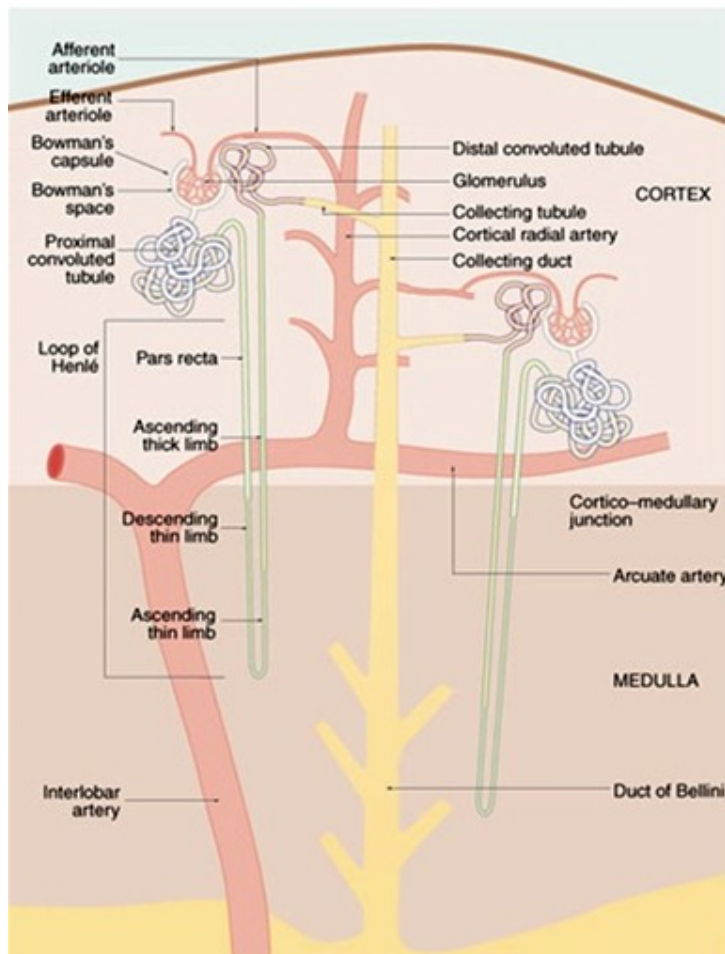
More Normal Tissue

- This is a white infarct in a kidney
- Infarction of arteries have sharp lines of demarcation that delineate the vascular field of that particular artery (often wedge shaped)
- Infarct is at the apex of the wedge
- Conical in shape, with triangular appearance on cross-section



Myocardial infarction in the interventricular septum of a dog

Why infarcts are Cone shaped



5) Shock

- Shock is also known as “**cardiovascular collapse**”
- Failure of the circulatory system to adequately perfuse vital organs
- Characterized by **Hypoperfusion** (**low systemic blood flow**) due to: ↓ **cardiac output** & ↓ **circulating blood volume**
- End results are **hypotension** followed by **impaired tissue perfusion & cellular hypoxia**
- **Types of Shock**

Shock is **classified** based on the **primary general cause** of the shock

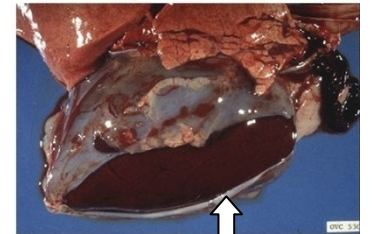
1) **Cardiogenic** shock

- o Caused by insults that reduce cardiac output (↓ hearts ability to pump blood)
 - Cardiac output = HR X stroke volume
 - Anything affecting HR and myocardial contractility can ↓ cardiac output
 - Myocarditis
 - Myocardial degeneration
 - Extrinsic compression (cardiac tamponade)
 - Ventricular arrhythmias
 - Outflow obstructions (pulmonary embolism)

o **Cardiac tamponade**

- occurs when fluid (usually blood) accumulates rapidly in the pericardial space (**hemopericardium**)
- Impedes the ability of the ventricles to dilate and fill with blood
- Will cause acute heart failure and result in cardiogenic shock
- **Tamponade** = compression of the heart due to collection of blood or fluid in the pericardial sac

Cardiac tamponade (Hemopericardium)

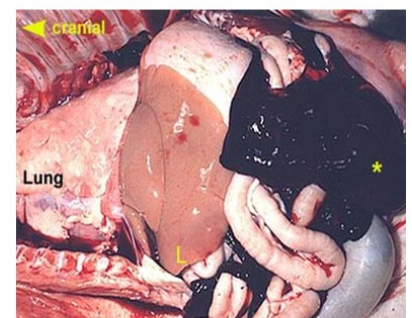


- HBC
- Neoplasia (**hemangiosarcoma** of the right atrium)

2) **Hypovolemic** shock

- o Caused by sudden and severe loss of blood volume
 - **Acute hemorrhage** involving > ¼ to ½ total blood volume
 - blood may be lost to exterior or into body cavity
 - Loss of intravascular & extravascular fluid
 - Secondary to water deprivation, vomiting, diarrhea
 - ↑ **vascular permeability**
 - Leads to loss of intravascular fluid, proteins, blood cells
 - Secondary to infections, toxicities, immune reactions that injure vessels
 - FIP (coronavirus)
 - equine viral arteritis
 - classical swine fever
 - human Ebola virus infection

Hypovolemic shock

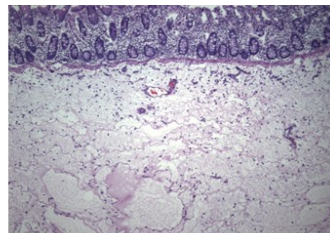


- Dog; HBC; ruptured spleen
- Liver is pale
- there is a large clot around the spleen
- Animal died of hypovolemic shock

- **Types of Shock** (continued...)

3) **Septic shock**

- Results from a bacterial infection (localized or systemic) where large quantities of endotoxin are released into the circulation
 - **Endotoxins** are complex components of bacterial cell walls of gram negative bacteria or breakdown products of cell wall degradation
 - **Lipopolysaccharide (LPS)** is the toxic molecule
 - LPS consists of a toxic FA & polysaccharide coat unique to each bacterial species
 - Analogous components in gram positive & fungi can have same effects
- In **low doses, LPS causes acute inflammation** intended to help eliminate the bacteria
- In **high doses, LPS causes:**
 - widespread endothelial damage
 - Initiation of the coagulation cascade
 - Decreased myocardial contractility
 - Peripheral vasodilation
 - Can lead to irreversible shock and DIC
- **Causes** of events associated with Septic Shock
 - Gram negative bacteria in localized infection (intestine, uterus, bladder, abdomen, pneumonia, etc)
 - Bacterial wall endotoxin (lipopolysaccharide) released in local inflammation
 - Endotoxin enters bloodstream
 - Activates circulating monocytes/macrophages
 - Monocytes/macrophages produce tumor necrosis factor (TNF)
 - Release of cytokines (IL-1, IL-6, IL-8)
 - Systemic vasodilation (hypotension) and systemic inflammatory response
 - Altered myocardial contractility
 - Widespread endothelial damage, platelet activation, coagulation cascade
 - Multiorgan failure
 - DIC
- **Examples** of Septic Shock



- Colic → altered permeability of vasculature → stasis → gram – proliferation
- **Severe colonic edema** in a horse with **endotoxic shock**.
- Fluid has escaped from the vascular system & has pooled in the colon wall
- Endotoxin (lipopolysaccharide) has damaged blood vessels

Hyperemia, blanching, hemorrhage, “toxic” line

- **Types of Shock** (continued...)

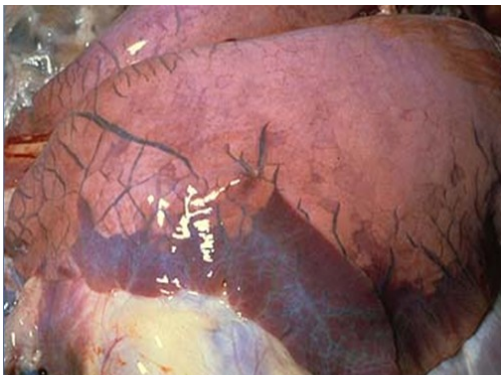
4) Anaphylactic shock

- Systemic manifestation of **acute hypersensitivity** (allergic) response
 - Idiosyncratic reaction occurring in certain predisposed individuals upon exposure to certain allergens
 - Insect stings, foods, medicines (etc.)
 - Upon exposure to antigens, histamine & other mediators are released causing **vasodilation** & increased **vascular permeability** with loss of intravascular fluid
 - Results in eventual cardiovascular collapse

- **Gross & Histologic lesions of Shock**

- Lesions of primary problem
- Systemic vasodilation leads to pooling of blood in various organs (congestion) and maybe hemorrhage
- Liver, gastrointestinal tract, lungs, kidneys and adrenal glands
- Degeneration/necrosis of cells due to hypoxia/anoxia

Gross

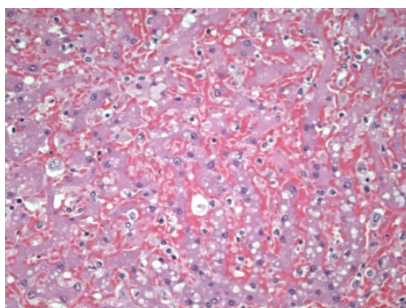


Lung edema & consolidation due to gram negative bacterial pneumonia

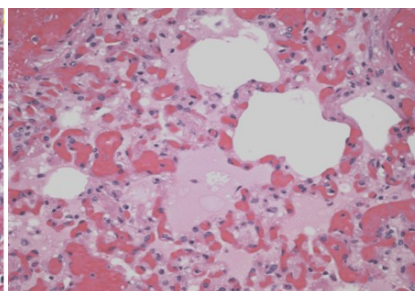


Diffuse (suffusive) hemorrhage in adrenal glands

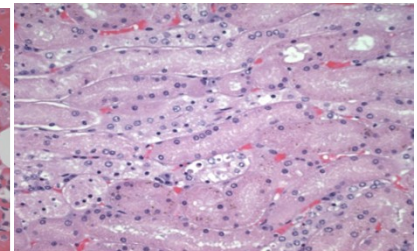
Microscopic



Blood pooling in liver sinusoids (congestion) due to systemic vasodilation



Intraalveolar edema & blood-filled capillaries (congestion)



Multifocal proximal kidney tubule necrosis due to hypoxia/anoxia proximal tubules are highly metabolically active & so require oxygenated blood.

- **Clinical Consequences of Shock**

- Biggest problem → oxygen does not get to cells (anoxia) → multiple organs will eventually fail
 - myocardial damage
 - kidney damage
- Endothelial injury – increased vascular permeability and loss of intravascular fluid
 - Further aggravate hypovolemia and anoxia
 - deplete blood volume and decrease cardiac output
 - Activate platelets and coagulation cascade (thrombosis)
 - depletion of clotting factors
 - hemorrhage with thrombosis (DIC)
- Decreased kidney function and muscle perfusion results in metabolic acidosis
 - Results in even further suppression of cardiac output
- Decreased perfusion of heart muscle causes anoxic injury to myocytes
 - Results in even further decrease in cardiac output

- **Cardiovascular & Systemic Responses to Shock**

- The body responds by attempting to increase cardiac output by shunting blood to vital organs (brain, heart, kidneys)
 - If these adjustments fail and inciting cause is not corrected, uncompensated shock results
 - Microvasculature is unresponsively dilated (end stage vasodilatory shock)
 - Death is the outcome
1. **Cardiac support**
 - epinephrine and norepinephrine from adrenal medulla to increase heart rate
 - aldosterone from adrenal cortex to retain sodium and water, thereby increasing blood volume
 2. **Vascular support**
 - Epinephrine and norepinephrine stimulate vasoconstriction
 - Renin-angiotensin system produce angiotensin II which stimulates vasoconstriction

Inflammation

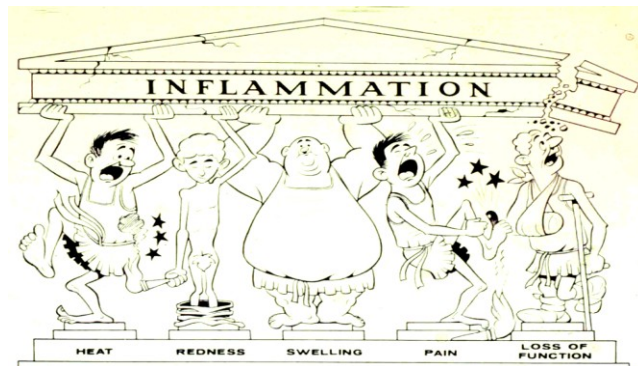
Introduction to Vascular & Cellular Inflammatory Events

Inflammation

- The reaction of living, vascularized tissues to injury
 - Vascular components associated with inflammation
 - Cellular components associated with inflammation
- The goal is to dilute, destroy, or wall off the injurious agent

- 5 Cardinal Signs of inflammation

- 1) **Heat** (Calor)
- 2) **Redness** (Rubor)
- 3) **Swelling** (Tumor)
- 4) **Pain** (Dolor)
- 5) **Loss of Function** (Functio laesa)



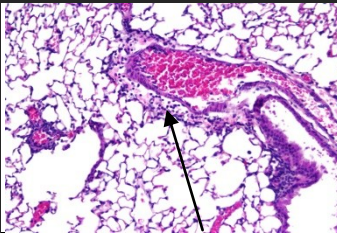



- The Inflammation Top 10


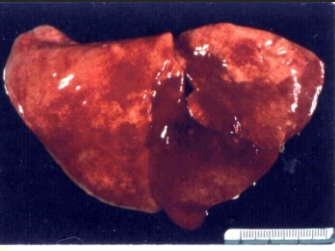


- 1) Inflammation is a good thing
- 2) However, inflammation can be bad
- 3) **Predictable series of events**, multiple participants
- 4) Only occurs in **living tissues**
- 5) **Defensive** mechanism, innate immunity
- 6) A response evoked by **initiating stimulus**
- 7) Fairly **stereotyped response** regardless of initiating stimulus
- 8) The **reactive components** come mostly from the **blood**
- 9) Highly redundant, many mediators
- 10) Sets up healing & specific immunity

- Initiating stimuli of Inflammation

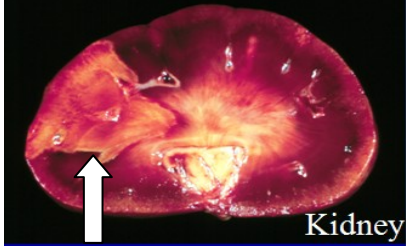

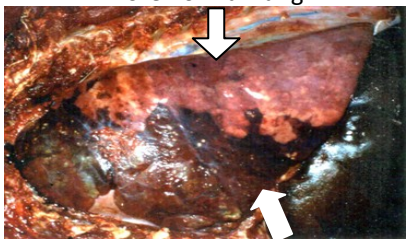
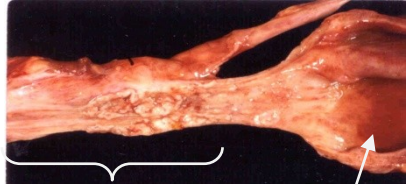

- Infections (bacterial, viral, fungal, parasitic)
- Microbial or other toxins; xenobiotics
- Trauma (blunt or penetrating)
- Physical or chemical agents (thermal, irradiation, caustics)
- Tissue necrosis
- Foreign bodies
- Immune (hypersensitivity reactions)

- **Classification** of Inflammatory Response
 - o **Severity:** how bad is it?
 - o **Duration:** how long has it been going on?
 - o **Distribution:** how widespread/is there a pattern?
 - o **Type of exudate**

Severity of Inflammation			
Minimal	Mild	Moderate	Severe
			
<ul style="list-style-type: none"> - barely discernable histologically - in the above Lung sample, a slight inflammation of the lymphocytes is visible 	<ul style="list-style-type: none"> - little to no tissue destruction & little cellular exudation - grossly detectable only if reddened or swollen - in the above picture, red dots indicate inflammation 	<ul style="list-style-type: none"> - usually some tissue damage - usually grossly visible - cellular exudation & vascular reaction easily detectable histologically 	<ul style="list-style-type: none"> - considerable tissue damage & extensive cellular exudation - easily detected grossly - Inflammation in the above tissue is so severe it is almost not recognizable as lung tissue

Duration of Inflammation			
Peracute	Acute	Subacute	Chronic
			
<ul style="list-style-type: none"> - Min to hours after initiation <p><i>Hallmarks</i></p> <ul style="list-style-type: none"> - Edema (pus filled) - Hyperemia (red) - Possible hemorrhage - Minimal cellular infiltration - Example: hives, urticaria 	<ul style="list-style-type: none"> - hours to 3-5 days after initiation <p><i>Hallmarks</i></p> <ul style="list-style-type: none"> - Edema - Extensive vascular engorgement with possible thrombosis - Fibrin exudation then neutrophils - Lymphatic dilation leading to swollen regional lymph nodes - 5 cardinal signs are very evident 	<ul style="list-style-type: none"> - several (3-5) to many (7-14) days <p><i>Hallmarks</i></p> <ul style="list-style-type: none"> - Minimal edema (pus reabsorbed) - Decreased vascular changes - Change of infiltrating leukocytes from neutrophils to lymphocytes, macrophages, & plasma cells - gradual transformation from acute to subacute & subacute to chronic 	<ul style="list-style-type: none"> - 7-14 days until resolution or death <p><i>Hallmarks</i></p> <ul style="list-style-type: none"> - Angiogenesis - Fibroplasia - Regeneration: clear manifestation of host reparative processes - Inflammatory cells are predominantly macrophages - Possible formation of epithelioid cells & multinucleate giant cells - Also infiltration of lymphocytes & plasma cells
<p>Duration has NOTHING to do with severity & These terms are subjective & vary by case</p>			

- **Classification of Inflammatory Response** (continued...)

Distribution of Inflammation	
Focal	 <p style="text-align: center;">Kidney Single Lesion (White Infarct)</p> <p><u>Focal</u></p> <ul style="list-style-type: none"> - Single lesion - Size not indicated (mm to many cm diameter) - Surrounded by normal appearing tissue - Discrete (easily recognizable)
Multifocal	 <p style="text-align: center;">Kidney Multifocal lesions</p> <p><u>Multifocal</u></p> <ul style="list-style-type: none"> - Scattered to numerous focal lesions - Sometimes modified with “to confluent” or “to coalescing” when foci begin to merge - Widespread (military) - Not diffuse
Locally Extensive	 <p style="text-align: center;">More normal Lung Locally Extensive Lung Inflammation</p> <p><u>Locally Extensive</u></p> <ul style="list-style-type: none"> - Used when a large region of an organ is diffusely involved - <i>i.e.</i> an entire lobe of an organ or confluent anteroventral portions of lungs in bronchopneumonia - <i>ex.</i> Lobar pneumonia shown on the left
Segmental	 <p style="text-align: center;">Inflamed segment of intestine (Stomach)</p> <p><u>Segmental</u></p> <ul style="list-style-type: none"> - Lengthwise portions of a tubular organ diffusely involved & interspersed among relatively normal portions - Primarily used in the intestine
Diffuse	 <p style="text-align: center;">Kidney “Gun Metal Kidney” entire kidney is inflamed</p> <p><u>Diffuse</u></p> <ul style="list-style-type: none"> - All the tissue or organ is involved - Severity may vary across the tissue, but entire organ is involved - <i>ex.</i> Gun Metal Kidney (shown on left) - <i>Note:</i> “diffuse multifocal” is an oxymoron; use “widespread multifocal” or “miliary” if the foci are small to indicate foci throughout a tissue/organ

- **Classification of Inflammatory Response** (continued...)

o **Types of Exudates**

1) **Acute**

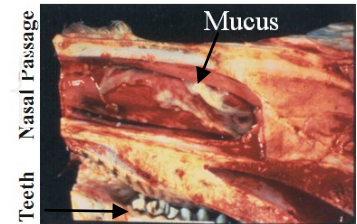
• **Serous**

- Protein-rich fluid exudate
- Inflammatory edema
- From plasma or secreted by serous mesothelial cells
 - Watery-type runny nose
 - Blister (shown here is peracute to acute)



• **Catarrhal**

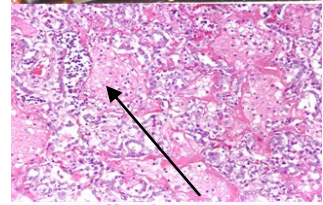
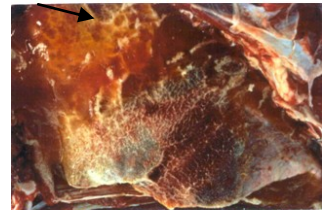
- Inflammation of a mucosal surface which is predominantly characterized by **hypersecretion of mucus**
 - Catarrhal rhinitis
 - Mucoïd enteritis



• **Fibrinous**

- Protein-rich exudate with adequate vascular permeability such that fibrinogen escapes the vessels and polymerizes in the tissue or on a surface to form fibrin
- **Gross** appearance of fibrin:
 - White to yellow, easily broken down, usually adherent mat of exudate on a serous or mucosal surface
 - Flecks to clumps of fibrin are frequently free-floating within fibrin exudates
 - Associated with acute inflammation
 - **Fibrinous pericarditis (shipping fever pneumonia)**, this is fibrinous inflammation of the pericardial sac, often seen in catal

Fibrin on surface of Lung



pink stuff is the fibrin

- *Note:* Beware of fibrous versus fibrinous**
 - **Fibrous** refers to fibrous **connective tissue**, which is a **product of fibroblasts**
It is **tough, white, and chronic**
 - **Fibrinous** refers to **fibrin** & is a **product of the coagulation cascade**
It has **low strength** & is associated with **acute inflammation**
 - fibrin forms the scaffold for fibroblasts to migrate across for wound healing

- **Classification of Inflammatory Response** (continued...)

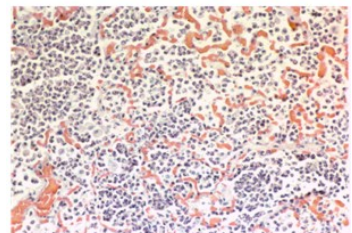
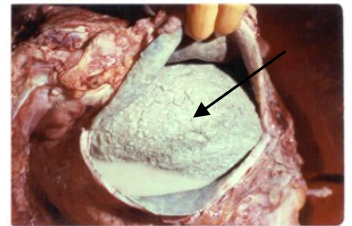
o **Types of Exudates** (continued...)

1) **Acute** (continued...)

• **Suppurative (purulent)**

- **Formation of pus** if the key feature!
- **Neutrophils** are the principle component of pus, along with dead cell, serum, etc.
- Used for all inflammatory processes when neutrophils are the principle cellular infiltrate
- Abscesses are localized accumulations of pus & are frequently surrounded by a connective tissue capsule
- Usually associated with acute inflammation, but may be seen in subacute to chronic inflammation in which there is a persistent inflammatory stimulus (e.g. infectious agent)
- Pure suppurative inflammation is most frequently associated with **pyogenic (pus-forming)** bacterial infections
- Boils, strangles in horses
- **Empyema** – accumulation of pus in a **natural cavity**
- **Phlegmon** – pus accumulated along a **natural tissue plane** (usually referred to as **cellulitis**)

Pericardial Sac with a Suppurative inflammatory reaction

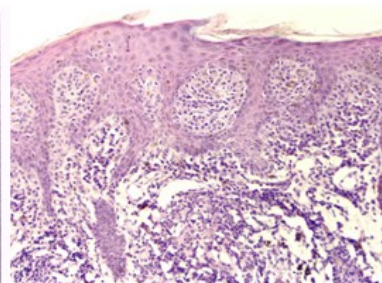


Lung

2) **Subacute**

• **Lymphocytic (lymphoplasmacytic)**

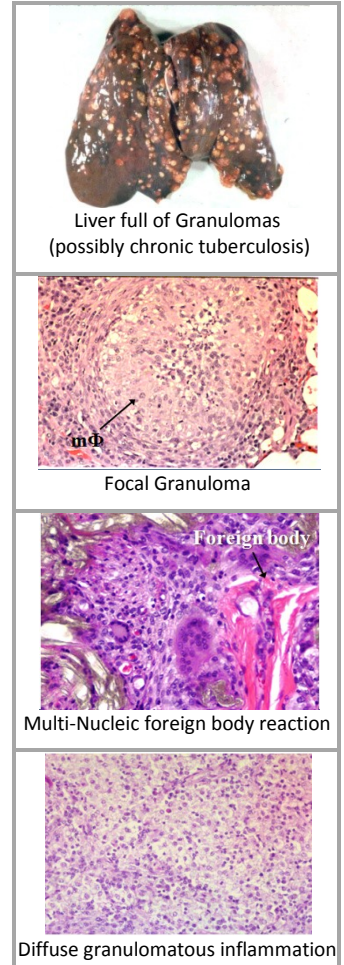
- Characterized by a **nearly pure** infiltrating population of **lymphocytes &/or plasma cells**
- often no gross lesions
- Seen most commonly with immune mediated disease & some viral diseases
 - **Immune mediated diseases:** interface dermatitis
 - **Viral diseases:** lymphocytic thyroiditis, ovine lymphocytic interstitial pneumonia
- ex. German Shorthair Pointer with **lupus erythematosus & pemphigus** (often no gross lesions)



3) Chronic

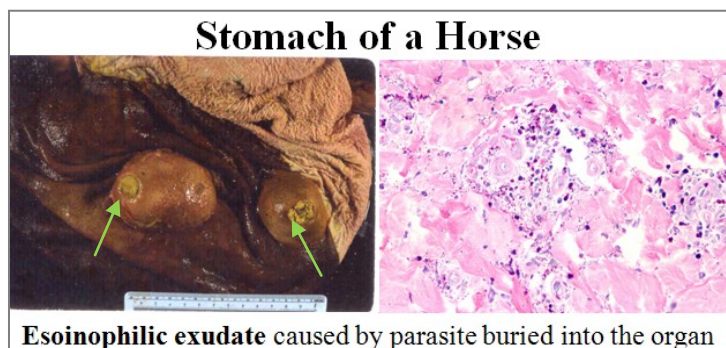
- **Granulomatous**

- Also called “**histiocytic inflammation**”
- Characterized by **macrophage infiltration**
- The primary source for macrophages in **granulomatous inflammation in the blood** via exudation of monocytes which mature into macrophages (mφ)
- These can further differentiate into **epithelioid cells** & merge to form **multinucleate giant cells**
- Some local expansion of mφ is also possible through expansion of resident histiocytes
 - Mφ within tissues can be referred to as **histiocytes**
 - Lymphocytes & plasma cells are nearly always present too
- Granulomas are localized accumulations of mφ usually centered around the causative agent or necrotic debris
- Appear grossly as a mass with or without a caseous center
- Granulomatous inflammation is **chronic** & is usually **accompanied** by **fibrosis** around or within the reaction
- Characteristic of **persistent infectious organisms** such as *Mycobacterium spp.*, fungi, parasites & protozoa also **indigestible foreign material**
- Tumor vs. Granuloma
 - **Tumor**: starts in one cell, that cell then proliferates uncontrollably (cancerous)
 - **Granuloma**: contains lots of cells, but proliferation is NOT uncontrollable (not cancerous)



4) Eosinophillic

- Characterized by **infiltration** of **eosinophils**
- Usually associated with **parasitism** or **allergic disease** & some **fungi** (pithium)
- **Eosinophils** give exudate a **lime green** tint



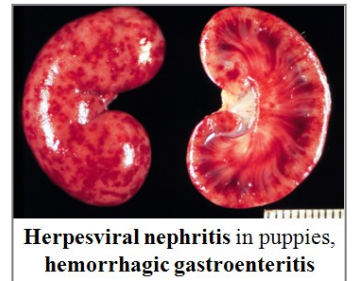
5) Necrotizing / Pseudomembranous

- **Necrotizing:** necrosis is the major feature with little cellular exudation (parvoviral enteritis)
- **Pseudomembranous:**
 - exudate forms a confluent layer of debris over the mucosal surface
 - Seen on mucosal surfaces only
 - **Diphtheritic** refers to a fibrinonecrotic, adherent pseudomembrane which is easily stripped away leaving an intact mucosal surface below



6) Hemorrhagic

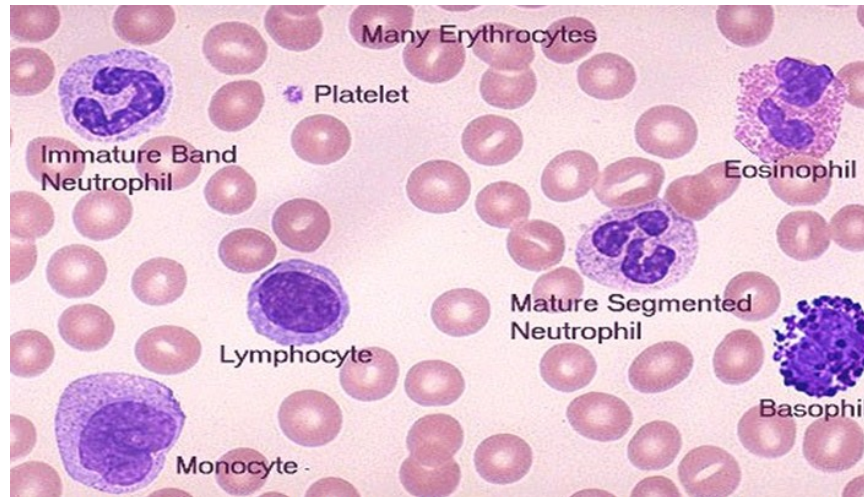
- Is it real?
- **Hemorrhagic exudate** refers to an **inflammatory process** in which **hemorrhage is the primary sign**
- RBCs can not actively exude into an area of inflammation
- **vascular damage** allows the Red Blood Cells to leak into the injured area
- so vascular damage is a prerequisite for this type



7) Combination of Types

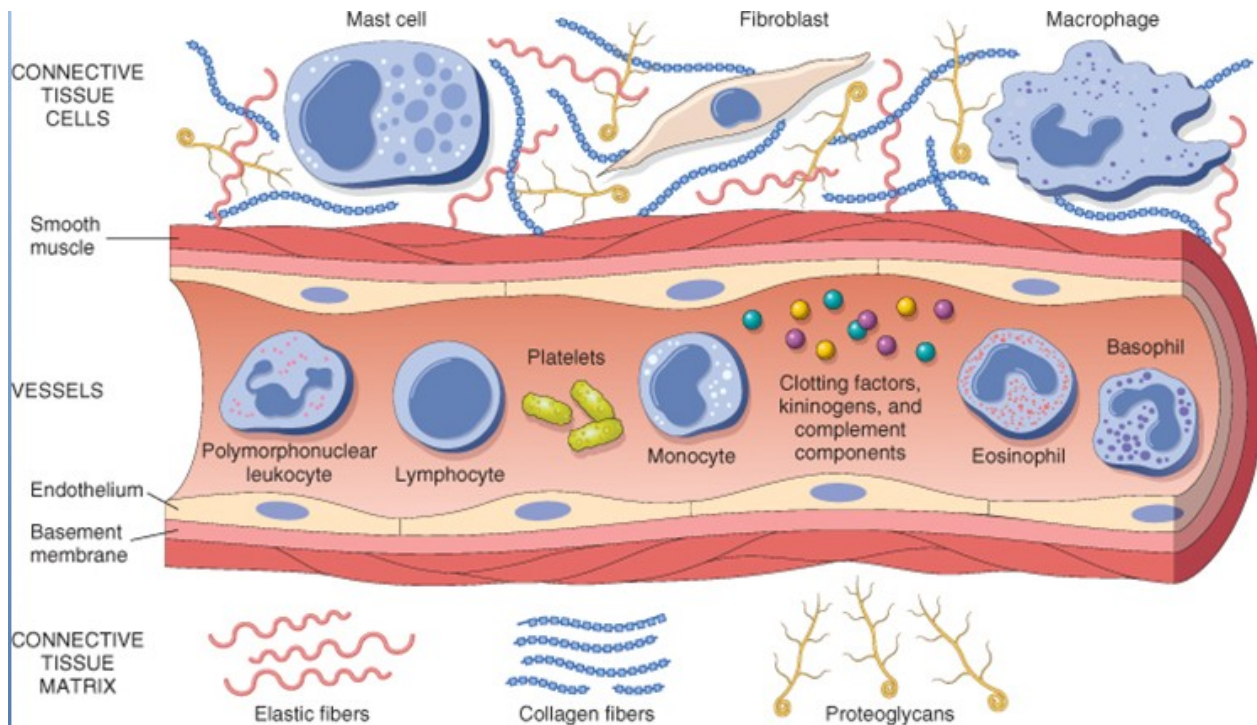
- Named by combining terms with the more acute "process" used as the first prefix
 - **Sero** - serous (e.g. serofibrinous)
 - **Fibrinio** - fibrinous (e.g. fibrinosuppurative)
 - **Muco** - mucooid (e.g. mucopurulent)
 - **Pyo** - suppurative (e.g. pyogranulomatous)

Inflammation Cellular Components of Inflammation










Cellular components **within blood vessel** associated with inflammation

- The **Immature Band Neutrophil** still has a **banded nucleus** because it has been pulled from the bone marrow (to fight infection) before it finished developing
- There are **no Macrophages** in this figure, because mΦ form when the monocytes leave the blood vessel & enter the tissue



The components of **acute & chronic** inflammatory responses: circulating cells & proteins, cells of blood vessels; and cells & proteins of the **extracellular matrix**.

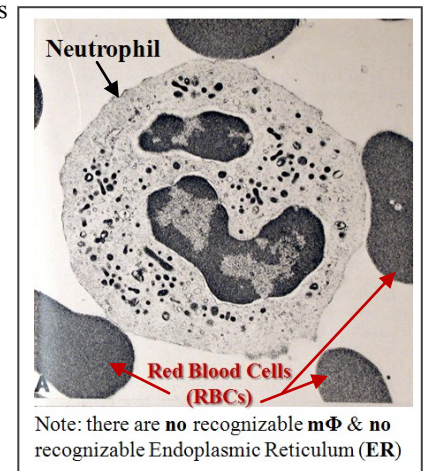
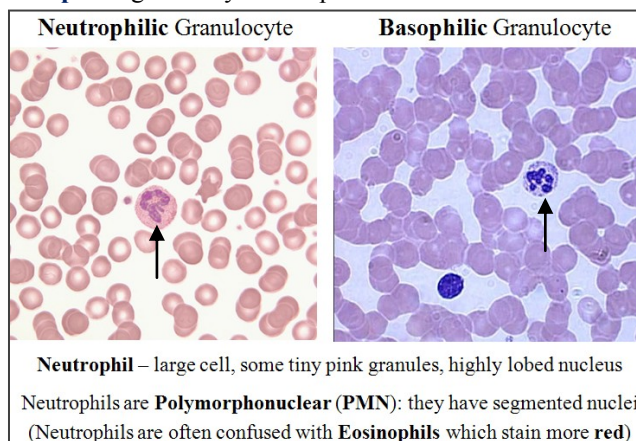
Cell type	Blood conc	Basic function	Major features	Life span
RBC Erythrocyte 	$5 \times 10^6 / \mu\text{l}$, 45% of blood vol.	O_2 and CO_2 transport	biconcave, no nucleus or organelles, 7.5 μm diam.	120 days
Platelet Thrombocyte 	$3 \times 10^5 / \mu\text{l}$	clotting	small cell fragments, granules store mediators of clotting, 2-3 μm diam.	10 days
Neutrophil PMN 	6,000/ μl	phagocytize bacteria, secrete inflammation mediators	multilobed nucleus, azurophil granules (red/purple), pink specific granules (hardly visible) 12- 15 μm diam.	< 1 day in blood, 1-2 days in tissues
Eosinophil 	200/ μl	attack parasites	bilobed nucleus, many large brick red specific granules, crystal inclusions, 12-15 μm diam.	< 1 day in blood, weeks in tissues
Basophil 	50/ μl	cause rapid increases in blood vessel permeability, immediate hypersensitivity	irregularly lobed nucleus, obscured by large deeply basophilic specific granules, 12-15 μm diam.	< 1 day in blood, hours in tissues
Lymphocyte 	2,000/ μl	<u>B cells</u> : differentiate into plasma cells and secrete specific antibodies <u>T cells</u> : recognize cell associated antigens and lyse foreign or virus infected cells, regulate other immune cells	round dark blue nucleus, thin rim of gray/blue cytoplasm, 7-9 μm diam.	years
Monocyte 	400/ μl	become tissue macrophages which scavenge debris, present antigen to lymphocytes	oval to kidney nucleus eccentrically located, chromatin more lacy than in lymphocytes, gray-blue cytoplasm, 12-17 μm diam.	days in blood, years in tissues as tissue m ϕ

- 8 Cellular Components of Inflammation

- | | | |
|---------------------------|-------------------------------|--------------------------|
| 1) Neutrophils | 4) Macrophages | 6) Platelets (revisited) |
| 2) Eosinophils | 5) Lymphocytes & Plasma cells | 7) Endothelial cells |
| 3) Mast cells & Basophils | | 8) Fibroblasts |

1) Neutrophils

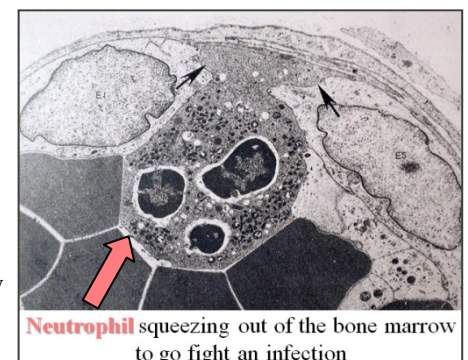
- Short-lived “**professional phagocyte**”: <1 day in circulation & <2 days in tissues
 - One-way ticket when they emigrate
- One of the **granulocytes** named for the **characteristic lack of staining** in mammals
 - **Eosinophilic** granulocyte components stain **Bright Red** with the **Acidic** stain
 - **Neutrophilic** granulocytes stain a **neutral pink**
 - **Basophilic** granulocytes components stain **Dark Blue** with **Basic** stains



- **Equivalent cell: heterophilic** (reptiles, birds, lagomorphs, rodents) granules that stain with **eosin**
- **Polymorphonuclear cell (PMN)** = 10 to 12 mm in diameter with segmented nucleus
- **Active in innate immunity**: major purpose to **phagocytize & release lytic enzymes**
- Involved in **formation of chemotaxins**
- **Major cytoplasmic organelles** are the **granules** that contain **preformed enzymes**
- Due to short life span, there is little need for other organelles, so mitochondria, RER, SER are scarce
- **Glycogen** is the **primary energy source**

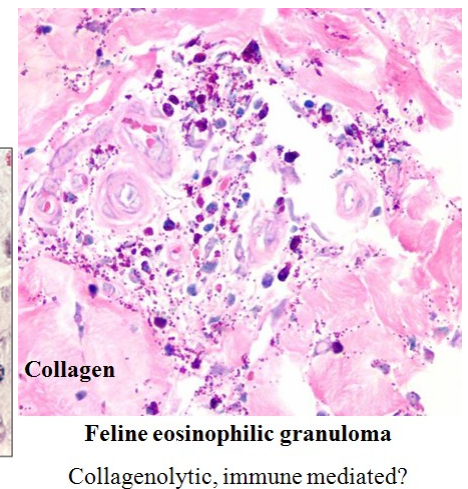
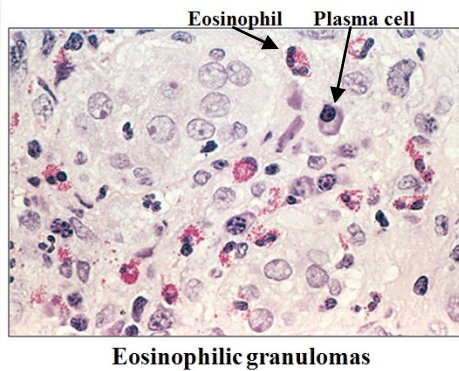
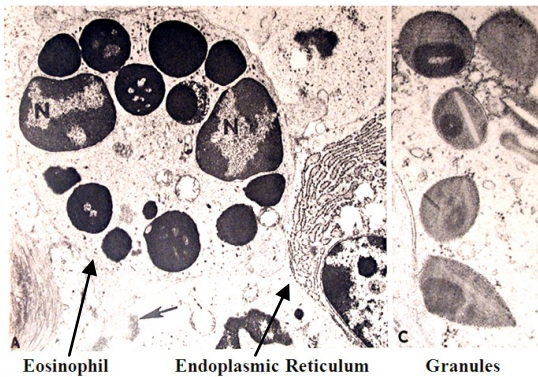
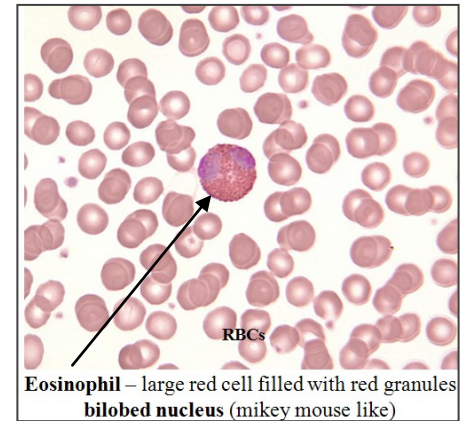
- “Left Shift”

- ↑ **mobilization** of **neutrophils** from the bone marrow
 - the **release of immature forms** (especially **bands cells & occasionally metamyelocytes**)
 - **left shift** (towards predominantly premature neutrophils)
- When immature band neutrophils are seen outside the bone marrow we know there is a serious inflammation occurring because the cells are being rapidly pulled out before they can finish developing in order to fight the infection



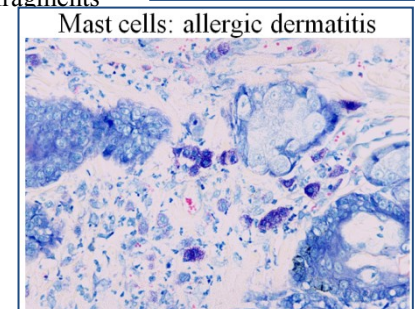
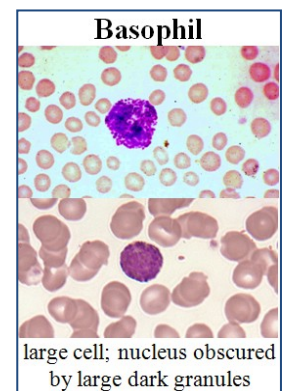
2) Eosinophils

- Second most abundant granulocyte (0.5-5% of circulating WBC)
 - Named for granules (acidophilic; **stain red**)
- Parasites, allergic inflammation, & certain fungal/protozoal infections
- Eosinophils **adhere to & degranulate** to fight off parasites
- Eosinophil release stimulated by IL-5 (also IL-3 and GM-CSF), inhibited by corticosteroids
 - Steroids decrease the overall inflammatory reaction, including the # of Eosinophils
- Eosinophils respond to many of the neutrophil chemotaxins but specifically to eotaxins, a major source of which are mast cells
→ hence prevalence of both Eosinophils & Mast cells in allergic reactions



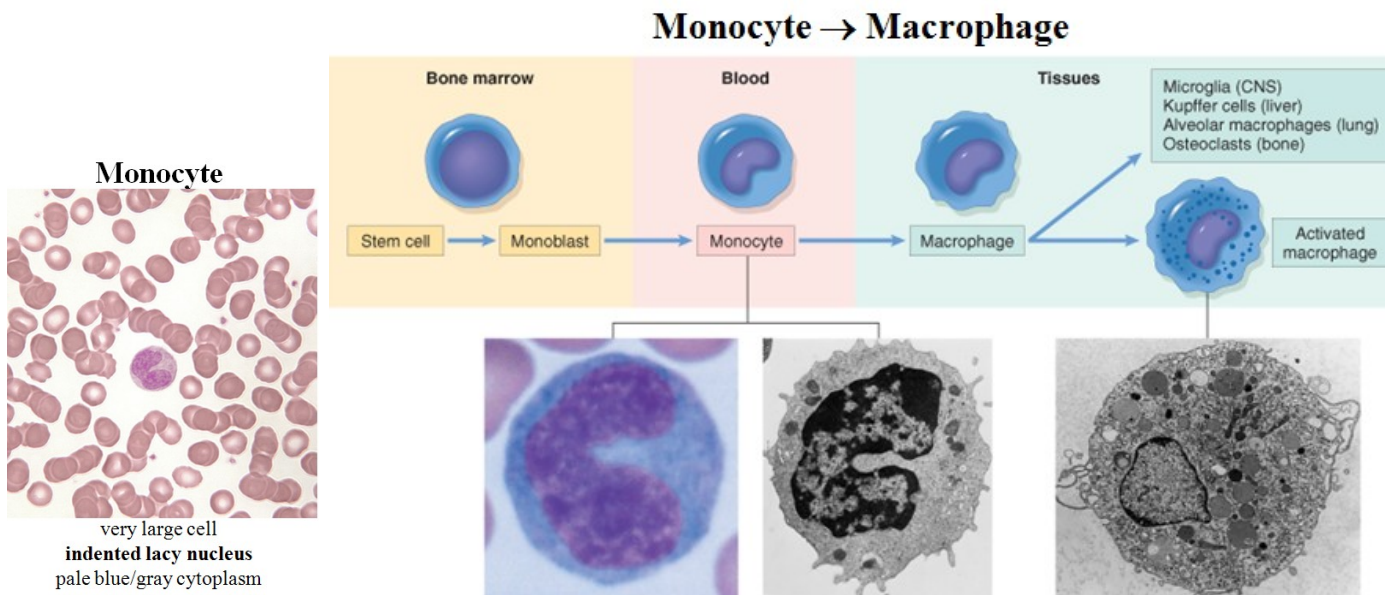
3) Mast cells & Basophils

- Similar function, different location
 - **Mast cells in tissues**
 - **Basophils** are an uncommon circulating granulocyte
- Contain metachromatic granules
- **stain violet** with special histological stains & routine cytological stains
- High affinity receptors for IgE (Fc portion)
- Degranulate rapidly when stimulated by IgE molecules bound to specific antigens
- Also degranulate when stimulated by physical agents, C3a/C5a complement fragments (anaphylatoxins), histamine releasing factors (PMN, mφ), IL-1
- **Mast Cells**
 - Can regenerate granules after degranulation
 - Retain proliferative capacity (can reproduce wherever they are)
 - Different subtypes are found in different locations
 - Usually located around small vessels
 - Most numerous at “contact” sites
 - e.g. Skin, respiratory tract, GIT



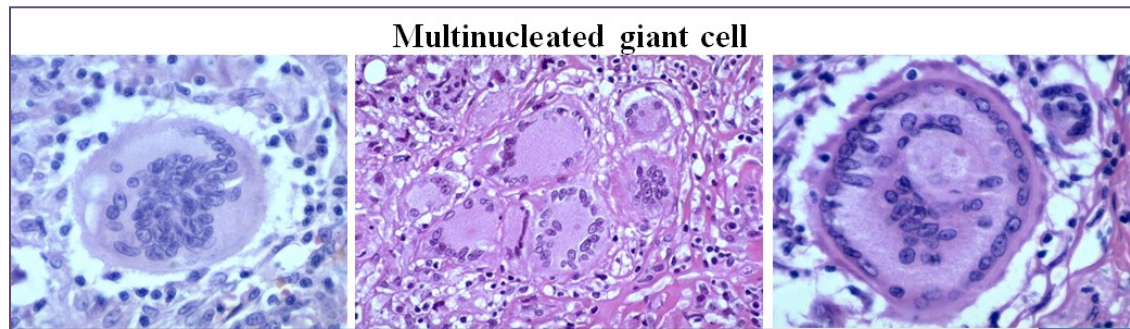
4) Macrophages (mφ)

- **Histiocyte** mφ: **tissue** macrophages
 - Similar to Epithelial & Multinucleate Giant cells, in that they are **activated macrophages**
 - often used synonymously with **alveolar** to refer to macrophages
- **Alveolar** mφ: macrophages within the **aveoli of the lung**, they clean up inhalants (dust, etc)
 - Similar to Epithelial & Multinucleate Giant cells, in that they are **activated macrophages**
 - often used synonymously with **Histiocyte** to refer to macrophages
- **Kupffer cell** mφ: **macropages in the liver** that deal with cleaning up bilirubin & bile
- **Microglia** mφ: macrophages in the **brain & spinal cord**
- **Osteoclast** mφ: macrophages on the **surface of bone**, they reabsorb old bone as the **osteoblasts** make new bone



- 3 categories of compounds associated with **activating macrophages**:
 - **Cytokines**
 - **Bacterial LPS**
 - **Extracellular matrix proteins**
- **Macrophages** have a much **Longer life span** (staying power) than neutrophils but macrophages are **Slower** than Neutrophils
- **Opsonins**
 - Any substance that binds to particulate antigens & induces their phagocytosis by macrophages & neutrophils
 - In both macrophages & neutrophils, opsonins will trigger phagocytosis by binding to specific cell-surface receptors, Fc receptors, & complement receptors on neutrophils and macrophages

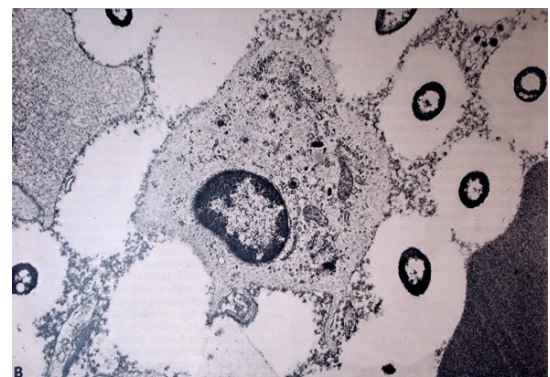
- Fuse to form **multinucleate giant cells** particularly when fighting off a bacterial infection



- Primarily recruited from blood monocytes, but have **local proliferative capacity**
- **Phagocytosis** → ↑ enzyme levels in & numbers of lysosomes, ↑ mitochondria, ↑ endocytosis, & ↑ killing ability
Can be down-regulated (**deactivated**) by TGF-β (TGF-β also stimulates fibrosis)
- Transformation of **macrophages** into **epithelioid** cells
 - More abundant, eosinophilic cytoplasm
 - Less phagocytic, more secretory functions
 - Cell mediated immunity is key — mediators: IFN-γ (and IL-4?) from T-lymphocytes
- Macrophages have receptors for opsonins, (i.e. Fc, C3b, fibronectin), stimulate phagocytosis & activation
- Macrophages (along with dendritic cells) are effective antigen-presenting cells & secrete immunostimulatory cytokines
- Equipped with full armament of reactive oxygen generating enzymes, defensins, & degradatory enzymes (especially neutral proteases) within lysosomes
 - Once macrophage engulfs something, it needs to break it down → uses enzymes for this

Macrophages are key players in the initiation of Specific Immune Responses in infections & inflammatory disease

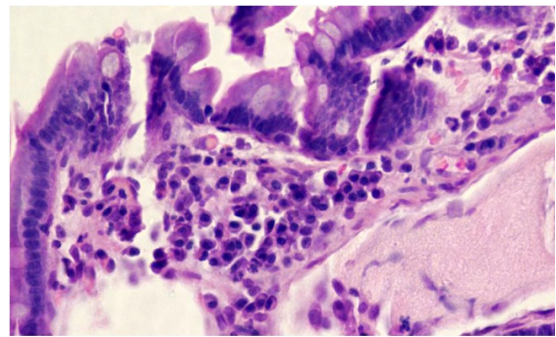
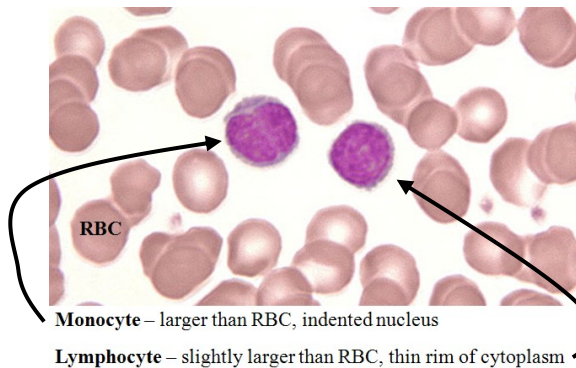
- **Extremely important “professional phagocyte”**
 - Not only infectious agents, but also responsible for removing any type of tissue debris
- **Important mediator cell**, secretes cytokines, chemokines, arachidonic acid metabolites, growth factors, nitric oxide, complement components, etc.



Macrophage ⊕ Anthrax!

5) Lymphocytes & Plasma cells

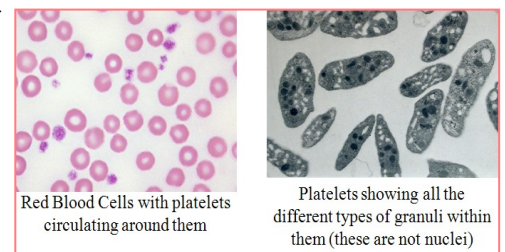
- Immune effector cells.
- Long lived & can recirculate from blood to tissues & back
- B-cells → plasma cells & produce antibody, one of the major opsonins
- **B-cells:** Differentiate into plasma cells & secrete specific antibodies
- **T-cells:** Recognize cell associated antigens & lyse foreign or virus infected cells.
Regulate other immune cells
- Some **lymphocytes** will **non-specifically infiltrate** inflamed tissues using mechanisms analogous to other inflammatory cells, but are **not as motile**.
- Secrete lymphokines (e.g. **IFN-g**, TNF-a, & IL-2), which modulate & expand local inflammatory reactions, especially granulomatous inflammation
 - **IFN- γ** : a very potent Macrophage activator that is secreted by lymphokines



Plasma cells

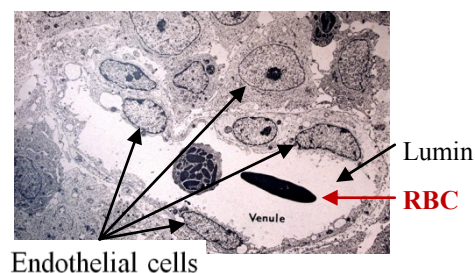
6) Platelets

- Platelets adhere to areas of vascular damage through interaction of adhesion molecules (mostly glycoproteins) to von Willibrand factor. vWF secreted by *EC* and adheres to collagen.
- **Adhesion → degranulation**
 - two types of granules alpha & dense bodies
 - express integrins on surface → platelet to platelet adhesion
 - express P-selectin on surface → neutrophil adhesion



7) Endothelial cells

- Roles in increased vascular permeability
- Role in vasodilation
- Activation by cytokines (IL-1 and TNF α)
- Role in healing



8) Fibroblasts

- Ubiquitous connective tissue cells present in substantial numbers in nearly every tissue
- **Angiogenesis** – leakage of large amounts of plasma proteins (especially **fibronectin & fibrin**) into ECM
- Fibroblasts are stimulated to migrate into site of injury & proliferate
 - Mediated by **growth factors** (e.g. TGF- β^* , FGF, PDGF, Epidermal GF) & cytokines (e.g. IL-1 & TNF-a)
 - Sources include $m\phi$, platelets, endothelial cells, PMN, & fibroblasts
 - **Fibroblasts** are an **autocrine feedback system** (fibroblasts stimulate the production of other fibroblasts)
- Fibroblasts deposit **extracellular matrix (ECM)**
- Fibroblasts also have role in ECM remodeling, secrete metalloproteinases (along with $m\phi$, PMN, epithelial cells.) & specific proteinase inhibitors
- During healing some fibroblasts develop extensive myofibrils that act similar to smooth muscle cells (they can contract) → myofibroblasts
 - these contract simultaneously with collagen deposition and are responsible for wound contraction
 - too much contraction can be detrimental
 - myofibroblasts disappear with completion of healing

Acute Inflammation

○ Vascular Events

● Transient Vasoconstriction

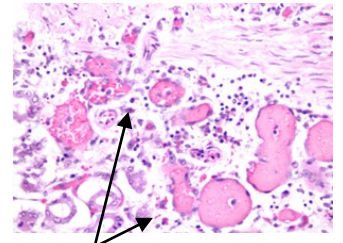
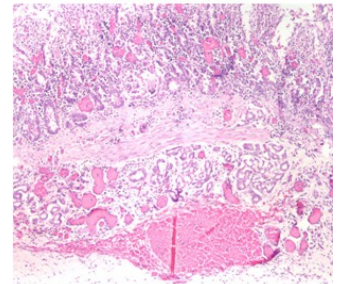
- Not always seen (may or may not occur)
- immediate & lasting only a few seconds
 - ex. Blanching of minor burn (skin turns white before turning red); or delay of bleeding following cut
- Caused by constriction of the **precapillary sphincters**
- Primarily a neurogenic / direct response (endothelin from endothelial cells)

● Vasodilation

- **Increased blood flow**
- starts in arterioles, progresses through capillaries, venules, & veins
- Very consistent
- Responsible for *rubor* (Redness) & *calor* (Heat)
- Caused by relaxation of the **precapillary sphincters**
- Opens capillary beds, frequently overloading venous drainage
- May look like **Venous congestion** under a microscope, but is actually *active hyperemia*

- **Mediators & Primary Sources of Vasodilation:**
 - **Early Phase Mediators**
 - **Vasoactive amines** —
 - Histamine (mast cells)
 - Serotonin
 - **Later Phase Mediators**
 - **Prostaglandins** —
 - PgD, PgE (macrophages); PgE is a pain (*dolor*) inducer
 - prostacyclin (EC) – short acting, rapid action
 - **Nitric Oxide** (macrophages)

Vasodilation

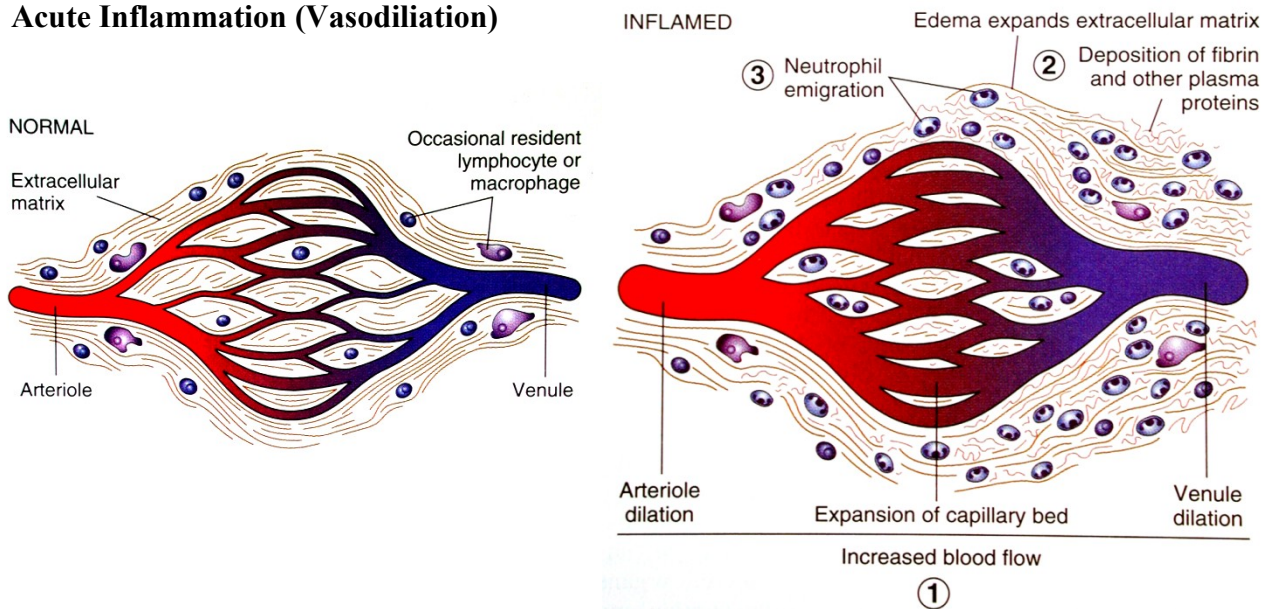


purple dots are inflammatory cells

○ Increased Vascular Permeability

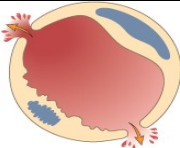

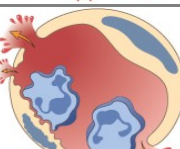
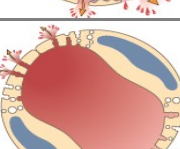
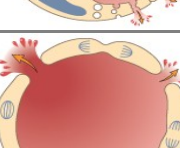
- Progresses from **Transudate** to **Exudate** → **Inflammatory Edema** (*tumor*)
- Some early **leakage of protein-poor fluid** due to increased hydrostatic pressure associated with congestion
- Mediators of inflammation affect the *EC* causing contraction & increased gaps between cells allowing increasingly larger protein molecules to escape
- Primary site of action is in the **venules**
- **Direct damage** can affect any site in the microvasculature, causing **increased permeability**

○ **Acute Inflammation (Vasodilation)**

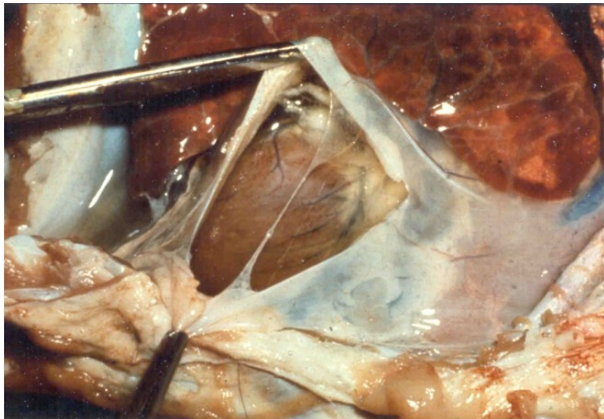


Vasodilation causes increased hydrostatic pressure in vessels → edema leakage (transudate)

○ **Vascular Leakage**

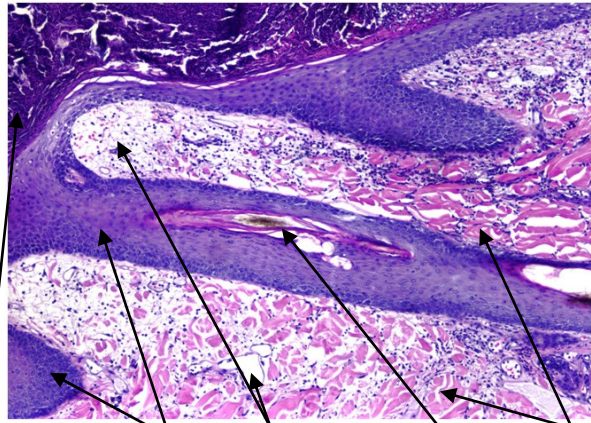
	<p>Gaps due to Endothelial Contraction (most common)</p> <ul style="list-style-type: none"> - Fast & Short Lived (min) - Venules - Vasoactive Mediators (histamines, leukotrienes, etc.) -
	<p>Direct Injury</p> <ul style="list-style-type: none"> - Fast & may be long-lived (hours to days) - Arterioles, Capillaries, & Venules - Caused by Direct Injury by Toxins, Burns, Chemicals -
	<p>Leukocyte-Dependent Injury</p> <ul style="list-style-type: none"> - Late Response & Long Lived (hours) - Mostly Venules - Pulmonary Capillaries - Neutrophils cause local damage → Leukocyte dependent damage to vessel walls
	<p>Increased Transcytosis</p> <ul style="list-style-type: none"> - Venules - Vascular Endothelium – derived growth factor - -
	<p>New Blood Vessel Formation</p> <ul style="list-style-type: none"> - Sites of Angiogenesis - Persists until Intercellular Junctions Form - -

Vascular leak (EC toxic damage)



septicemic leakage of pericardial sac

Inflammatory Edema



Crust (like scab) skin edema (clear) Hair Follicle Collagen (pink)
(collagen should extend all the way to the skin, but edema is there)

○ **Permeability Mediators** (these 6 increase permeability)

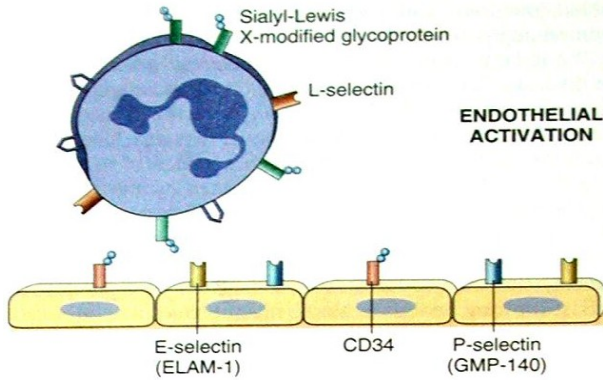
- **Vasoactive amines**
 - Histamine ($m\phi$)
 - Serotonin (platelets)
- **Complement**
 - C3a, C5a (blood)
- **Bradykinin**
 - (blood) also a major pain inducer (*dolor*)
- **Leukotrienes**
 - LTC₄, LTD₄, LTE₄ (leukocytes)
- **Platelet-activating factor (PAF)**
 - EC, leukocytes
 - Important in cytoskeletal reorganization
- **Cytokines** (IL-1, TNF) - $m\phi$

○ **Slowing or Stasis of Blood Flow**

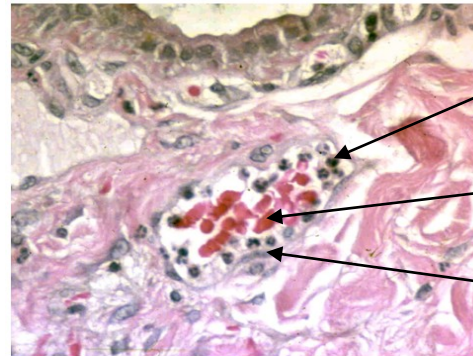
- 2° effect of the combination of vasodilation, ↑ the caliber, ↑ permeability, ↓ the fluid content of the vascular walls
- Causes a loss of laminar flow in the capillaries & allows the margination of leukocyte
(white blood cells are pushed to the sides of the vessel walls)

○ Cellular Events in Acute Inflammation

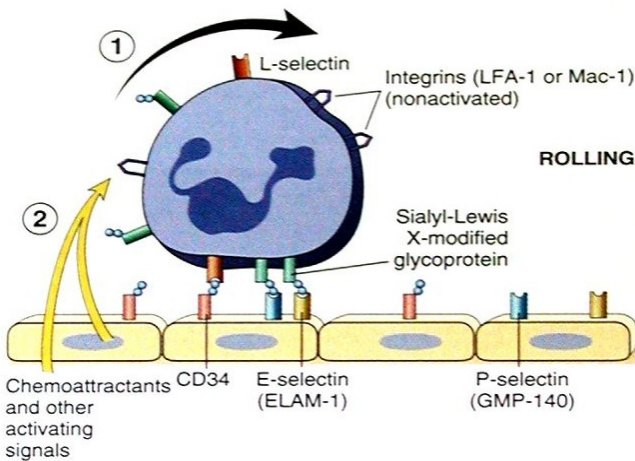
(1) Margination of Leukocytes along vessel wall



- Slowed flow/stasis
→ PMN out of central column of blood flow
- EC & PMNs express transient adhesion molecules (selectins)
- Selectins are preformed, so surface expression is within minutes



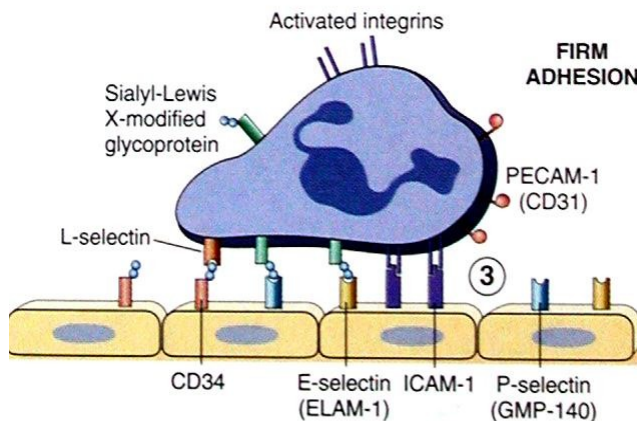
Neutrophil margination



(2) Leukocyte (Neutrophil) Rolling

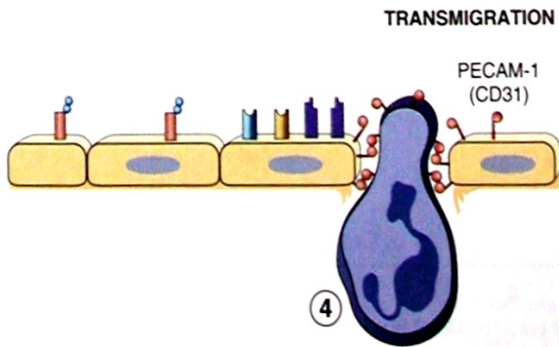
- Caused by loose & transient adhesion
- PMN rolls along EC lining of vessels
- **Mediators:** Histamine, Thrombin, PAF, IL-1, TNF

(3) Firm Adhesion (a.k.a. “pavementing”)

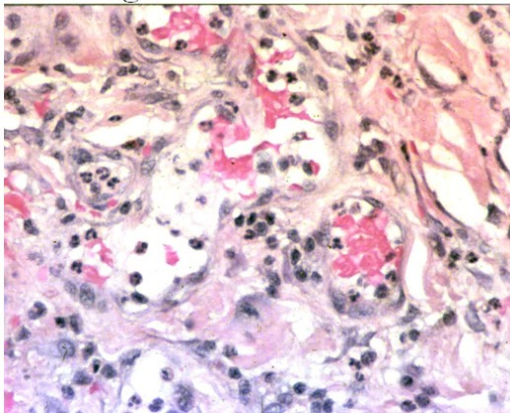


- Requires increased inflammatory stimulus causing up-regulation of endothelial adhesion molecules
- Requires upregulation & activation of integrins on neutrophils
- These molecules are constitutively expressed at low levels, but upregulated by inflammatory mediators, primarily cytokines (takes more time to develop than do the selectins)
- **Mediators**
 - Affecting EC: IL-1, TNF α (m ϕ , injured tissue)
 - Affecting neutrophils: IL-1, TNF α , PAF, IL-8 (TNF = Tumor Necrosis Factor)

(4) Neutrophil Emigration & Chemotaxis



Emigration & Chemotaxis



- Adherent neutrophils, stimulated by chemotaxins, extend pseudopodia through gaps in EC & emigrate into tissues
- **Chemotaxins** cause cytoskeletal reorganization & extension of pseudopodia in direction of concentration gradient of chemotaxins → ameboid movement (crawl)
- P-selectin/PCAM-1 important adhesion molecules in emigration
- Adhesion molecules along EC intercellular gaps (PECAM-1/P-selectin) allow adherence to extracellular matrix proteins in tissues
- BM lysed by collagenase (small opening, may slightly increase vascular permeability)
- usually the opening isn't large enough to allow RBCs to leak out (no extravasation of RBCs)
- This is a one way ticket...once neutrophils leave circulation, they do not return
 - Maximum lifespan is 2 days
 - Much less in active inflammation
- By the same process, neutrophils migrate along the concentration gradient of **chemotaxins** to the site of tissue damage.
- Neutrophils adhere to various extracellular matrix proteins during this process

C

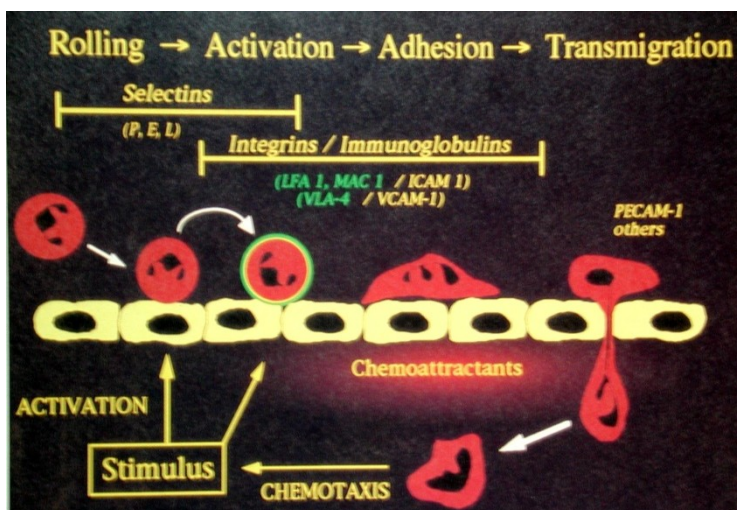
Chemotaxins

Endogenous

- **Chemokines** (mostly from inflammatory cells)
 - a-chemokines (C-X-C) [neutrophils, etc.]
 - IL-8, NAP-2, GRO, etc.
 - b-chemokines (C-C) [WBC other than neutrophils]
 - MIP, MCP, RANTES, eotaxin
- **Other Inflammatory cell derived**
 - LTB₄, HETEs, PAF
- **Plasma**
 - C5a, FDPs
- **Necrotic cells**

Exogenous

- Bacterial: fMLP
- Necrotic cells



(5) Phagocytosis

- When inflammatory cells reach the injured site, they undergo Phagocytosis, which is an Active cellular process where by cells engulf, kill, &/or remove offending substances

1. Recognize & Attach

- Surface attachment of the leukocyte to the particle & recognition
- Aided by *opsonization*: antibodies, C3b, fibronectin

2. Engulf

- Extension of pseudopodia around object
- Fusion of membrane → *phagosome*

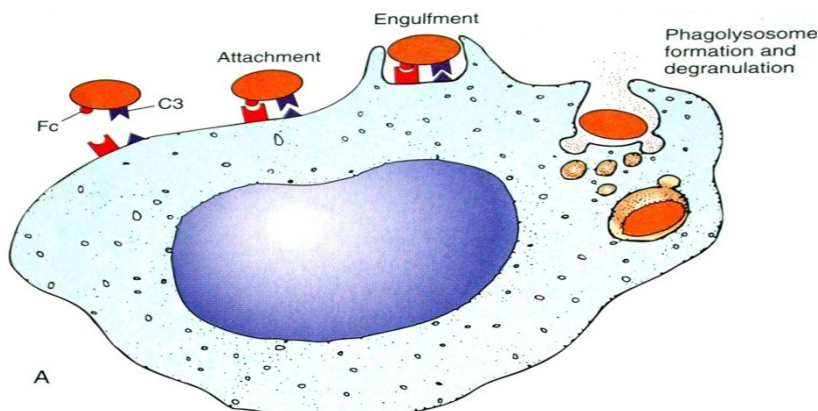
3. Phagosome / Lysosome fusion

- *Phagolysosome*
- → expulsion of lysosomal contents into phagolysosome (*degranulation*)

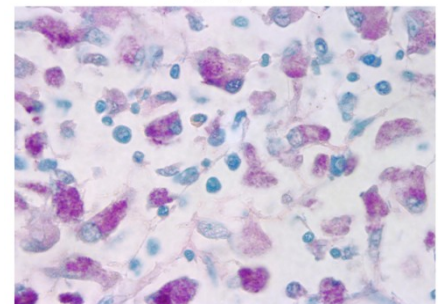
4. Respiratory burst

- → production of reactive oxygen species (bactericidal)
- Compound cells that cause the Respiratory burst include:
 - Superoxide hydrogen peroxide
 - hydroxyl radical
 - hypochlorous acid

5. Extrusion of debris (inconsistent)



Phagocytosis

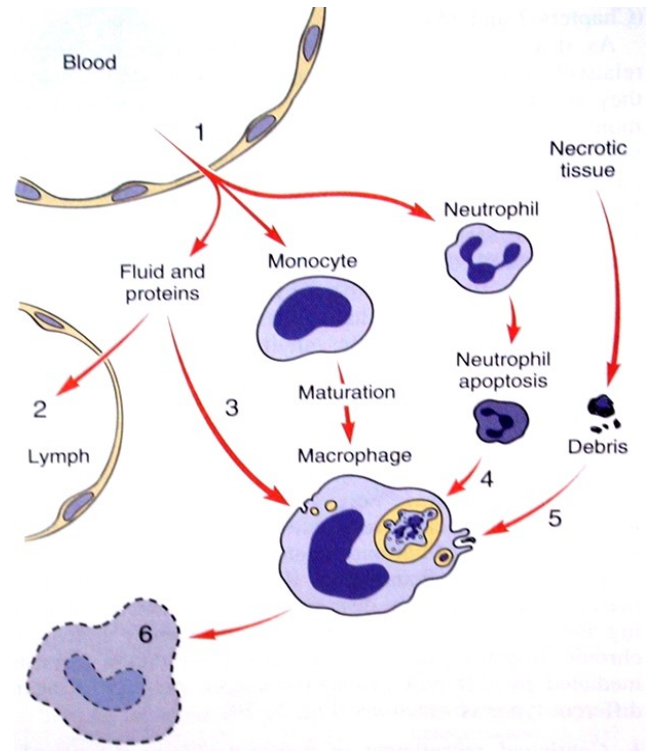


- Phagocyte-mediated tissue damage (4 different processes that cause localized tissue damage):
 - Neutrophils are short-lived in tissues & are sloppy eaters.
 - This leads to variable degrees of tissue damage caused by the inflammatory response.
 - Neutrophils tend to undergo phagosome/lysosome fusion prior to phagosome closure
 - Results in regurgitation of lysosomal enzymes & reactive oxygen species into surrounding tissue
 - Frustrated phagocytosis occurs when the particle is too large to be engulfed
 - The neutrophil discharges its enzymes, etc. in an attempt to destroy → large degree of tissue damage
 - **Suicide** – phagocyte dies at the site of inflammation & releases lysosomal enzymes into the surrounding tissue

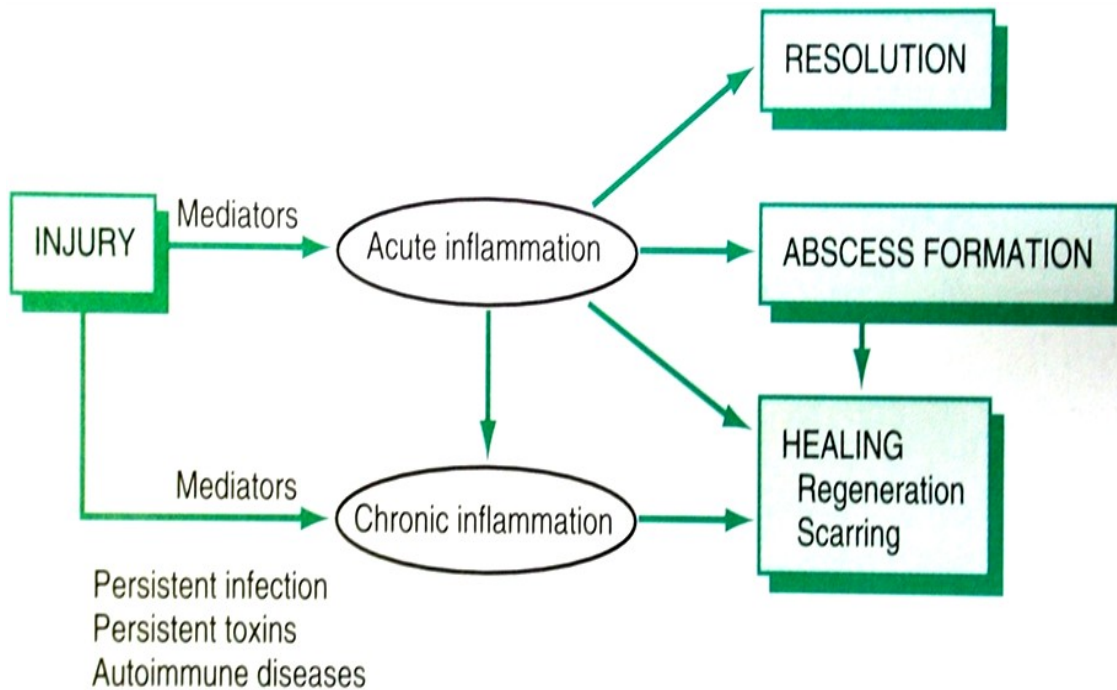
- **Systemic Effects** (Acute-phase response)
 - **Fever:**
 - **IL-1 & TNF** circulate throughout the body
 - Eventually they come into contact with the **Thermoregulatory center of hypothalamus**
 - Local production of PGE
 - vasomotor center
 - Sympathetic nerve stimulation
 - Vasoconstriction in skin
 - Decreased heat dissipation
 - Fever (can be good to have a fever)
 - Phagocytosis is more effective at higher temps
 - Bacteria can't live at higher temps
 - IL-1 & TNF →
 - ↓ appetite
 - ↑ slow-wave sleep
 - Protein catabolism
 - Release of acute phase proteins by liver
 - Accelerated release of WBC from marrow
 - Stimulation of release of colony stimulating factors
 - Further production and release of WBC
(you don't want to use them all up because you will need them to continue to go & fight the infection)

○ **Resolution of Acute Inflammation**

- **Complete resolution**
 - injury limited, short-lived injury
 - Neutralization of injurious stimulus
 - Return of physiological state of vasculature (no longer permeable, chemotaxis stops, etc.)
 - Cessation of cellular inflammation
 - PMN & debris removal
- **Healing by fibrosis (scarring)**
 - tissues that do not regenerate
 - or after extensive tissue damage
- **Abscess formation**
 - walled off collection of pus, usually caused by certain “pyogenic” bacteria (“pyo-“ refers to neutrophils)
- Persistence with progression to chronic inflammation



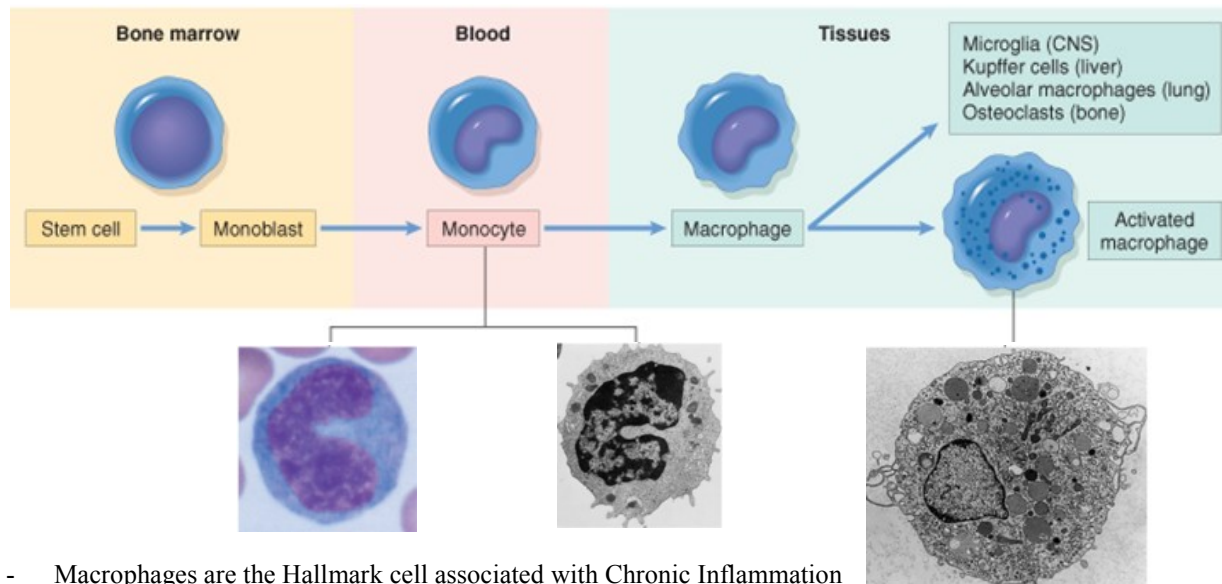
○ **Outcomes**



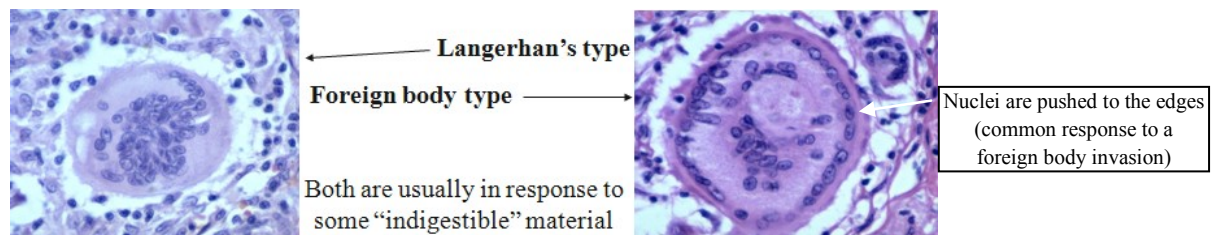
Chronic Inflammation

- Persistence of acute inflammation
 - Repeated bouts of inflammation/necrosis (with incomplete resolution)
 - e.g. chronic gastric ulcer, chronic sinusitis in the nose
 - Indigestible / intracellular stimulus
 - certain organisms elicit a chronic response with no appreciable acute inflammation (e.g. survive in phagocytes)
 - Also fungal and protozoal organisms which can survive in cells that phagocytize them
 - Prolonged exposure to toxicants (exogenous or endogenous)
 - Autoimmune disease
 - Foreign bodies
 - Inflammation of prolonged duration (weeks to ??) in which active inflammation, tissue destruction, & attempts at repair are proceeding simultaneously
 - Often insidious onset (don't notice, no initial pathology)
 - Can be low-grade, smoldering and asymptomatic to tremendously debilitating
- **General Characteristics**
- Chronic inflammation is generally granulomatous inflammation
 - Infiltration is primarily with mononuclear cells, especially macrophages
 - May be mixed; pyogranulomatous, eosinophilic granulomatous (like parasites), or lymphoplasmacytic
 - Tissue destruction (often inflammatory cell-induced)
 - Attempts at healing/repair by connective (granulation) tissue proliferation
- **Words used to describe Chronic Inflammation**
- Histiocytic
 - Granulomatous
 - Lymphohistiocytic
 - Eosinophilic granulomatous
 - Pyogranulomatous
 - **Exception:** lymphocytic/plasmacytic

○ Macrophages



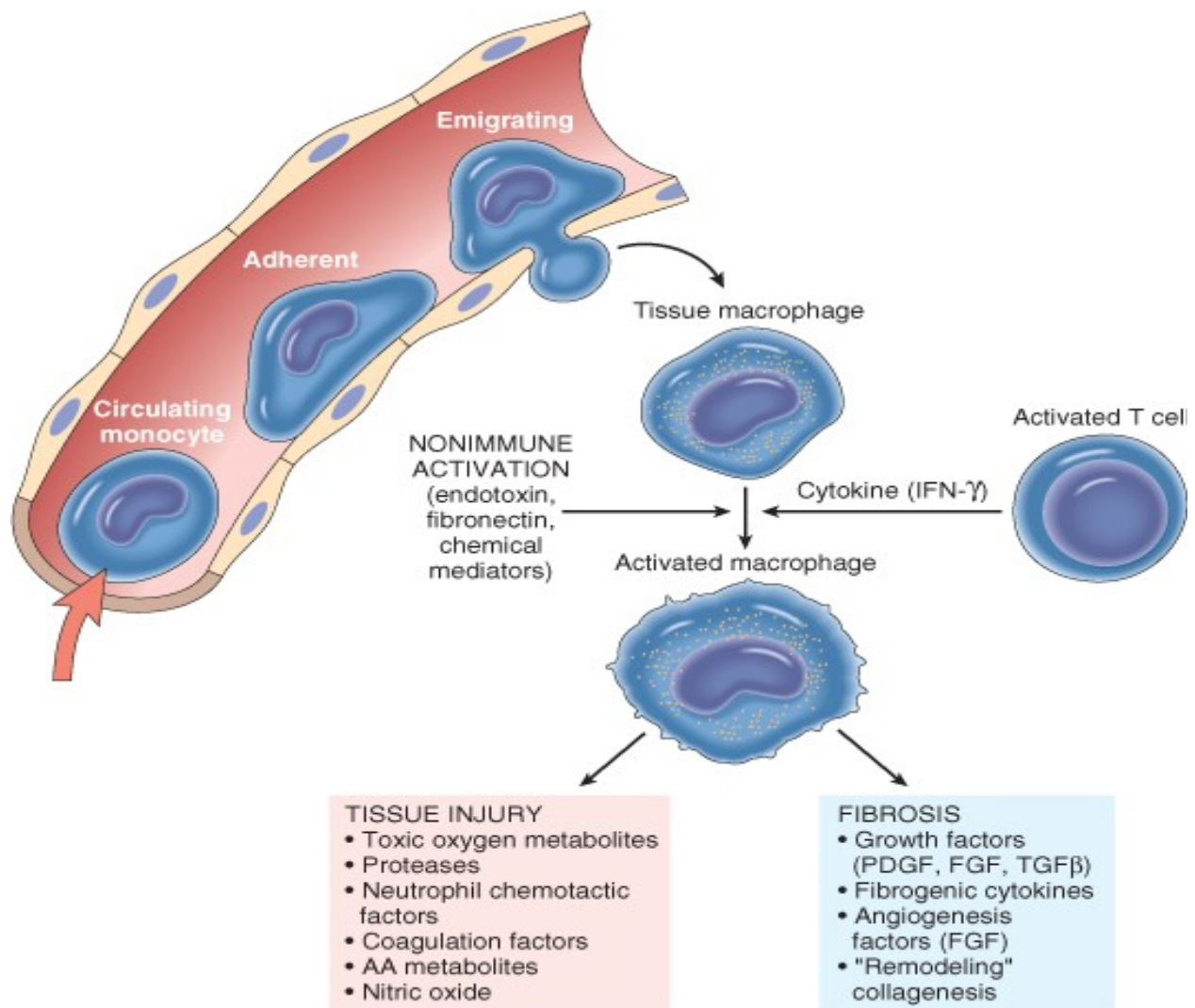
- Macrophages are the Hallmark cell associated with Chronic Inflammation
- ** The hallmark of granulomatous inflammation is infiltration by macrophages**
- Primary source is blood monocyte recruitment (adhesion, emigration, & chemotaxis)
- A few $m\phi$ can proliferate locally, but the majority emigrate from the blood as monocytes & rapidly mature into $m\phi$
- $m\phi$ in tissues often referred to as *histiocytes*, so histiocytic & granulomatous inflammation are nearly synonymous
 - If distinct granulomas are being formed, “granulomatous” is preferred over “histiocytic”
- Tissue lifespan is much longer than neutrophils
- After about 1-3 days of the inflammatory process, monocytes begin to be the predominant cell emigrating into areas of inflammation
- Capable for further differentiation into epithelioid cells & into **multinucleate giant cells**



- Examples of “indigestible” material include:
 - *Mycobacterium spp.*
 - Fungi
 - Foreign bodies
 - Nematode larvae
- Macrophages are important regulators of the inflammatory response & secrete many of the eicosanoids (arachidonic acid metabolites), cytokines, & chemokines that drive the response
- Also secrete many of the growth factors which stimulate healing process
- like Polymorphonuclear cells (PMNs), “professional phagocytes” clean up cellular debris & eliminate microorganisms

- **Roles of activated macrophages in chronic inflammation**

- Macrophages are activated by cytokines from immune-activated T cells (particularly IFN γ ;) or by nonimmunologic stimuli such as endotoxin.
- The products made by activated macrophages that cause tissue injury and fibrosis are indicated.
- AA, arachidonic acid
- PDGF, platelet-derived growth factor
- FGF, fibroblast growth factor
- TGF β : transforming growth factor β



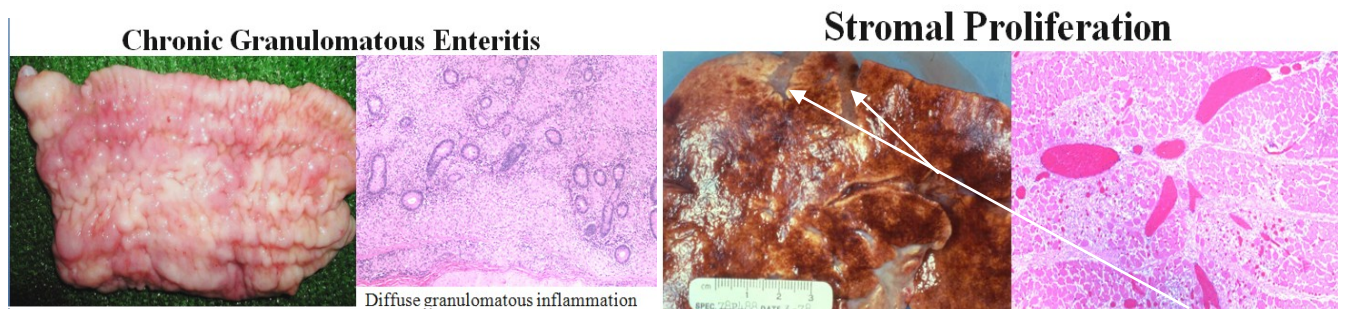
○ **Cellular Proliferation**

- The second consistent characteristic of chronic inflammation is
- **Regenerative proliferation**
 - Proliferation of parenchymal cells
 - Will successfully regenerate damaged tissue if the damage is not too severe
- **Stromal proliferation**
 - Most commonly fibrovascular proliferation (granulation tissue)
 - Occurs when damage is too severe for regeneration or when permanent cells are lost
 - Can be diffuse, bridging a deficit → results in scarring
 - Can encapsulate an area of chronic inflammation → results in abscess or encapsulated granuloma
 - Primarily stimulated by growth factors, secreted by mφ

○ **Chronic Inflammation of Other Cells**

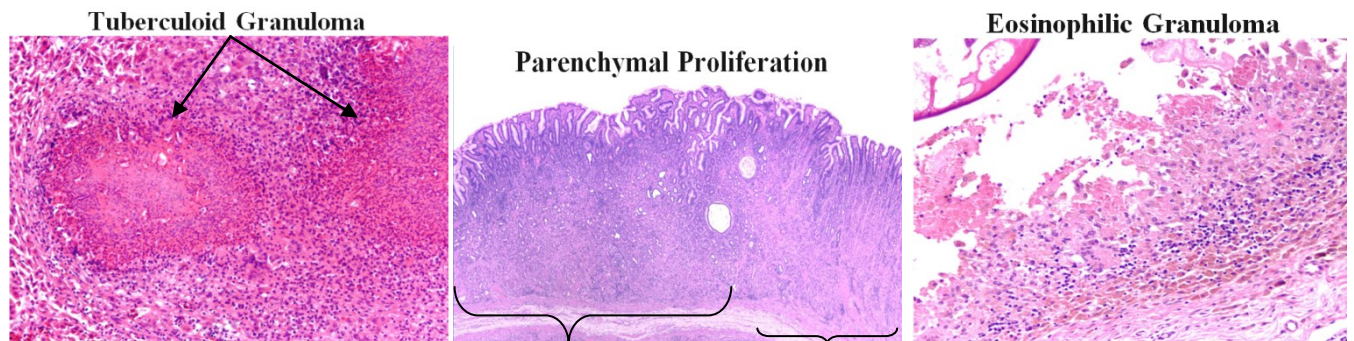
- **Lymphocytes:** secrete lymphokines, react to monokines
- **Plasma cells:** secrete antibody
- **Mast cells:** allergic and IgE-mediated
- **Eosinophils:** allergic and parasitic
- **Neutrophils:** response may persist for long time

○ **Examples of Chronic Inflammation**



Intestinal Wall is 3-4 times thicker than it should be

Lungs (left) & Muscles (right) can't regenerate so they form fibrous connective tissues



Name for a lesion, doesn't matter what's causing it

Proliferated more normal

Chemical Mediators of Inflammation

○ Mediators of Inflammation

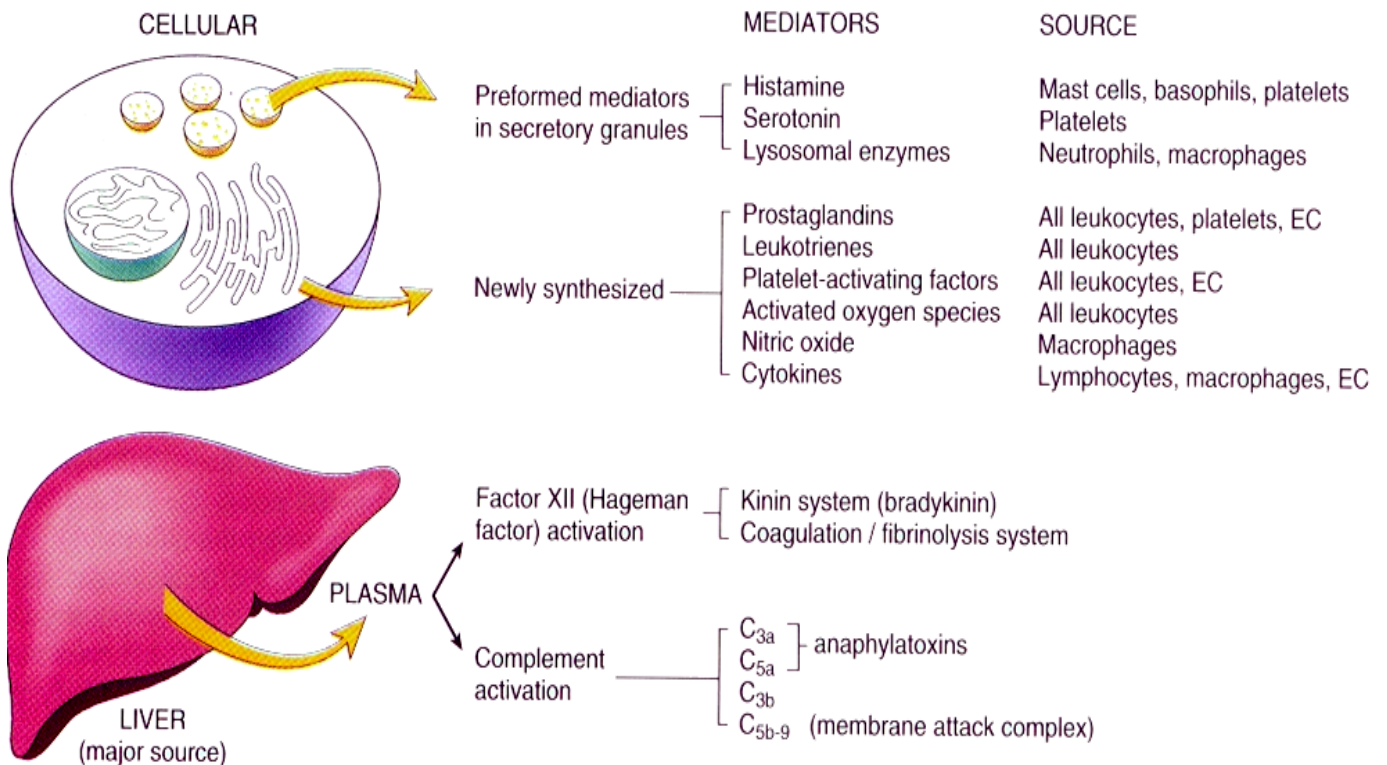
- Any molecule that acts as a messenger to blood vessels, inflammatory cells, or other cells to contribute to the inflammatory response
- Can be Exogenous or Endogenous
- Can be preformed or newly synthesized
- Can act in an **autocrine**, **paracrine**, or **exocrine** manner
 - **Autocrine**: one cell that affects only itself
 - **Paracrine**: one cell affecting the adjacent cells
 - **Exocrine**: one cell affecting any cell in the body
- There is considerable redundancy in actions and most have regulatory mechanisms involving specific inhibitors, antagonists, degradatory enzymes, etc.

Note:

Don't lose the overall concepts of the events of inflammation by becoming lost in the maze produced by the myriads of mediators!

It is MUCH more important that you understand the vascular & cellular events of inflammation than you know the actions of every interleukin!

○ Chemical Mediators of Inflammation



○ Vasoactive Amines

- Preformed & released very early

• Histamine

- Histamine does the opposite of what an anti-histamine would do
- Preformed mediator from granules of mast cells (also basophils & platelets)
- Major mediator of vasodilation & increased vascular permeability (acts at precapillary sphincter)
- Also bronchoconstriction and constriction of large blood vessels
- MC degranulation stimulated by
 - Physical injury
 - Binding of immunoglobulin (esp, IgE)
 - C3a & C5a (anaphylaxis related to complement fragments)
 - Releasing proteins from WBC
 - Neuropeptides
 - Cytokines (IL-1, IL-8)
- Acts on microcirculation via the H1 receptor
- Deactivated rapidly by **histaminases** (enzymes designated to break down histamine)

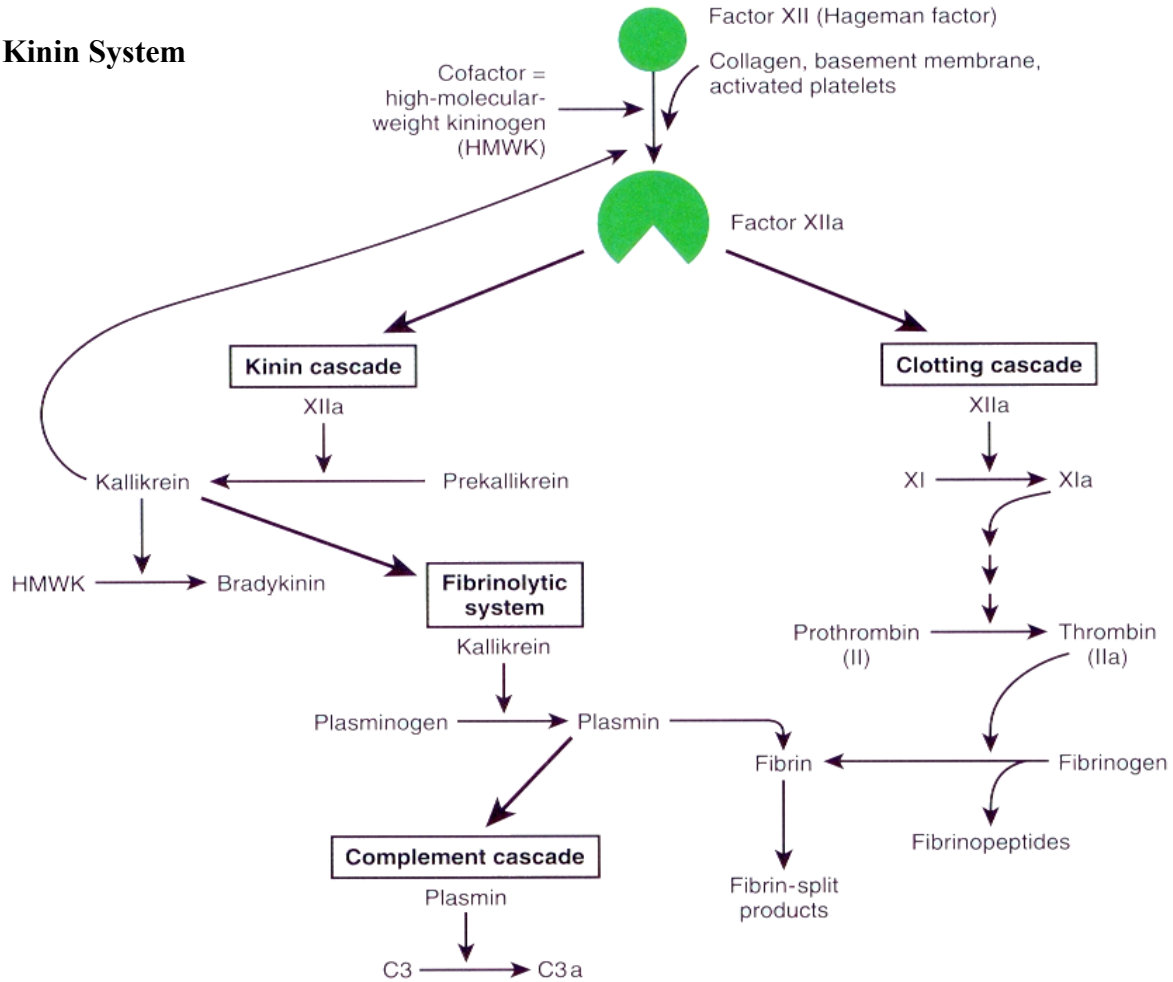
• Serotonin

- Primary source is platelets for most animals
- Mast cells in rodents
- Released during platelet-release action stimulated by
 - Thrombosis
 - Collagen damage
 - Antigen/antibody complexes
 - ADP
 - Platelet Activating Factor (PAF)
- Effects similar to histamine
- Inactivated by monoamine oxidases

○ Kinins

- Kinins are blood plasma proteins that influence:
 - smooth muscle contractions
 - smooth muscle is any muscle not under voluntary control (bladder, intestine, etc.)
 - affect blood pressure (especially hypotension)
 - increase blood flow throughout the body
 - increase the permeability of small capillaries
 - stimulate pain receptors

○ **Kinin System**

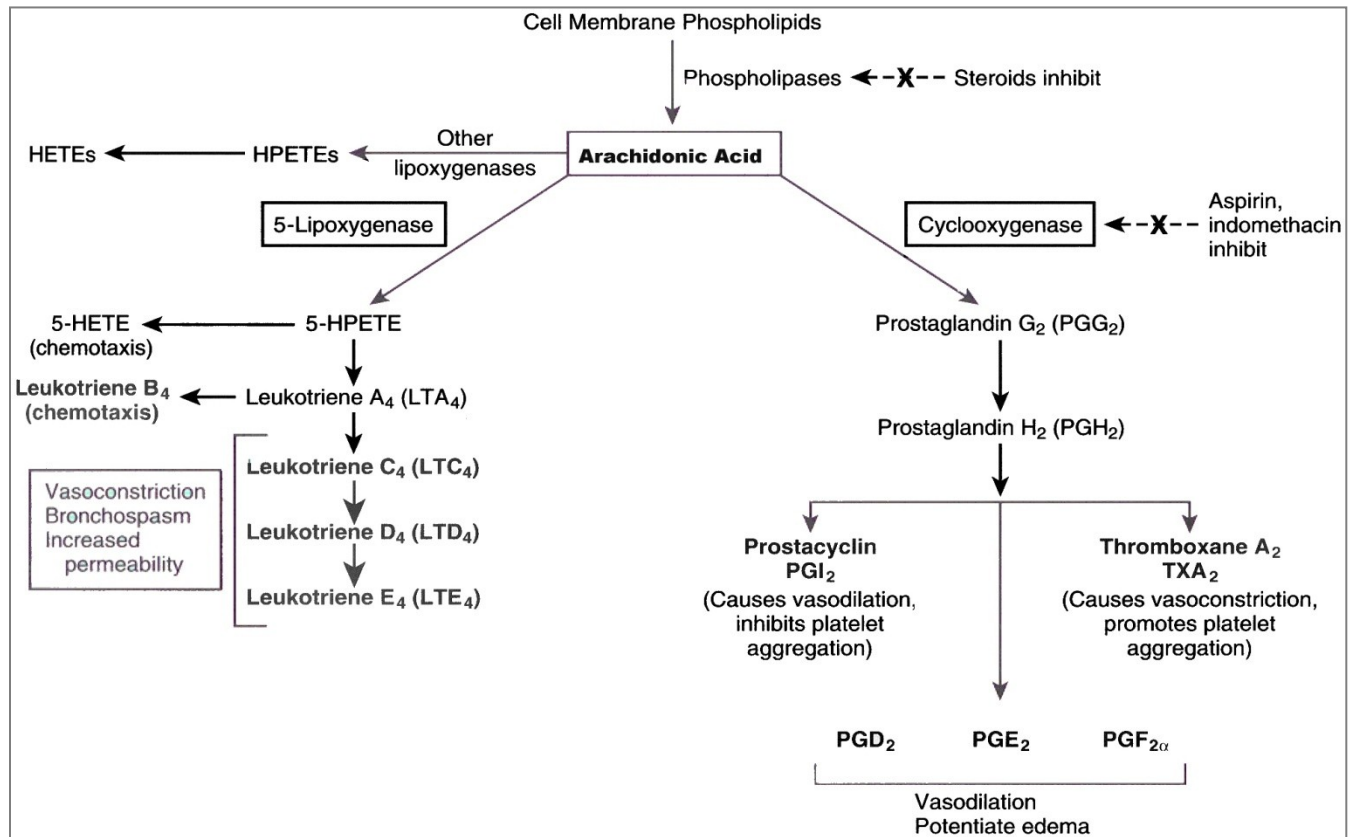


- **Bradykinin** (short lived, specific inactivator)
 - Most important; derived from plasma
 - Generated from prekallikrein by activated coagulation **factor XII (Hageman factor)**
 - Produced when intrinsic coagulation cascade is activated
 - Can cause either **vasoconstriction** or **vasodilation**
 - Can also cause **Brochoconstriction**
 - Increased vascular permeability via EC contraction
 - ****Major cause of pain of inflammation****
 - Inactivated in minutes by kininases
- **Activation of other systems**
 - complement
 - fibrinolysis
 - **eicosanoids** (Arachidonic Acid Metabolites)
- Leukokinins & C-kinins are derived from WBC complement respectively
- Along with other blood-derived kinins have similar effects, but are less important

- **Arachidonic Acid Metabolites** (Leukotrienes & Prostaglandins)
 - *a.k.a.* eicosinoids
 - AA is cleaved from membrane phospholipids by phospholipases (inhibited by corticosteroids)
 - AA converted to prostaglandins & thromboxane-A₂ (prostanoids) by cyclooxygenases (COX-1 & COX-2)
 - COX-2 upregulated during inflammation
 - COX-1 constitutively expressed (always present) & involved in many physiological functions
 - COX-3 centrally acting (only really expressed in the Brain)
 - **Classical NSAIDS** (aspirin, phenylbutazone, ibuprofen, flunixin) inhibit COX-1 ± COX-2
 - Side effects such as GI ulcers
 - Newer specific COX-2 inhibitors
 - **Variably cause:**
 - Vasodilation
 - Vasoconstriction
 - Bronchoconstriction (constriction of the small airways throughout the lungs)
 - Platelet aggregation
 - Platelet inactivation
 - Pain
 - Fever
 - **Created de novo:** not preformed
 - from phospholipids of cell membrane
 - Eicosanoids are locally active and rapidly spontaneously decay or are enzymatically destroyed
 - **Sources:** they can come from many different types of cells
 - WBC, mast cells, platelets, EC
 - AA converted to 5-HPETE by 5-lipoxygenase & subsequently to 5-HETE or leukotrienes
 - 5-lipoxygenase inhibitors are recently on the market for anti-inflammatory effects in asthma
 - **Lipoxygenase products** acts on the Arachidonic Acid (AA) pathway that produces **leukotrienes**
 - primarily from leukocytes
 - 5-HETE (and LTB₄) chemotactic for WBCs
 - LTB₄: neutrophil chemotaxin
 - LTC₄, LTD₄, LTE₄ - (slow-reacting substance of anaphylaxis)
 - Potent inducers of vasoconstriction, bronchoconstriction increase vasopermeability
 - **Cyclooxygenase products** enzyme acting on the other arm of the AA pathway that produces **prostaglandins**
 - from most cells
 - PGE₂, PGF_{2a}, PGD₂, PGI₂: prolonged vasodilation, leakage, pain, fever (PGE₂)

Arachidonic Acid Metabolites

(Leukotrienes & Prostaglandins)



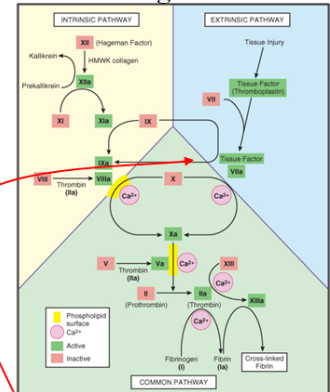
○ Coagulation cascade

- Third component of the hemostatic process (but is basically happening simultaneously with the 2nd component)
- Major contributor to thrombosis
- Cascade of enzymatic conversions that turn inactive proenzymes into activated enzymes
- Culminates in the formation of thrombin
- Thrombin then converts the soluble plasma protein fibrinogen precursor into the insoluble fibrous protein fibrin
- Each reaction in the pathway results from the assembly of a complex composed of:
 - An **enzyme** (activated coagulation factor)
 - A **substrate** (proenzyme form of coagulation factor)
 - A **cofactor** (reaction accelerator)
- These components are assembled on a phospholipid complex & help together by **Ca ions**
 - Clotting tends to remain localized to sites where such assembly can occur
 - *e.g.* on the surface of activated platelets or endothelium

○ Clotting Cascade

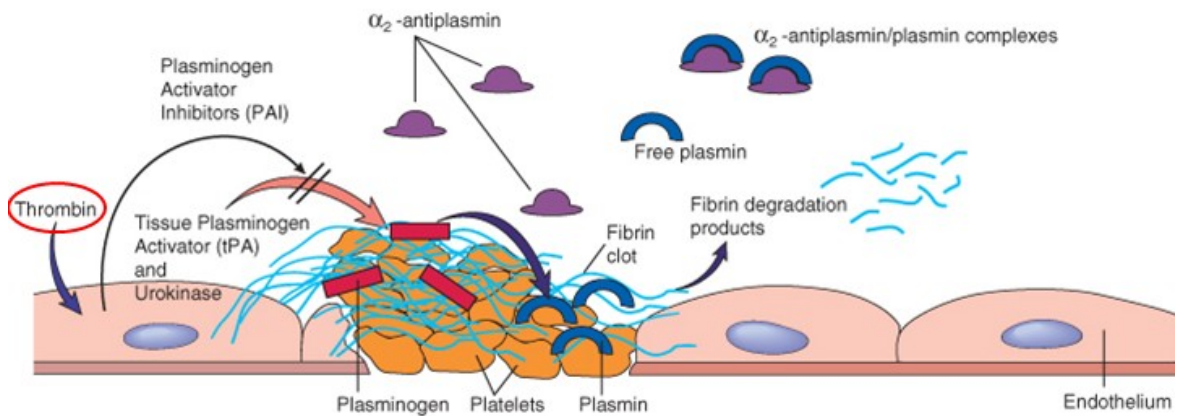
- **Intrinsic**
 - initiated *in vitro* by activation of the Hageman factor (factor XII)
- **Extrinsic**
 - initiated by tissue factor
 - a cellular lipoprotein exposed at site of tissue injury
- Artificial *in vitro* divisions (in the body they're usually occurring simultaneously)
- Note the common link b/w the pathways at the level of factor X activation
- Besides inducing coagulation, activation of the clotting cascade also initiate the **Fibrinolytic Cascade** that limits the final size of the clot

Clotting Cascade

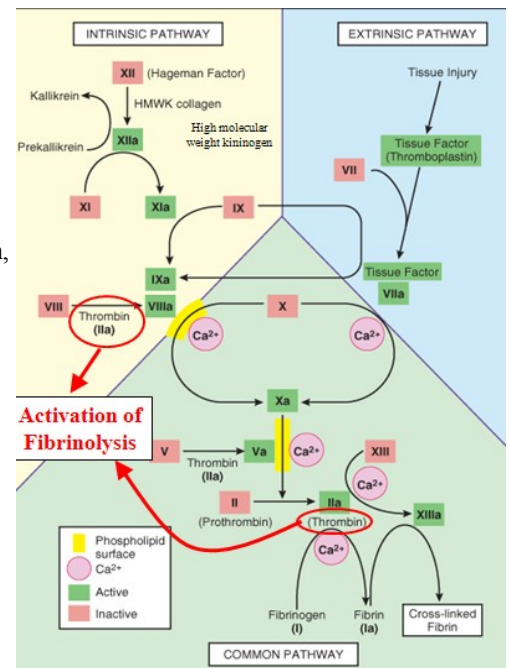


Also have interactions between the 2 pathways via tissue factor-factor VII complex, which activates IX

Fibrinolytic Cascade

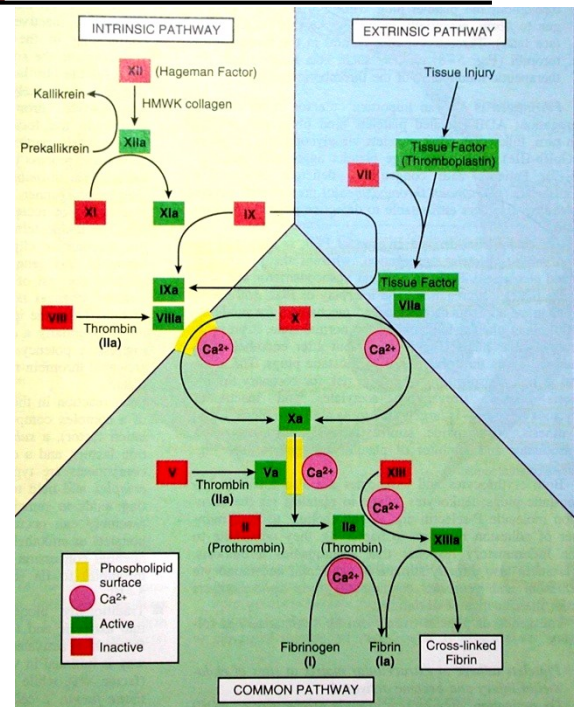


- Coagulation & Inflammation are tightly linked because the same compounds are used in both sides of the cascade
- Acute inflammation, by activating or damaging the endothelium, can trigger coagulation & induce thrombus formation
- Conversely, the coagulation cascade induces inflammation, primarily via the actions of thrombin.

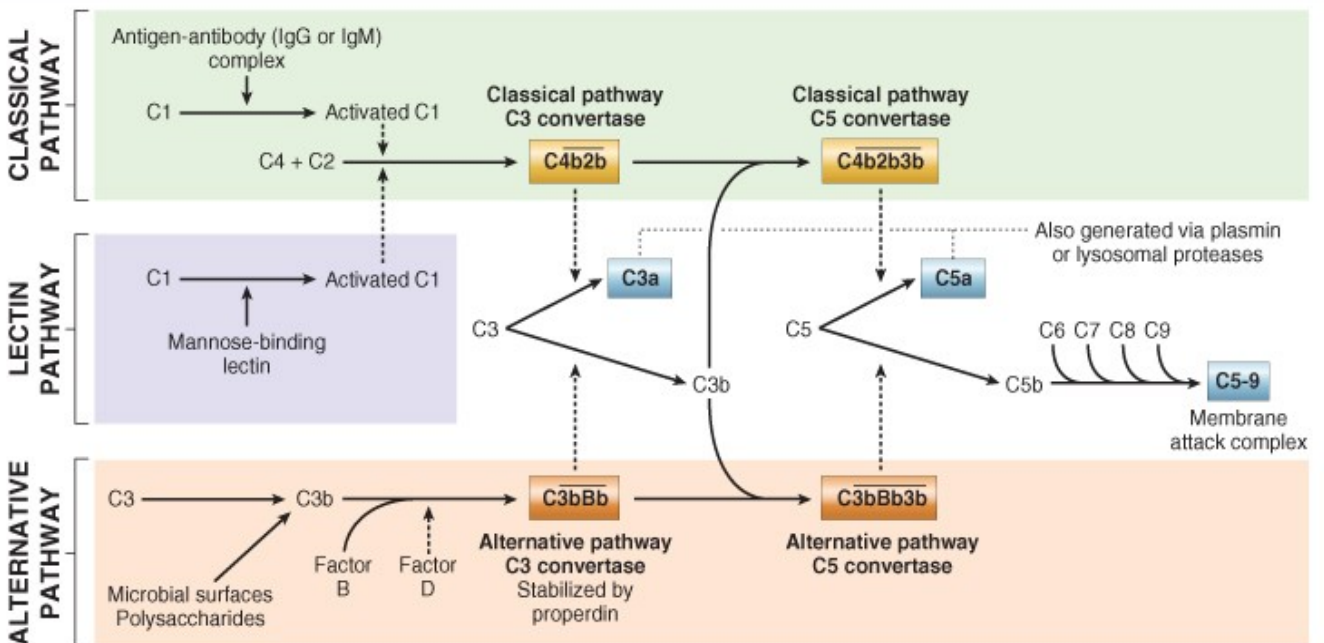


○ Plasma Proteases

- **Hageman factor (factor XII)**
 - Activated by negatively charged surfaces
 - Initiates blood clotting intrinsic pathway
 - Stimulates activation of the fibrinolytic system
 - Generates kinins (bradykinin)
 - **Activates the complement cascade**
- **Blood clotting system:**
 - Thrombin (factor IIa) causes increased leukocytes adhesion & fibroblast proliferation
 - Its action on fibrinogen produces fibrinopeptides, which ↑ vascular permeability & are chemotactic
 - Factor Xa causes increased vascular permeability & leukocyte exudation



○ Complement Cascade



Cleavage of C3:

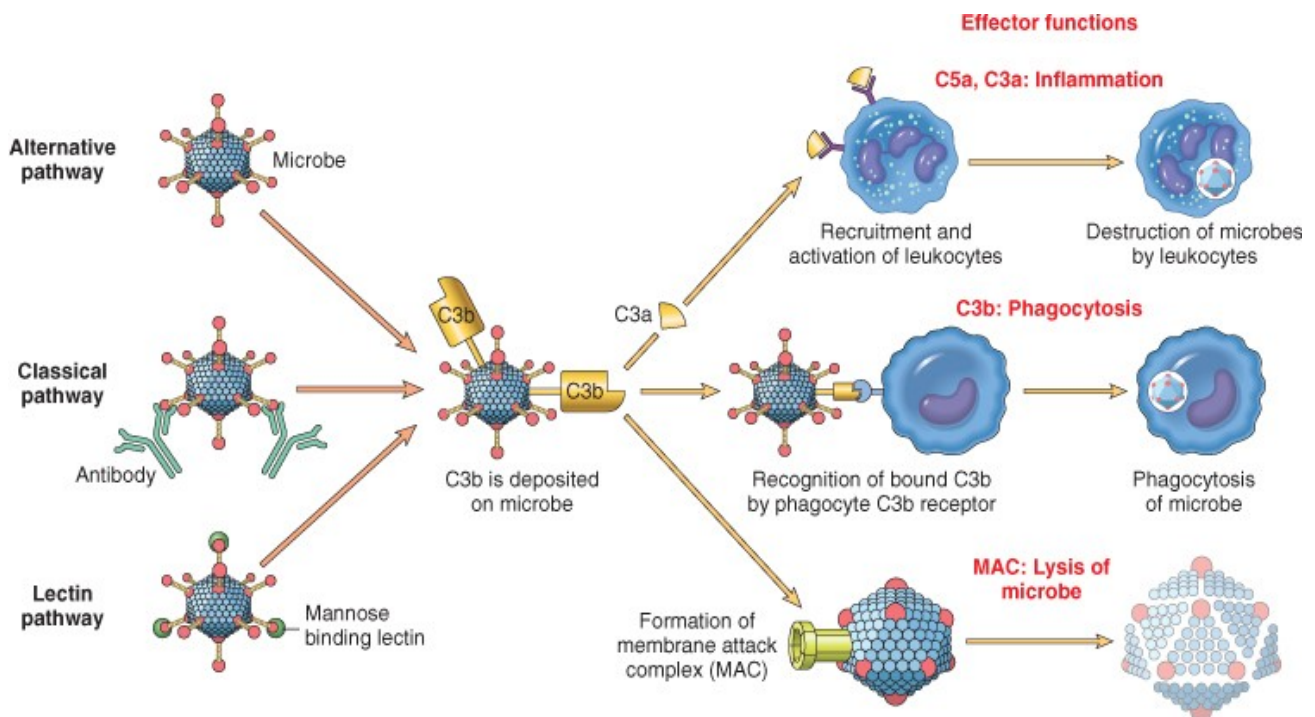
1. **Classical pathway** – fixation of C1 to IgM or IgG combined with antigen
2. **Lectin pathway** – plasma mannose-binding lectin binds to CHO on microbes & directly activates C1
3. **Alternative pathway** – triggered by microbial surface molecules

○ **Complement Cascade** (continued...)

- About 20 circulating proteins, many of which are proteases when activated (compounds inactive in the plasma)
- ***Key step:** activation of C3 (cleavage into C3b & C3a)
→ the point where the intrinsic & extrinsic systems converge
- Complement system is closely regulated by specific protein inhibitors
- Classical pathway involves recognition of IgG or IgM bound to a cell membrane by C1
- Alternate pathway (**properdin system**) is activated by bacterial cell wall components, such as the Lipopolysaccharides (LPS), immunoglobulin aggregates, complex polysaccharides, etc.
- **C3a & C5a (anaphylatoxins)** cause increased **vascular permeability & vasodilation** by causing **histamine release** from mast cells
- **C5a** is also **potent chemotaxin** for PMNs, monocytes, eosinophils, & basophils
- **C3b** is an **important opsonin**
 - Fixes to bacterial cell walls and interacts with specific receptors on PMNs & mφ to induce Phagocytosis

- **Biologic Functions:**

- 1) **C5a, C3a: Inflammation** – recruitment and activation of leukocytes
→ **destruction of microbes by leukocytes**
- 2) **C3b: Phagocytosis** – recognition of bound C3b by phagocyte C3b receptor
→ **phagocytosis of microbe**
- 3) **MAC** (formation of Membrane Attack Complex) → **lysis of microbe**



○ Platelet Activating Factor (PAF)

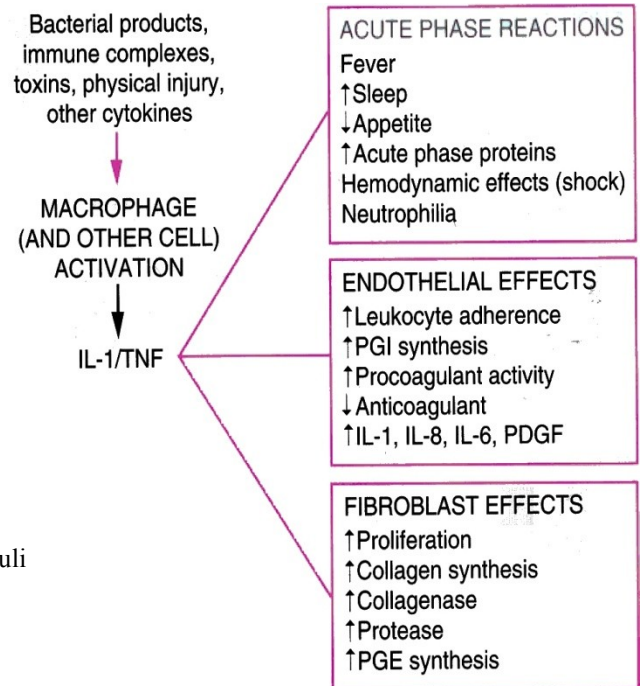
- **Source** – PAF is produced by numerous cells types (platelets, mast cells, m ϕ , EC...)
- Formed by initial phospholipid cleavage by phospholipase A2 (PLA2) with subsequent acetylation
- **Functions:**
 - Prolong & sustain inflammatory reaction
 - Stimulates platelet aggregation
 - Vasoconstriction
 - Bronchoconstriction
 - Vasodilation & increased permeability when PAF is secreted at very low concentrations
 - Enhances leukocyte adhesion by upregulating integrins
 - Stimulates WBC degranulation
 - Oxidative burst
 - Chemotaxic
 - Also boosts eicosanoid production by WBC

○ Cytokines

- Small polypeptides with autocrine, paracrine & endocrine like activity
- Protein mediators produced mainly by m ϕ , mast cells, EC, etc.
- Produced during immune & inflammatory reactions
- **Types** of Cytokines
 - **Interleukins (IL)**
 - **Interferons (IFN)**
 - **Chemokines**
 - **Growth Factors (GF)**
 - **Colony Stimulating Factors (CSF)**
- **5 Classes** of Cytokines
 - 1) Cytokines that regulate **lymphocyte function**: IL-2, IL-4, IL-5, IL-10, TGF- β
 - 2) Cytokines involved with **innate immunity**: TNF- α , IL-1, IFN- α & β , IL-6
 - 3) Cytokines that **activate inflammatory cells** in conjunction with m ϕ : IFN- γ , TNF, IL-5, IL-10, IL-12
 - 4) **Chemokines**: IL-8, eotaxin, (others)
 - 5) Cytokines that **stimulate hematopoiesis**: IL-13, IL-7, GM-CSF, M-CSF, G-CSF, stem cell factor

○ Interleukin I & TNF

- **Master Inflammatory Cytokines**
- **Source:**
 - primarily activated macrophages (IL-1, TNF α) or T cells (TNF β)
 - also produced by many other cells
- **Effects**
 - acute phase response
 - endothelial effect
 - fibroblast effect
- Secretion stimulated by LPS, immune complexes, toxins, physical injury, & other inflammatory stimuli
- Can act in autocrine, paracrine, or endocrine fashion
- **Inflammatory effects**
 - Activation & priming of PMNs (TNF) & macrophages
 - Increased release of proteolytic enzymes
 - Neutrophilia via increased release
- **Endothelial Effects**
 - Increased adhesion molecule synthesis & expression (allows neutrophils to marginate & migrate)
 - Vasodilation (via NO/PGI₂ release)
 - Endothelial retraction
 - Procoagulation (easier to clot)
 - PAF, tissue factor, t-PA inhibitor
 - Synthesis of cytokines, chemokines, eicosinoids, NO, increased surface thrombogenicity
- **Fibroblast Effect**
 - increased collagenase production
 - increased protease production
 - increased PGE production
 - Proliferation of the Fibrous Connective Tissue
- **Leukocyte effects**
 - Cytokine secretion
 - Activation of different WBCs

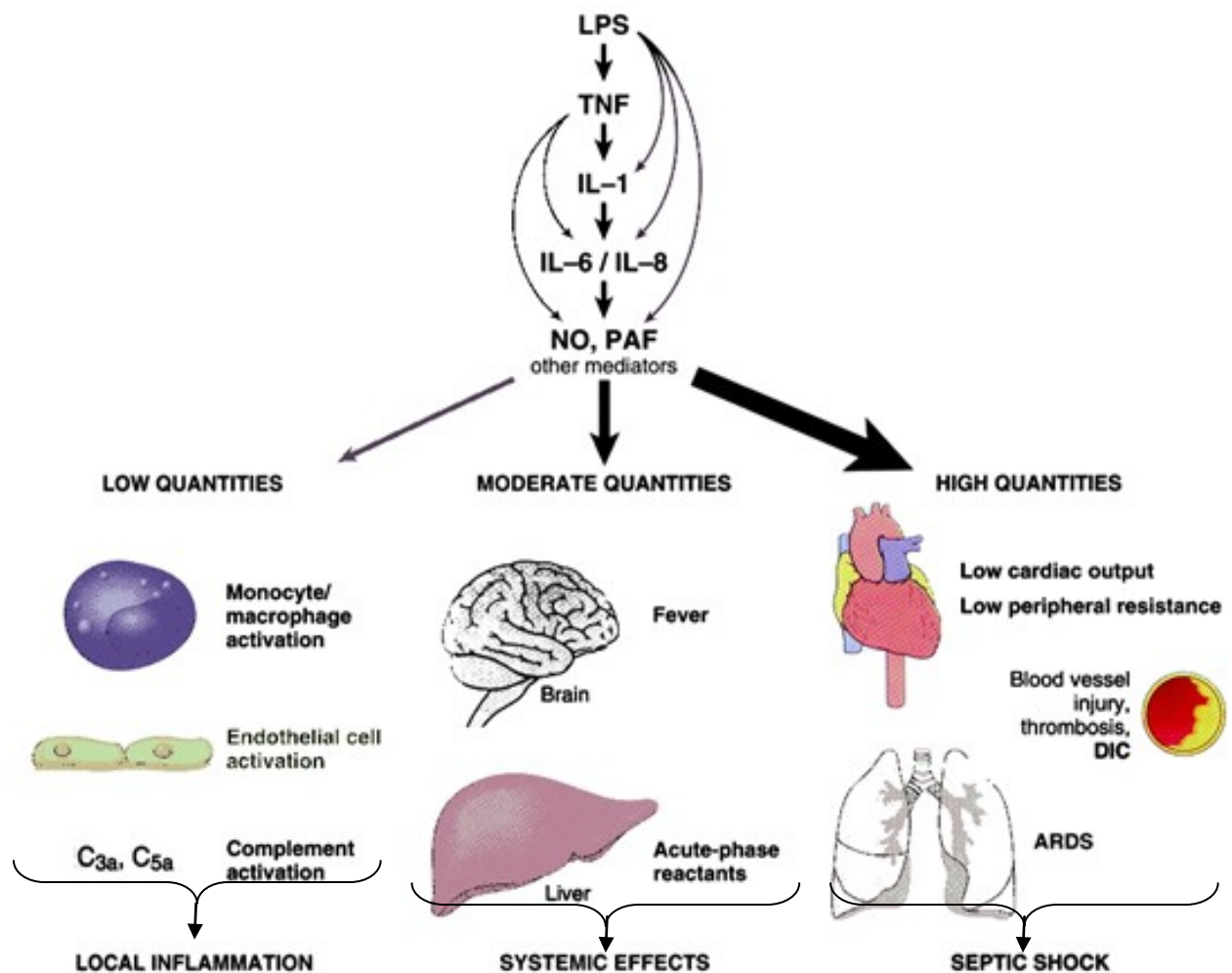


- **Interleukin I & TNF** (continued...)
 - With IL-6, IL-1 & TNF induce acute phase response:
 - Fever
 - Anorexia
 - Increased slow-wave sleep
 - Release of PMNs into circulation (i.e. Neutrophilia)
 - Hemodynamic effects → shock

Note: Glucocorticoids will inhibit the above responses
 - Prolonged over-release of TNF α leads to cachexia (neoplasia or chronic infections)

Interleukin 1 & TNF

Systemic vs. Localized Effects

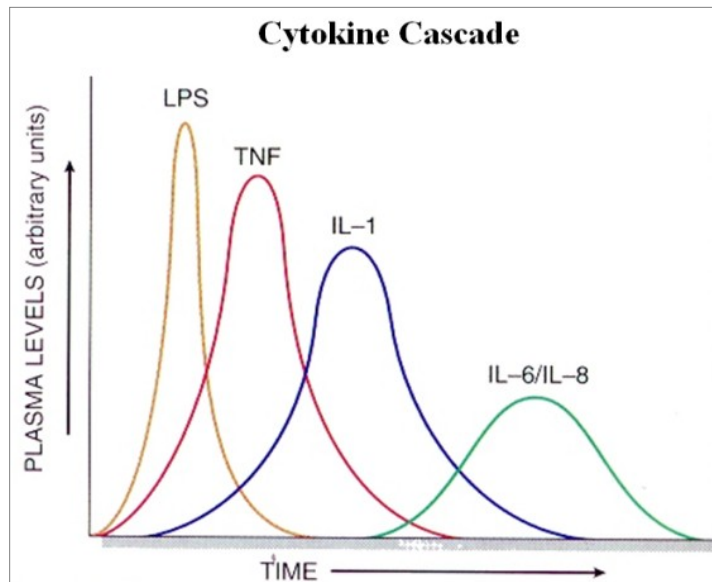


○ Other Interleukins

- **IL-6**
 - from macrophages, EC
 - Induced by IL-1/TNF
 - important in acute phase response
- **IL-4, IL-10, IL-13**
 - from T cells
 - macrophage inhibitors
 - drives immune response to humoral branch (Th2) & away from the cell mediated side
- **IL-12 & IFN γ**
 - from T cells
 - drive cell mediated (Th1) immunity
 - macrophage activation
- **IL-8**
 - from macrophages, EC
 - part of chemokine group (so it will also have an affect on the neutrophils)
 - neutrophil activation

○ Chemokines

- All bind to cell G protein-linked cell surface receptors & cause cytoskeletal alterations
- **C-X-C (alpha) class:** IL-8 is typical
 - secreted by m ϕ , EC in response to IL-1 & TNF, bacterial products
 - most active on PMN
- **C-C (beta) class:** MCP-1, MIP-1a, RANTES, eotaxin
 - attract monocytes, eosinophils, lymphocytes, basophils, but not PMN (neutrophils)
 - **Exception:** eotaxin is specific for eosinophils
- **C (gamma) class:** lymphotactin
 - Specific for lymphocytes
- **C-X₃-C class:** fractalkine
 - Exists as membrane form
 - monocyte and T lymphocyte strong adhesion
 - Soluble form → chemotactic for same



After Lippopolysaccharides (LPS) are injected into the system

→ TNF is released into the system

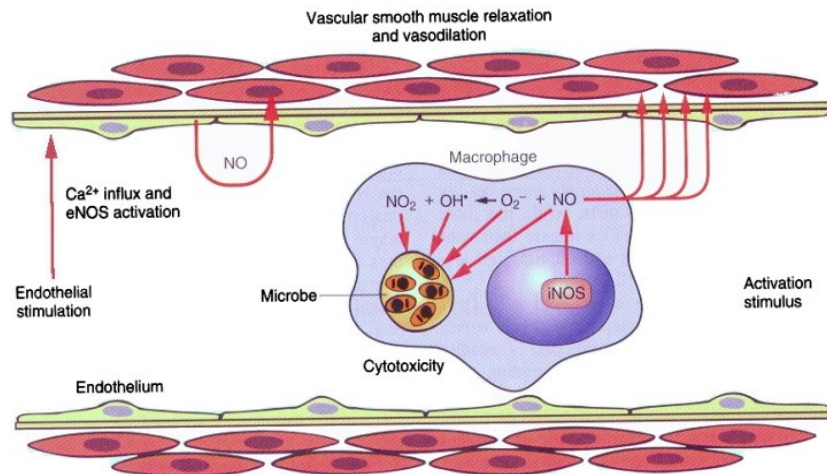
→ Followed by IL-1

→ & then eventually IL-6 & IL-8

○ Interferons

- **IFN α , IFN β**
 - primarily antiviral effects
 - inhibits cell replication
- **IFN γ**
 - from T cells (Th1)
 - potent macrophage activator

○ Nitric Oxide (NO)



• Sources & Functions

- **Endothelium** - vasodilation, platelet inhibition
- **Macrophages** - cytotoxic free radicals
- **Neurons** – not important in inflammation

• Major actions:

- **Vasodilation**
 - short acting gas first recognized as the endothelium-derived relaxing factor
 - causes vasodilation by relaxation of arteriolar smooth muscle
- An effector of the host defense against certain pathogens
- A signaling molecule, particularly in the CNS

- Constitutively expressed in EC (eNOS) & neurons (nNOS) & can be rapidly upregulated by increased cytoplasmic calcium

- Induced in mφ (iNOS) by TNFα & IFNγ in the inflammatory response

- Inflammation is important for :

- **Vasodilation**
- Reduces platelet aggregation, inhibits mast cells
- At higher levels (such as occurs when iNOS is activated) reduces WBC recruitment

- In the host's response to infection:

- Over-secretion due to iNOS activation leads to the peripheral vasodilation of septic shock
 - iNOS can produce more NO than eNOS or nNOS
- Reactive species generated from NO are bactericidal
 - *e.g.* peroxynitrite, ONOO⁻; generated by NO reacting with superoxide

- NO & reactive intermediates rapidly, spontaneously decay, and are inactivated by heme groups

○ **Neuropeptides**

- Substance P & others (**neurokinin**)
 - Early release
 - Stimulate histamine release from MC
 - Vasodilation & increased permeability

○ **Growth Factors (GFs)**

- GFs bind to cell-surface receptors, initiate signal transduction, DNA synthesis, & subsequent cell mitosis (Common theme)
- In healing, most are produced & act locally
 - mφ, platelets, fibroblasts, & EC
 - GFs can act in autocrine, paracrine, or endocrine fashion
- Some are also chemotactic for EC & fibroblasts

Growth Factors			
		<u>Source</u>	<u>Function</u>
1	PDGF Platelet derived GF	Pt, EC, mφ, smooth muscle	Mitogenic and chemotactic for fibroblasts; Stimulatory and chemotactic for mφ; indirect angiogenic activity; early trigger wound healing
2	FGF Fibroblast GF	mφ, epithelial cells, smooth muscle	Chemotactic and stimulatory for EC; chemotactic for mφ
3	EGF Epidermal GF	Pt	Stimulates epithelial cell proliferation; stimulates angiogenesis
4	TGF-α Transforming growth factor α	mφ, Pt, epithelial cells	Similar to EGF; same receptor but more potent angiogenesis stimulator
5	TGF-β Transforming growth factor β	mφ, Pt, lymphocytes	Chemotactic for mφ and stimulates secretion of other GF, chemotactic for mitogenic for fibroblasts, stimulates angiogenesis
6	VEGF Vascular endothelial GF	mφ, epithelium	Strong promoter angiogenesis; receptor found only on EC; promotes vascular permeability
7	IGF Insulin-like GF	Liver, fibroblasts, muscle	Promotes muscle and peripheral nerve regeneration
8	KGF Keratinocyte GF	fibroblasts	Stimulates epidermal growth; part of FGF family of GFs

○ Inhibitors, Reducers, & Suppressors of the Inflammatory Process

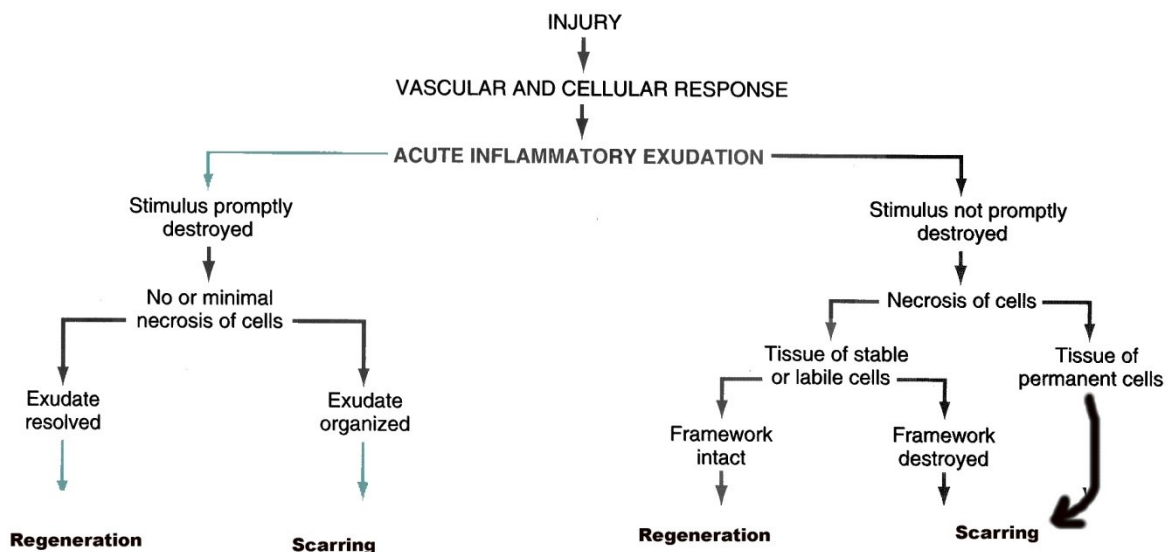
Non-specific Methods

- **Dilution** - mediator concentration is important
- **Natural Instability** - spontaneous degeneration
- **Inactivators** - both specific & nonspecific
 - **Proteinases** - continue to chew on peptides
 - **Kininases** - breakdown bradykinin
- **Antiproteinases** - prevent formation of more active compounds & deactivate existing compounds

○ Specific Inhibitors

- **Inhibitors of cell response** - corticosteroids, epinephrine
- **Antagonist cytokines** - switch inflammatory cells off
 - TGFb, IL 4, IL10, IL13
- **Competitive antagonist**
 - compete for receptor – IL-1ra
 - compete for cytokine - soluble receptors

○ Outcomes of Inflammation & Necrosis



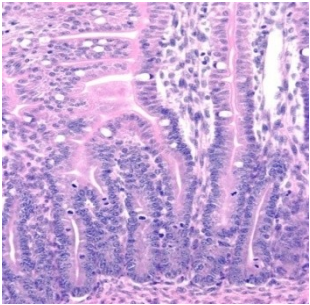
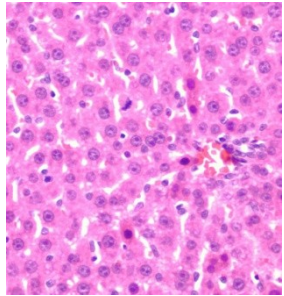
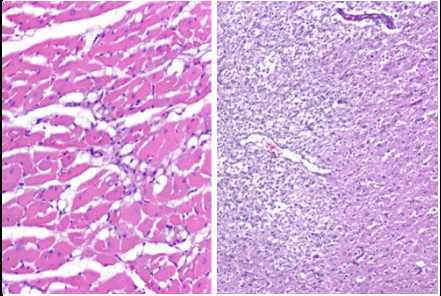
Healing & Repair

Healing & Repair

- How do we fix the damage?
 - 1) **Regeneration**
 - Restoration of original tissue architecture and function
 - 2) **Repair**
 - Fill in the deficits with connective tissues (scarring)
 - There will be alterations in both architecture & function

Regeneration:

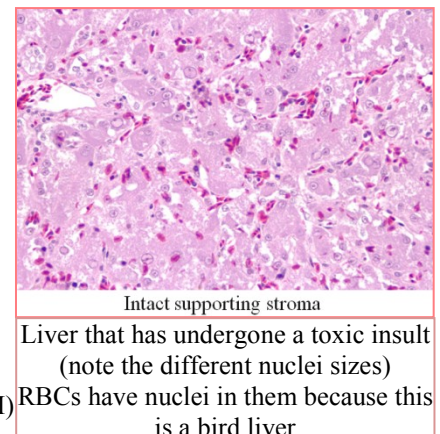
- **Types of Cellular of Regeneration**

Types of Cells Capable of Undergoing Regeneration		Cells <u>NOT</u> capable of Regeneration
Labile cells  <p>Intestinal epithelial cells</p>	Stable cells 	Permanent cells  <p>Brain Skeletal Muscle</p>
<ul style="list-style-type: none"> - constantly proliferating throughout life - Epidermis - Mucosal epithelial cells - bone marrow 	<ul style="list-style-type: none"> - retain the capacity to replicate, but have very low turn over rate - All glandular parenchymal cells - Mesenchymal cells - Endothelial cells (Clood Vessels) - Liver 	<ul style="list-style-type: none"> - no practical capacity to replicate - Neurons - Cardiac muscle - Kidney, Brain, Skeletal Muscle

- **Parenchymal cells** migrate across existing stromal framework & multiply to restore tissue integrity
- Regeneration results in the replacement of lost cells by their own kind
 - o thereby returning the tissue to normal structure & function

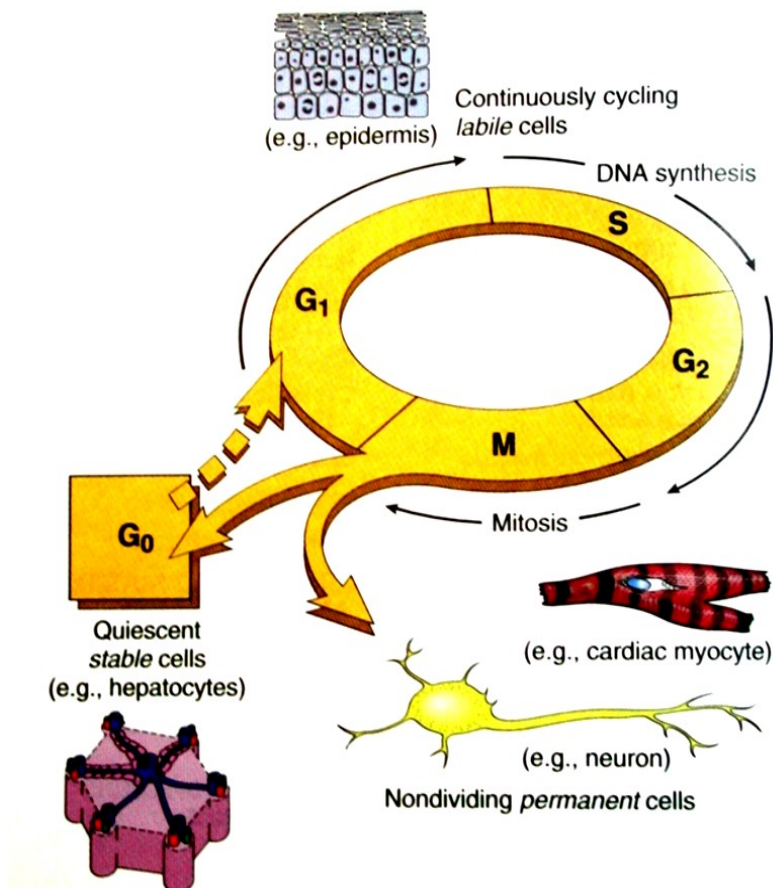
- **Cellular Requirements** for Regeneration:

- o Cells of the injured tissue must be **capable of dividing**
 - **Labile** cells: **continually dividing (stem cells)**
 - **Stable** cells: **not normally dividing**, but can be induced to re-enter the cell cycle
- o **Intact Supporting stroma**, especially of the **basement membrane (BM)**



- Hindrances to Regeneration

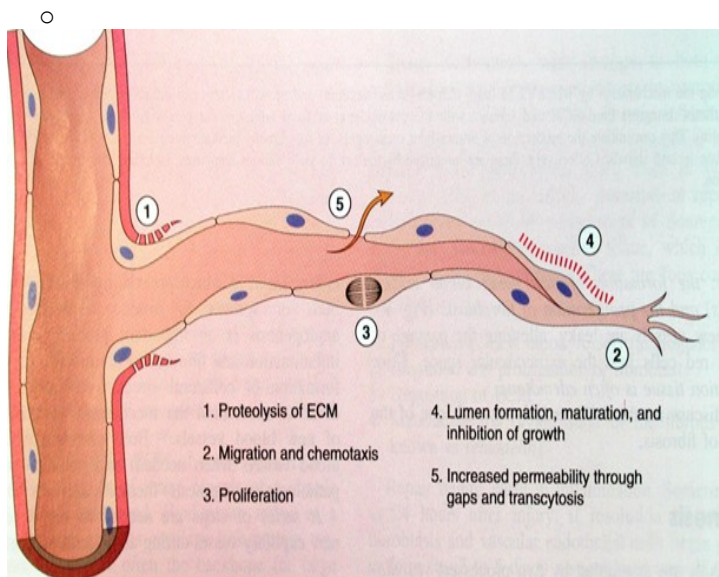
- Destruction of original supporting stroma / architecture
 - Chaotic proliferation of parenchymal cells
 - Replacement of original stroma with fibrous connective tissue
- Excessive exudation / infection
 - Tissue destruction by leukocyte or bacterial enzymes
 - PMNs secrete numerous proteases (collagenases, elastases)
 - Which digest the basement membrane & supporting connective tissues
 - Bacteria often have similar enzymes & / or toxins which may kill the parenchymal or inflammatory cells
- Excessively large defects
 - Stroma will not remain exposed indefinitely before fibrovascular proliferation is initiated
 - Large deficits must be filled with granulation tissue before stromal cells can regrow
- Permanent cells
 - Cannot effectively proliferate, so MUST heal by fibrous tissue replacement



Repair

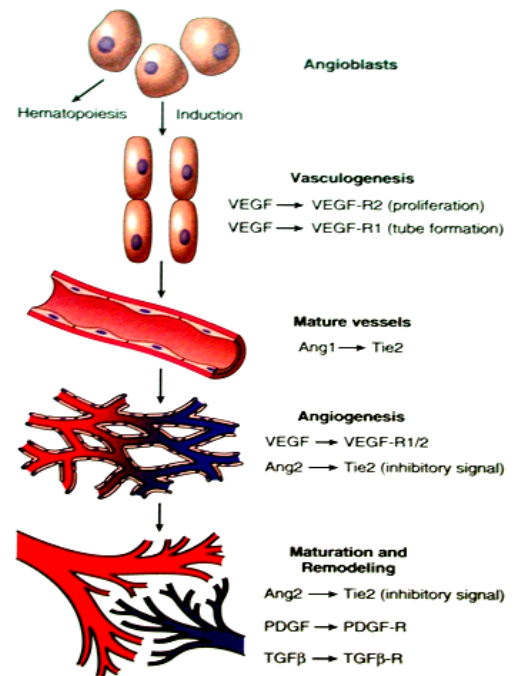
- When the requirements for regeneration are not met
 - then the gaps produced by lost cells heal by connective tissue replacement
- Repair by fibrosis / connective tissue / granulation tissue
- Wound healing
- **Connective Tissue Repair**
 - o Conditions for regeneration are not met
 - o Overview
 - **Angiogenesis:** Formation of new blood vessels (or capillary networks)
 - **Fibroplasia:** Migration & proliferation of fibroblasts
 - Deposition of **Extracellular Collagen Matrix (ECM)**
 - Maturation, contraction, & organization of fibrous tissue (**remodeling**)

- Angiogenesis

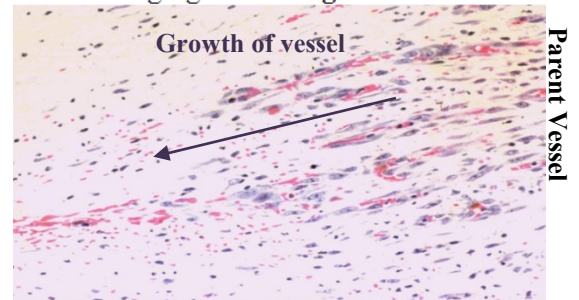


Formation of new blood vessels (angiogenesis) via FGF & VEGF

1. Proteolysis of the parent vessel's basement membrane
2. Migration and chemotaxis of the endothelial cells
3. Endothelial cell proliferation
4. Maturation and formation of capillary tubes (remember new vessels are leaky)
5. Recruitment of supporting cells



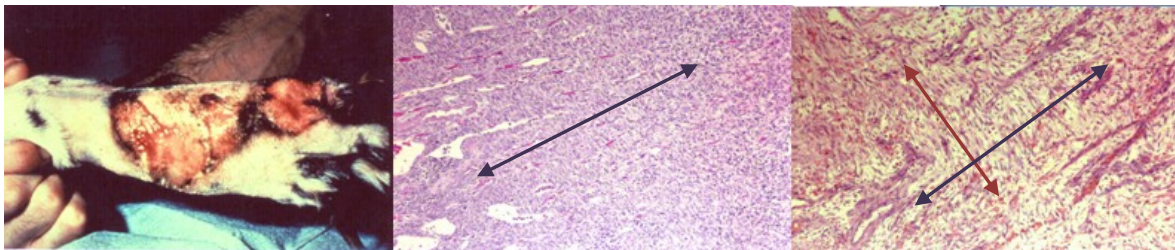
Angiogenesis: Regulation



- Fibroplasia

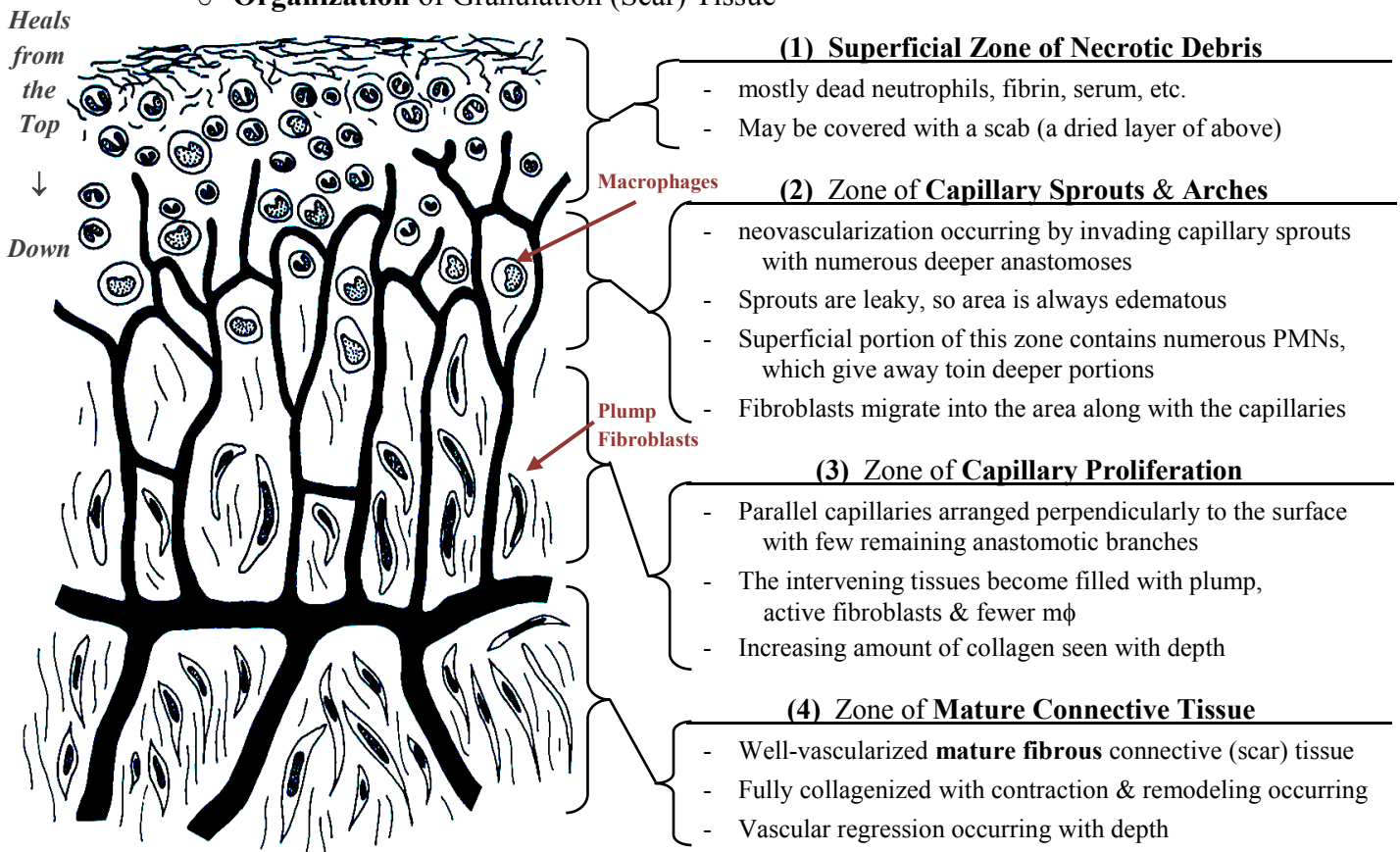
- Fibroplasia via TGF- β , FGF, TNF, PDGF
- New vessels are leaky \rightarrow fibrin and plasma fibronectin in ECM \rightarrow matrix for fibroblast in-migration
- Migration & proliferation of fibroblasts
 - Migrate along scaffolding of extracellular proteins such as fibronectin & fibrin
 - Accompany capillaries
- Deposition of ECM, especially collagen
- Remodeling, collagenization, contraction & vascular regression

- Granulation Tissue (occurs when body can't replace damaged tissue with the same type of tissue \rightarrow scar formation)



Fibroblasts Vessel Growth

○ Organization of Granulation (Scar) Tissue

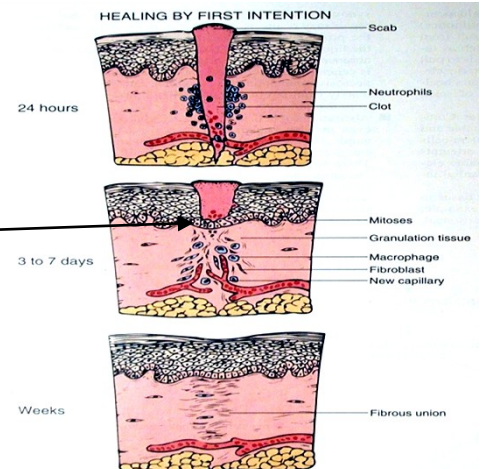


- Wound Healing

o First Intention Healing

- occurs when there is **minimal tissue damage & edges are closely opposed (small tissue gap)**
- Goal of surgical procedures
- Epithelial continuity can be restored as early as 48 hours
- Clean edges closely apposed by sutures
- Allows epithelium to migrate across defect before it fills with granulation tissue (can occur as early as 48 hrs)
- About 10 days before any significant collagenization of the wound occurs

1. Wound fills with blood clot
2. Acute inflammation
3. Simultaneous proliferation of endothelial cells, fibroblasts, & epithelial cells at periphery of wound
4. Endothelial cells & fibroblasts grow across wound & **epithelium** grows over surfaces (**bridges**)
5. Clot and fibrin removed
6. Granulation tissue matures by deposition of collagen, contraction, & remodeling to form scar.
 - About 20% original strength is restored within 3 weeks
 - reaching a maximum of 70% original strength in months

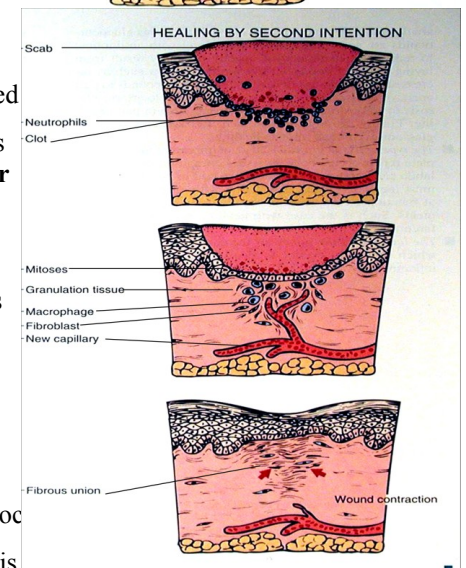


o Second (third) Intention Healing



Dog Leg after being drug behind a car (2nd intention healing)

- occurs when **tissue gap is large** or when a wound is contaminated
- Granulation tissue comes first, before the Epithelial bridge forms → which makes the process **take longer & produce more scar**
- Defect must fill in from edges and base with granulation tissue before re-epithelialization can proceed
- Some references refer **3rd intention healing in infected wounds**



o Nervous System

- **CNS:** healing is by replacement with astroglial scar (fibrous astrocytes)
- **Peripheral nervous system:** nerves can regenerate if axon tube is intact

o Remodeling & Scaring

- Inflammation subsides
- Decreased fibroblasts & EC
- Myoid differentiation of fibroblasts leading to wound contraction
- Crosslinking of collagen into thicker bundles → proteolysis → further contraction → further crosslinking...

1) Discuss post mortem changes including rigor mortis, algor mortis, liver mortis, *et al...*

Post mortem (PM) changes are changes that occur after the organism has died.

- **Algor Mortis:** cooling of the body (equilibration of temperature)
 - 10° change – 2X enzymatic activity
 - ↓ 10° to get ½ the autolysis
 - Wool, thick hair, fat are good insulators (↑ autolysis) in these cases
- **Livor Mortis:** gravitational settling of the blood before it clots
 - downside becomes discolored
 - this is a PM change, NOT a lesion, In forensics, can be used to tell if a body has been moved
- **Rigor Mortis:** PM contraction of muscles
 - Occurs in most used muscles first (masticulation, thorax, extremities)
 - Follows an **agonal period of relaxation**
 - Onset 2-4 hours PM & lasts 24-48 hours
 - will go away & not come back if muscles are stretched, due to ion release
 - Occurs when **glycogen & creatine phosphate** are depleted
 - ATP depletion
 - With the muscle tissue causing it to freeze up
 - **Examples:**
 - Dog dead of strychnine poisoning:
Animal died in **convulsions** → no glycogen or creatine phosphate left → **RAPID onset** of rigor
 - Feedlot steer that is well fed & rested:
Muscles full of glycogen & CrPO4 → Muscles **degenerate before rigor** sets in
→ **DELAYED** (or slow) onset, that may not even occur

2) Describe gross characteristics of PM autolytic change & discuss the **cause(s) of each.**

- Changes in **color** (organs look **lighter** or **darker**)
 - Dead tissues are **lighter** than normal due to **loss of cytochrome oxidases**
 - Dead tissues are **darker** than normal because the tissue is filled with blood
- Changes in **texture**
 - Muscles contract initially, then relax → **Tissues** tend to be **softer**, due to **loss of strength**
- **Leakage of pigments**
 - **Hemoglobin imbibition:** blood leakage → **red** stained tissue
 - **Bile imbibition:** bile leakage → **green** stained tissue
- **Pseudomelanosis**
 - Seen in & around **intestine**; Hydrogen sulfide + hemoglobin = FE sulfide (**black**)
- **Gas formation**
 - Can cause organs to move
 - Can cause diaphragmatic herniation or rupture
 - Can cause gut to twist
 - Sometimes hard to differentiate from **Anti Mortem (AM)** lesions
- **Putrefaction**
 - **Decomposition** of animal **proteins** by **anaerobic** microbes (especially purifying bacteria) → **putrid odor (rotten)**
- **Skeletalization**
 - When bones become exposed due to advanced decomposition

3) Discuss the gross & microscopic similarities & differences between necrosis & autolysis.

Necrosis: pathologic death of one or more cells in part of an organ or tissue due to irreversible cell damage

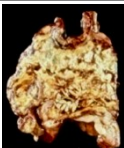
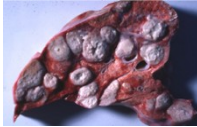
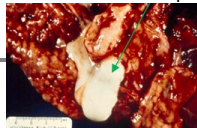
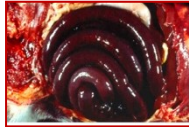
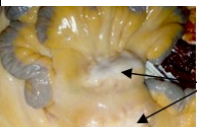
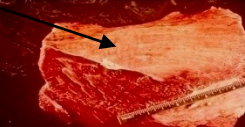
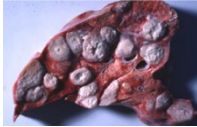
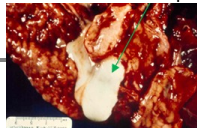

Autolysis: enzymatic digestion of cells by autogenous enzymes occurring after somatic death

	Similarities	Differences	
		Necrosis	Autolysis
Gross Appearance	<ul style="list-style-type: none"> - Changes in color <ul style="list-style-type: none"> - dead tissue is lighter than normal - dead tissue is darker if filled with blood 	<ul style="list-style-type: none"> - Inflammatory response in dead tissue - Living & dead tissue in the same section - Calcification of Dead Tissue (dystrophic mineralization) - Liquefaction & Removal (by mΦ) - Liquefaction & Encapsulation (Abscess formation, bone sequestra) - Replacement with Fibrous Connective (Scar) Tissue - Liquefaction & Migration <ul style="list-style-type: none"> ▪ Draining fistulas ▪ Phlegmon (spreading inflammation → pus / gangrene) - Desquamation (shedding of dead tissue) 	<ul style="list-style-type: none"> - No Inflammation in dead tissue - Only dead tissue is in the same section - Irregular pale staining - Changes in texture <ul style="list-style-type: none"> ▪ Muscles contract & then relax ▪ Softer Tissues (loss of strength) - Pigment Leakage <ul style="list-style-type: none"> ▪ Hemoglobin imbibition (blood leakage → red stain) ▪ Bile imbibition (bile leakage → green stain) - Pseudomelanosis H₂S + hemoglobin = FE sulfide (black stain) - Gas formation (→ organs to move, gut to twist, etc) - Putrefaction - Skeletalization
Microscopic Appearance	<ul style="list-style-type: none"> - Dead cells = dead cells - Nuclear changes are the same <ul style="list-style-type: none"> - Pyknosis (shrunken, dense nucleus) - Karyorrhexis (fragmented nucleus) - Karyolysis (loss of nucleus) - Cytoplasmic changes are the same <ul style="list-style-type: none"> - Increased eosinophilia - Cytoplasmolysis (cytoplasm is broken up & gone) - Coagulation (cytoplasm is denser & stains more pink) 	<ul style="list-style-type: none"> - Red blood cells within vessels are intact 	<ul style="list-style-type: none"> - Red blood cells within vessels have lysed

4) Discuss factors that may influence the rate of PM autolysis & means of minimizing PM autolysis.

- The rate of PM autolysis is temperature dependent: ↑ temperature → ↑ autolysis rate
- Some **species** are prone to more rapid rates of autolysis (ex. mice)
- Some **organs** are prone to more rapid rates of autolysis (ex. livers)
-

5) Discuss 5 types of tissue necrosis; its gross & micro features & pathogenesis, & affected tissues.

	(1) Fat Necrosis	(2) Coagulative Necrosis	(3) Caseous Necrosis	(4) Liquefactive Necrosis	(5) Gangrenous Necrosis
Description	- type of Coagulative necrosis - when fat undergoes necrosis the fat & glycerine combine with metallic ions to form soap (saponification) -	- Fat & Zenker's necrosis - Coagulation of proteins in the tissue - Specific diagnostic lesion -	- assoc. w/ granulomatous inflammation - seen a lot with fungal dz -	- Enzyme breakdown of tissues (tissue liquefies) -	- Moist & Dry Gangrene - Necrosis caused by loss of blood supply - Necrotic tissue invaded by saprophytic bacteria (putrefactive)
Gross	- Loss of shine - Dull, oblique - Firm - Soap-like consistency 	- Tissue retains original form - coherent strength in tissue - Firm, pale, dry consistency - Becomes friable (crumbly) - Surrounded by hyperemia (reddened area)	▪ Dull ; slightly greasy ▪ ~ liquefactive, but Firm ▪ no cohesive strength ▪ usually pale to white ▪ cottage cheese texture ▪ Easily separated 	- fluid filled cavity in a tissue - thin line b/w liquefactive & caseous necrosis - White to pale tan, brown, red, green colored liquid - Cream/puddy-like texture - more foul smelling - often surrounded by fibrous connective tissue capsule 	Moist Gangrene - Swollen, soft, pulpy - Dark in color - Putrefactive smell - Insensitive (no viable blood) - Cold (no body heat) 
Micro	- Cell outline remains - Cytoplasm is replaced by a pale blue soap-like material - Solid to stippled 	- Tissue organization remains - Cell outline remains - Loss of cellular detail - Nuclear changes - Cytoplasmic Coagulation - Hypereosinophilia 	- Loss of all tissue outline (no discernible tissue) - Amorphous, granular debris, mass - Infiltrated with mΦ, multinucleated giant cells - often surrounded by fibrous connective tissue capsules 	- Pink proteinacious fluid - or hole, if the fluid has already poured out - edges are "frayed" tissue 	Dry Gangrene - Tissue is shrunken, wrinkled, leathery, & firm - Pale or darker than normal - Marginal hyperemia (red line) 
Pathogenesis (Causes)	- Pancreatic Fat Necrosis - Vitamin E deficiency - Traumatic Fat Necrosis (from lying on hard surface) - Metabolic Fat Necrosis -	- Local Heat - Local Chemicals (Formalin, Phenol, Alcohol) - Ischemia (no blood supply) - Bacterial Toxins -	- Bacterial Infection by 1) Bacterial proteases enzymes break down bacterial cells 2) Neutrophil proteases enzymes breakdown WBCs (neutrophils) - Some chemicals	1) Central nervous system - Low amounts of coagulative protein - High amounts of lipids - Creates low pH 2) Abscess - Liquid center (pus)	Moist Gangrene - Twisted intestine - Devitalized intestine - Lung aspiration Dry Gangrene - Vascular compromise or ischemia (frost bite) - Parasitic fungus (Ergot) - ↓ # bacteria proliferating
Outcome	- Saponified fat remains in the abdominal cavity - Saponified fats may have no effect or may cause mechanical effects → functional breakdown	- Removes necrotic tissue through slow digestion - Progresses to liquefactive n. - Mineralization - Sequestration	- Encapsulation (typical with tuberculosis) - Liquefaction - Mineralization -	- Walled off abscesses - Remain as fluid - Reabsorbed - Replaced by scar tissue -	-
Tissues	-	- Zenker's Necrosis is specific to striated muscle (skeletal or cardiac)	-	-	- Seen in the extremities (tail, ears, toes, etc.) -

6) List the outcomes of necrosis.

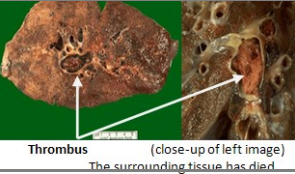
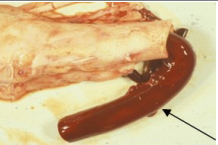
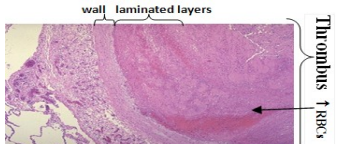
- **Organ dysfunction**
- **Calcification** of dead tissue (**dystrophic mineralization**: necrotic cells that are not destroyed or reabsorbed begin attracting calcium)
- **Liquefaction & Removal** of dead tissue
- Liquefaction & **Encapsulation** of dead tissue (**abscess** formation, encapsulation with **bone sequestra**, etc.)
- Liquefaction & **Migration** of dead tissue (**draining fistulas**, **phlegmon**=spreading inflammation → pus or gangrene)
- Replaced by **Fibrous Connective Tissues** (Scar tissue formation)
- **Desquamation** (shedding of dead tissue from a surface)

7) Differentiate fibrin & fibrous tissue; their origin, morphologic features & fate.

	Fibrin (Fibrinous) Tissue	Fibrous Tissue
Description	<ul style="list-style-type: none"> - Tissue made of Fibrin - Fibrin is an insoluble protein present in blood cells during normal blood-clotting - 	<ul style="list-style-type: none"> - Fibrous connective tissue - Containing, consisting, or resembling fibers -
Origin	<ul style="list-style-type: none"> - product of the coagulation cascade - fibrin is formed from the plasma protein Fibrinogen by the action of thrombin in the presence of Ca²⁺ - 	<ul style="list-style-type: none"> - product of fibroblasts -
Morphologic Features	<ul style="list-style-type: none"> - low strength - 	<ul style="list-style-type: none"> - white - Tough, its collagen fiber content provides strength -
Fate	<ul style="list-style-type: none"> - associated with acute inflammation - 	<ul style="list-style-type: none"> - Chronic

Note: fibrin forms the scaffold for fibroblasts to migrate across for wound healing

8) Discuss differences between thrombosis & PM clots.

	Thrombosis	Postmortem (PM) Clots
Description		when an animal dies, blood clots in vessels & forms a mold in the shape of the vessel (or the heart chamber)
Surface	<ul style="list-style-type: none"> - Dull - Rough, stringy on surface - may not fit vessel 	<ul style="list-style-type: none"> - Shiny - Smooth - molded to vessel
Cut Surface	<ul style="list-style-type: none"> - Granular - Layered - laminations 	<ul style="list-style-type: none"> - Homogenous - Uniform - Shiny & smooth
Consistency	<ul style="list-style-type: none"> - Brittle (crumbly) - Friable 	<ul style="list-style-type: none"> - Resilient - Elastic
Color	<ul style="list-style-type: none"> - Stippled - irregular color - yellow to gray to red - layered with each part different colors 	<ul style="list-style-type: none"> - Current jelly clot – homogenous red - Chicken fat clot – homogenous yellow (plasma)
Attachment	Attached somewhere because it originates from a platelet sticking to vessel wall	Not attached to vessel although may form around valves
Gross	<ul style="list-style-type: none"> - Rough surface - attached to vessel wall - Difficult to remove - Usually pale color (early thrombi may be red) - Due to protein & fibrin 	<ul style="list-style-type: none"> - Shiny & gelatinous - Fills entire chamber - Easily Removed - Usually red, but may have yellow plasma near the surface & be red at the base (as RBCs settle before clotting) 
Microscopic	Attached to vessel wall Laminations – alternating pale layers of platelets admixed with some fibrin & darker layers (↑ RBC) 	

9) Discuss the types, pathogenesis, outcome of infarction & tissues prone to have infarcts.

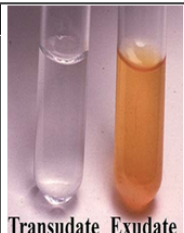
<p>Overview (description)</p>	<p>Infarct: a localized area of anoxic necrosis</p> <ul style="list-style-type: none"> - Infarcts are classified on the basis of their color (which has to do with the amount of hemorrhage) 		
<p>Types</p>	<p>Red Infarcts</p>	<p>White Infarcts</p>	<p>Septic Infarcts</p>
<p>venous occlusion in loose tissue (lung) which allows blood to collect in the infarcted zone & in tissue with dual circulation (small intestine)</p> <p>venous blockage</p> <p>↑ blood in a tissue</p> <p>Thrombus</p> <p>pervious (loose) tissue</p> <p>New</p> <p>Red for a few hours</p> <p>Lungs & intestines</p>	<p>• Caused by obstructed veins</p> <p>↓</p> <p>• Necrosis 2° to hypoxia</p> <p>• Twisted intestine (colonic torsion) collapses the veins but the more muscular aa allow some blood to be pumped into the area</p> <p>• Congested red intestines</p>	<p>arterial occlusion' solid organs (heart or kidney) density of tissue limits the amount of blood that can seep into an area of ischemic necrosis</p> <p>Arterial blockage</p> <p>No blood in tissue</p> <p>Embolism</p> <p>Dense Tissue</p> <p>Old</p> <p>White due to RBC breakdown</p> <p>Heart & Kidneys</p>	<p>occur when emboli fragment from bacterial vegetation on a heart valve</p> <p>cause inflammation</p> <p>can spread infection to other tissues</p>
<p>Pathogenesis</p>	<p>Ischemic necrosis of tissue caused by occlusion of either the arterial supply or the venous drainage in a particular tissue</p> <ul style="list-style-type: none"> - Most infarcts result from thrombotic or embolic events in arteries - Although venous thrombosis may cause infarction, it usually results in venous obstruction & congestion <ul style="list-style-type: none"> ▪ Infarcts caused by venous thrombosis are more likely in organs with single venous outflow (e.g. Testis & Ovary) 		
<p>Outcomes</p>	<p>All infarcts heal by scarring because all tissue is dead (including the stroma) & there is nothing left to heal</p> <p>Consequences of ischemia/necrosis</p> <ul style="list-style-type: none"> • Earliest change is cell swelling & disintegration of mitochondria • Loss of energy → cell membrane damage <ul style="list-style-type: none"> - Allows water, electrolytes, & plasma proteins to leak into cells - Increases intracellular Ca → irreversible cytopathic changes & necrosis - Cellular enzymes are released into interstitial fluid as the cell dies & starts to kill surrounding cells 		
<p>Tissues Prone to Infarctions</p>	<p>Arteries (due to Thrombotic or Embolic events)</p> <p>Testis & Ovaries (due to obstruction of single venous)</p> <p>Lungs & Intestines (Red Infarcts)</p> <p>Heart & Kidneys (White infarcts)</p>		

- 10) Discuss common causes & pathogenesis, gross appearance, & consequences of edema.
Also give example conditions for each formative pathogenesis.

Overview of Edema	
Edema: increased fluid extravasation into interstitial/extracellular spaces (including body cavities)	
Common Causes & Pathogenesis	<ul style="list-style-type: none"> ○ Intracellular edema <ul style="list-style-type: none"> ● Depression of metabolic systems of the tissues or lack of adequate nutrition to cells <ul style="list-style-type: none"> - Depressed ionic pumps → Sodium (Na) & water leak in ● Inflammation <ul style="list-style-type: none"> - Increased permeability of cell membranes → Sodium (Na) & water leak in ○ Extracellular edema <ul style="list-style-type: none"> ● Abnormal leakage of fluid from blood capillaries ● Failure of lymphatic system to return fluid from interstitium ● Renal retention of salt and water ○ Non-inflammatory edema (Transudate) <ul style="list-style-type: none"> ● <u>Low</u> protein levels ● Fluid accumulation due to hydrostatic imbalances between intravascular & extravascular compartments DESPITE normal vascular permeability ● Clear, colorless, or slightly yellow ○ Inflammatory edema (Exudate) <ul style="list-style-type: none"> ● Related to ↑ endothelial permeability ● <u>High</u> protein levels ● Caused by leakage of plasma proteins (albumin) & leukocytes (white blood cells) ● Usually opaque
Gross Appearance	<ul style="list-style-type: none"> - Acute (rapid) onset - Swollen, distended, tends to gravitate ventrally (sagging tissues) - Tissue pits on pressure & indentations remain after pressure is removed - Tissue is cool to touch (unless inflammation is also present) - Tissue is not red or painful
Consequences	<ul style="list-style-type: none"> - Edema is considered to be a space displacing lesion (exerts pressure in a closed area) - Edemas are generally easily resorbed if cause is removed
Examples of Conditions for each Formative Pathogenesis	

- 30) Know the Differences Between Transudates & Exudates

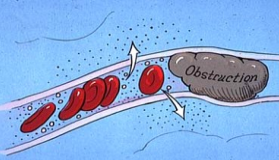
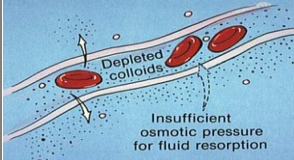
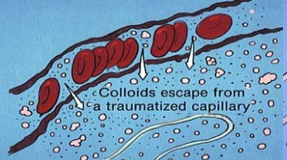
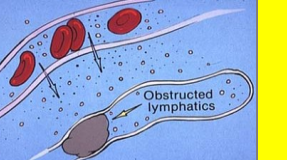
	Transudate Edema (Non-Inflammatory)	Exudate Edema (Inflammatory)
Specific gravity	≤ 1.1015	>1.017
Protein content	< 2.5 gm/dL	> 3 gm/dL
# Nucleated Cells Present	< 1000	> 1000
Fibrin clots	none	Yes – fibrin is escaping
Clarity	Clear	turbid
Color	None (clear)	Yellow-orange



29) Be able to name enema of different anatomical areas & give species examples as to which are most likely where (gross appearance of edema)

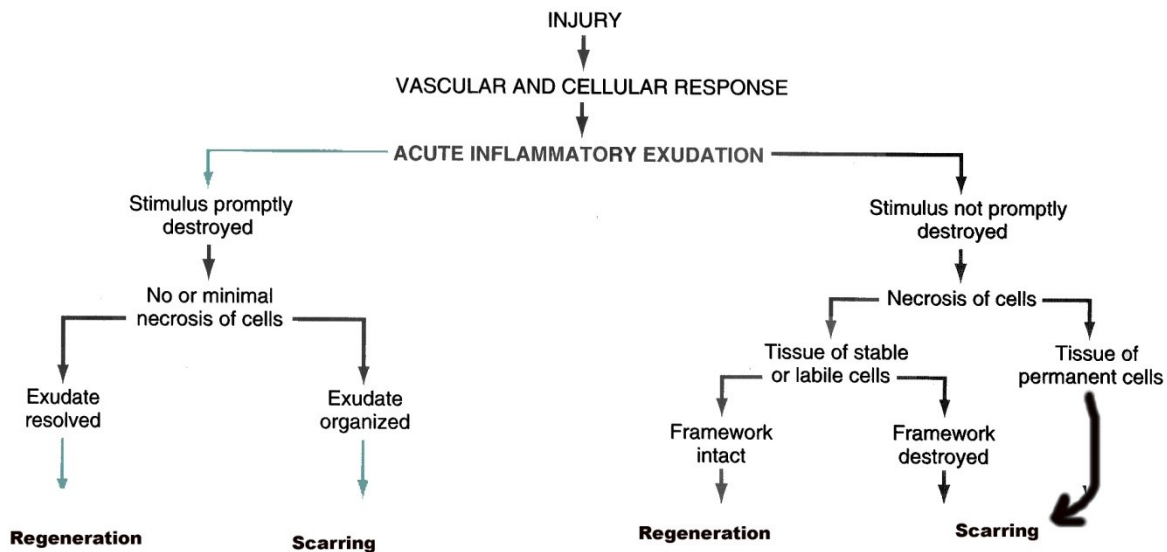
Site-based Nomenclature		Edema by Species
<p>"Hydro-"</p> <ul style="list-style-type: none"> - Hydrothorax – fluid in pleural cavity - Hydropericardium – fluid in pericardial sac - Hydrosalpinx – fluid in uterine tube - Hydrocephalus – accumulation of fluid in the brain - Hydrocoele – fluid-filled cyst anywhere in body - Hydroperitoneum (ascites) – edema in the peritoneal cavity - Anasarca – severe and generalized edema, with profound SQ tissue swelling <p>Hydrops-"</p> <ul style="list-style-type: none"> - Hydrops of gall bladder - Hydrops allantois – accumulation of fluid in the placenta - Dropsy – accumulation of fluid in a body cavity 		<p>Different species develop edema in different places</p> <ul style="list-style-type: none"> ○ Cats: <ul style="list-style-type: none"> - Hydrothorax ○ Dog <ul style="list-style-type: none"> - ascites ○ Horse <ul style="list-style-type: none"> - Ventral abdomen - Ventral thorax - If severe – distal extremities ("stocking") ○ Bovine <ul style="list-style-type: none"> - Intermandibular space - Brisket area (thoracic inlet)
Anasarca (SQ Edema)	Ascities Edema	Septicemia Edema
<ul style="list-style-type: none"> - Different distributions, depending on the cause - Can be diffuse or may be more conspicuous at sites of highest hydrostatic pressures - distribution is frequently gravity dependent 	<ul style="list-style-type: none"> - presence of clear, yellow-tinged fluid - Fluid distends loose connective tissues or - Fluid accumulates in body cavities <ul style="list-style-type: none"> ▪ Peritoneal ▪ Pleural ▪ pericardial 	<p>ex.1: Pig suffering from edema disease</p> <ul style="list-style-type: none"> - Due to septicemia w/certain strains of E. coli - These bacteria produce a toxin - The toxin acts on endothelial cells → allowing fluid to leak out - Pigs also frequently exhibit conjunctival edema (cannot open eyes)

31) Understand the pathogenesis of edema

Edema Pathogenesis Review					
	(1)	(2)	(3)	(4)	(5)
	↑ Hydrostatic Pressure	↓ Plasma Colloidal Pressure	↑ Vascular Permeability	Lymphatic Obstruction	Heart Failure/Na Retention
Depiction					
Description	<ul style="list-style-type: none"> - Venous obstruction or impaired outflow → ↑ hydrostatic pressure as blood backs up → sodium & fluid leak into the interstitial tissue 	<ul style="list-style-type: none"> - ↓ Hepatic protein synthesis - ↑ Protein loss through kidneys → ↓ colloids in capillary blood - Hyperproteinemia → fluid & sodium are not re-absorbed - interstitial fluid accumulation 	<ul style="list-style-type: none"> - Endothelial cell damage → ↑ capillary permeability to fluids, salts, & colloids → ↑ colloids in the interstitium → re-absorption of fluid - lymphatics may drain colloids 	<ul style="list-style-type: none"> - Lymphatic obstruction → Accumulation of fluids, salts, & colloids in the capillaries 	<ul style="list-style-type: none"> - Can't consume enough salt to cause sodium (Na) retention - ↑ Tubular re-absorption of sodium
Diseases that cause	<ul style="list-style-type: none"> - Congestive Heart Failure - Cirrhosis of the Liver 	<ul style="list-style-type: none"> - Hypoalbuminemia (liver failure) - Cirrhosis of the Liver - Kidney disease - Malnutrition / starvation - Protein-losing Gastroenteropathies - Gastrointestinal parasitism 		<ul style="list-style-type: none"> - Inflammation - Neoplasia - Post-surgical - Post-irradiation 	<ul style="list-style-type: none"> - Congestive Heart Failure - Kidney disease

11) **Review mechanisms of inflammation, including causes, vascular & cellular events, chemical mediators...the BIG picture only!!!**

Mechanisms of Inflammation	
Causes (initiating stimuli)	<ul style="list-style-type: none"> - Infections (bacterial, viral, fungal, parasitic) - Microbial or other toxins; xenobiotics - Trauma (blunt or penetrating) - Physical or chemical agents (thermal, irradiation, caustics) - Tissue necrosis - Foreign bodies - Immune (hypersensitivity reactions) - -
Vascular Events	<ul style="list-style-type: none"> - Transient Vasoconstriction - Vasodilation - Increased Vascular Permeability - Vascular Leakage
Cellular Events	<ul style="list-style-type: none"> - Margination of Leukocytes along vessel wall - Leukocyte (Neutrophil) Rolling - Firm Adhesion ("pavementing") - Neutrophil Emigration & Chemotaxis - Phagocytosis
Chemical Mediators	


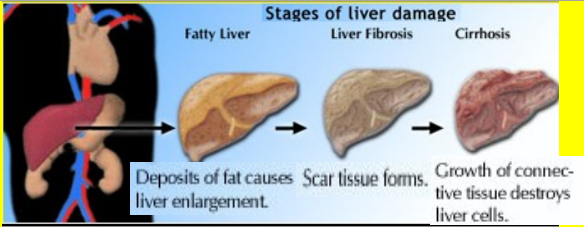


- 12) **Classify inflammatory exudates in terms of their primary or major components, then discuss a likely etiology, gross & microscopic features, & tissues in which a particular type of exudate occurs frequently.**

Types of Exudates					
	Major Components	Etiology	Gross- & Micro-	Tissues affected	
Acute	Serous	- Protein rich fluid exudate - Inflammatory Edema	- From plasma or secreted by serous mesothelial cells	- Watery / runny nose - Blister	
	Catarrhal	- Inflammation of a mucosal surface predominantly characterized by hypersecretion of mucus	-	- Catarrhal rhinitis - Mucoid enteritis	
	Fibrinous	- Protein-rich exudate vascular permeability such that fibrinogen escapes the vessels & polymerizes in the tissue or on a surface to form fibrin	-	- Fibrin is white to yellow - Easily broken down - Usually adherent mat of exudate on a serous or mucosal surface - Flecks to clumps of fibrin are frequently free-floating within fibrin exudates	- Fibrinous pericarditis (shipping fever pneumonia) fibrinous inflammation of the pericardial sac, seen in catal
	Suppurative (Purulent)	- Neutropils are the principal component of pus	- Formation of Pus! - Frequently associated with Pyogenic (pus forming) bacterial infections -	- Abscesses (localized pus) frequently surrounded by a connective tissue capsule -	- Boils, & strangles in horses - Empyema (accumulation of pus in a natural cavity) - Phlegmon (pus accumulation along a natural tissue plane) - Ex. cellulitis
Lymphocytic (Subacute)	- Nearly pure infiltrating population of lymphocytes &/or plasma cells -	- Seen with immune mediated & viral diseases	- Often no gross lesions -	- Interface dermatitis (immune mediated disease) - Lymphatic thyroiditis (viral dz) - German shorthair pointer with lupus erythematosus & pemhigus	
Granulomatous (Chronic)	- "histocytic inflammation" - Granulomas are localized accumulations of mΦ - Followed by fibrosis around or within the reaction -	- Macrophage infiltration via exudation of monocytes - monocytes mature into mΦ - mΦ can differentiate into epitheloid cells - epitheloid cells can merge to form multinucleate giant cells - characteristic of persistent infectious organisms (fungi, parasites, protozoa, <i>Mycobacterium</i> spp.)	- a mass with or without a caseous center -	-	
Eosinophilic	- Characterized by infiltration of eosinophils	- Usually associated with parasitism or allergic disease & some fungi	- Eosinophils give exudate a lime green tint	-	
Necrotizing / Pseudomembranous	- Necrotizing: necrosis is a major feature with little cellular exudation -	-	- Pseudomembranous: exudate forms a confluent layer of debris over the mucosal surface	-	
Hemorrhagic	-	- Vascular damage allows the RBCs to leak into the injured area	- Hemorrhage is the primary sign - RBCs don't actively exude into the inflamed area	-	

- 13) Discuss types & pathogenesis of pathological pigmentation & discoloration of tissues; remember to look over the bilirubin pathways & icterus.

14) Discuss etiology, pathogenesis & fate of fatty changes in the liver

Fatty Changes in the Liver	
Overview	<ul style="list-style-type: none"> - Fatty change is a sort of sub-set of cell swelling; It has nothing to do with adipose (fat) tissue - It's the accumulation of neutral fats, ie. Triglycerides (TG) in a cell - It is a common change in injured cells (Especially cells that metabolize lots of lipids) such as... <div style="display: flex; justify-content: space-around; text-align: center;"> Hepatocytes Myocardial cells Renal tubular epithelial cells Diabetes mellitus </div> - Sick cells tend to accumulate TG & undergo fatty change
Gross Appearance	<ul style="list-style-type: none"> - yellow discoloration (kidney/liver) - Enlarged (liver) - Hepatocytes are chocked full of fat 
Micro-Appearance	<ul style="list-style-type: none"> - Small to large - Clear - Non-membrane bound - Intracytoplasmic vacuoles - Nuclei are pushed to the cell periphery
Etiology	
Pathogenesis	<ul style="list-style-type: none"> - Overload <ul style="list-style-type: none"> ▪ Increased mobilization of fats (anorexia) → ex. Fat Cats stop eating ▪ Diabetes mellitus → ex. animals with diabetes mellitus also stop eating - Injury to Cells by Toxins or Anoxia - Deficiencies in Methionine or choline - Lipidosis <ul style="list-style-type: none"> ▪ Normal in young animals (milk diet) ▪ Normal following fatty meals
Outcome (Fate)	

15) (a) List & Understand the Cellular Responses to Cell Injury

Nature and Severity of Injurious Stimulus	Cellular Response
Altered physiologic stimuli: <ul style="list-style-type: none"> • Increased demand, increased trophic stimulation (e.g. growth factors, hormones) • Decreased nutrients, stimulation • Chronic irritation (chemical or physical) 	Cellular adaptations: <ul style="list-style-type: none"> • Hyperplasia, hypertrophy • Atrophy • Metaplasia
Reduced oxygen supply; chemical injury; microbial infection <ul style="list-style-type: none"> • Acute and self-limited • Progressive and severe (including DNA damage) 	Cell injury: <ul style="list-style-type: none"> • Acute reversible injury • Irreversible injury → cell death <ul style="list-style-type: none"> ◦ Necrosis ◦ Apoptosis • Subcellular alterations in various organelles
Metabolic alterations, genetic or acquired	Intracellular accumulations; calcifications
Prolonged life span with cumulative sublethal injury	Cellular aging

15) (b) **Define & give an example of each of the following ...**

Agenesis: "absence of the beginning." There is nothing there, total lack of development, The organ has **no function**, because there is nothing present to represent the organ. Fairly rare, but it does happen

Anaplasia: "backward form." Backward development (**reversion**) of **differentiated cell** population to a more undifferentiated, primitive, or embryotic cell type. Typically seen in **rapidly proliferating** cell populations (**tumors**). Always indicates a **neoplastic process**. Anaplasia correlates to the **degree of cellular malignancy**. ex. **Anaplastic Tumors**

Aplasia: "absence of form." A **primordium** is formed, but there is **no cellular differentiation** → The organ has **no function**
Primordium: An organ or tissue in its earliest recognizable stage of development
ex. Aplastic cerebellum of Calf Brain; Aplasia is often seen in the **kidneys of kittens & pigs**

Atrophy: the **cells get smaller**, through the wasting of tissues, organs, or the entire body, as from death & re-absorption of cells, diminished cellular proliferation, ↓ cellular volume, pressure, ischemia, malnutrition, ↓ function, or hormonal changes ex. **Testicular Atrophy, Muscular Atrophy, Adrenal Cortical Atrophy**

Carcinoma in situ: Within place, site of origin. A population of neoplastic cells that have not yet spread (still in place); a little nest of neoplastic cells. Have not broken through the basement membrane, therefore, a malignant tumor that is easily removed. Want to diagnose neoplasia at this stage (1st recognition of malignancy)

Dysplasia: "sick form." Malformation during maturation such that there is a loss of normal tissue relationships & arrangements of tissue elements. The part is never normal because the malformation occurs during the part's development. Typically occurs **during embryogenesis**, especially in **joint development** (ex. **hip dysplasia**).

Dystrophy: progressive changes that may result in defective nutrition of an organ or tissue

Hyperplasia: ↑ **# of cells** in an organ or tissue, which causes enlargement of the surrounding organs
Hyperplasia is a **Catabolic** Process (does NOT require energy; passive; associated with "breaking down" processes)
ex. Often seen in **Kitten Kidneys** (one has Atrophy & the other Hyperplasia); **Prostatic hyperplasia (XS)**

Hypertrophy: general ↑ in the bulk of a part or organ, not due to tumor formation, essentially the cell size ↑ without ↑ the # of cells.
Hypertrophy is an **Anabolic** Process (active, requires energy) & it can be either good or bad.
ex. **Cardiac hypertrophy**

Hypoplasia: "small form." Partial formation of an organ, Organ fails to achieve normal size (**too small**).
Correct organ cellular differentiation (can tell what the organ is). The organ may have **limited function**.
ex. **Palatoschisis (cleft palate)**

Involution: return of a large organ to its normal size

Metaplasia: "next form." Transformation or replacement of one adult cell type with another.
Caused by of chronic inflammation the body is trying to protect the organ from further injury.
ex. "**Side bones**" in horses; **Barrett** metaplasia; **respiratory** epithelium becomes **stratified squamous endothelium**

Neoplasia: "new form" of tissue. Pathologic process that results in the formation & growth of a **neoplasm**
Neoplasm: a tumor, which is an **abnormal** tissue that grows by **cellular proliferation more rapidly** than normal & continues to grow after the stimuli that initiated the growth has ceased
ex. **Squamous cell carcinomas** (most common type of skin tumor)

16) **Recognize & explain the following...**

Diphtheritic Membrane	Pseudomembrane	Granuloma	Cellulitis	Gangrene

17) **Be able to name inflammation of organs**

19) **Define & give examples of etiology, pathogenesis, morphologic changes**

20) Understand the differences between clinical signs & symptoms

Sign= objective, quantitative, visible

Symptoms: subjective, qualitative, internal (associated with humans not animals)

Syndrome: a set of **clinical signs** that occur with enough regularity to be recognized as a **distinct entity**

21) Explain & give examples of subcellular responses to injury/necrosis

o Nuclear Change

- Chromatin clumping
- Condensation (**pyknosis**)
 - **Pyknosis**: a common subcellular, pathologic term meaning a thickening or ↓ in the size of the cell or its nucleus
- Dramatic nuclear change is usually indicative of necrosis (nuclear pyknosis is a stage of necrosis)

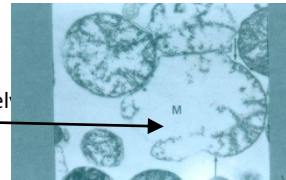
o Ultrastructural Changes

• Plasma membrane

- Loss of surface features
 - **Microvilli**: one of the minute projections in the cell membrane that greatly increases the surface area
 - **Cilia**: motile extension of the cell surface
- Desmosome breakdown
- "**bleb**" formation on the cytoplasmic membrane

• Mitochondria

- **Swelling**
 - may eventually rupture, if it ruptures the cell will most likely die
- Loss of dense granules
- Calcium deposits



• Endoplasmic Reticulum (ER)

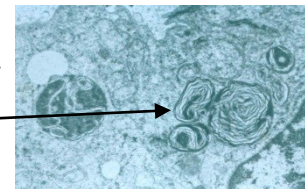
- Dilatation (contributes to vacuolar microscopic appearance)
- Dissociation of ribosomes → until they eventually fall off

• Phospholipids

- The phospholipids are from damaged organelle membranes accumulate to form "**myelin figures**"

• Lysosomes

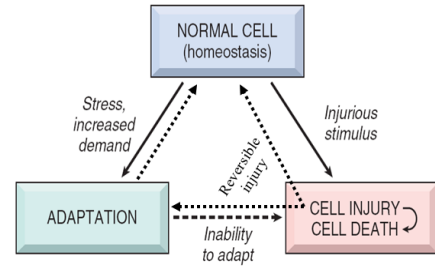
- Dilation & rupture → pH decreases to the point where the cell can't recover
- Usually a late event/terminal event in a cell injury
- Lysosomes are packed with **concentrically laminated**, peroxidized, **autophagocytized** cell membranes



Normal Cells	Reversible Ischemic Changes	Irreversible Ischemic Changes
Normal epithelial cell of proximal tubule. Note microvilli (mv) lining the lumen (L) , nucleus (N) , & normal apical vacuole (V) .	<ul style="list-style-type: none"> • Microvilli are lost & have been incorporated into the apical cytoplasm • Blebs form & are extruded in the lumen • Mito are slightly dilated 	<ul style="list-style-type: none"> • Markedly swollen mito containing amorphous densities • Disrupted cell membranes • Dense, pyknotic nucleus

22) Hallmarks of irreversible cell injury

- Severe mitochondrial swelling
- Large flocculent densities in mito matrix
- Increased loss of proteins, enzymes, co-enzymes out of the cell
- Greatly increased membrane permeability
 - **Leakage of enzymes**
 - **ALT & ALP** (enzymes that are released during liver damage)
 - **CPK** is released during heart damage
 - Thus, the levels of these enzymes can be used to estimate organ damage
 - **Initiation of inflammation**



23) Understand & list differences between necrosis & apoptosis

- Originally thought to be completely distinct from necrosis
- now it is believed that there is a fairly large degree of overlap between them
- Two ends of a spectrum

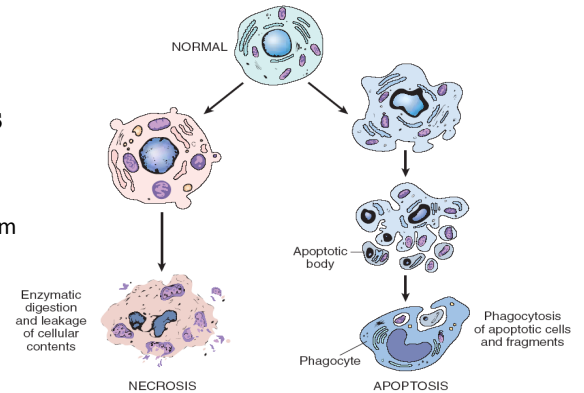
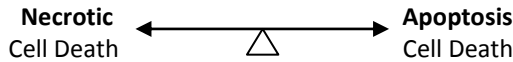


TABLE 1-2 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

24) (a) List examples of causes of necrosis

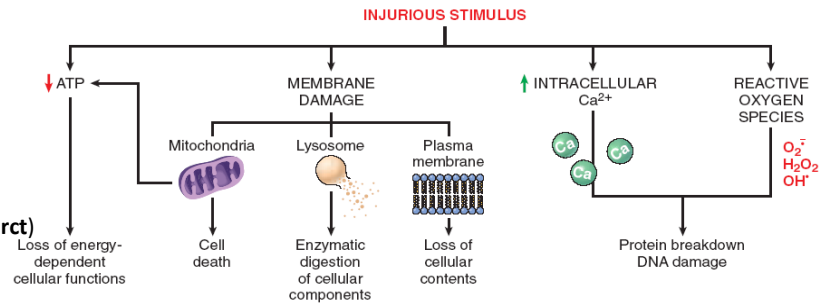
Causes of Necrosis

- Acute (rapid) loss of blood supply (**ischemia**)
 - **ischemia** : restriction in blood supply, usually due to problems in the blood vessels → tissue damage or dysfunction
- Loss of nerve supply (such as an atrophic muscle)
- Loss of endocrine stimulation
- Endotoxins coming from bacteria can cause wide spread cellular necrosis
- Mechanical/thermal injury
- Chemical injury
- Pressure

24) (b) be able to explain mechanisms of cell necrosis

Mechanisms of Cell Necrosis

- **Passive** form of cell death
- Occurs in the absence of energy
- Doesn't require metabolism to complete
- Frequently affects large numbers of cells (ex. **infarct**)
- Generally associated with injurious insults
- **Sites of damage in cell injury**



1) **Mitochondrial ATP production Stops**

- ATP depletion & decreased ATP synthesis are frequently associated with both **hypoxic & chemical (toxic)** injury
- ATP depletion to <5% to 10% of normal levels has widespread effects on many critical cellular systems
 - Small losses in ATP critically effect the cellular systems

2) **Plasma membrane energy-dependent NA pumps shut down**

3) **Na⁺/H₂O enter cell**

4) **Cell Swelling/Membrane stretching** (This is the pathogenesis for cell swelling)

5) **Glycolysis allows the cell to function at a decreased level**

- Glycogen stores are depleted
- Lactic acid accumulates
- Cell pH drops → induction of Heat Shock Response

6) **Failure of CA²⁺ pumps → CA²⁺ enters the cell → many effects**

- Can occur simultaneously with #5
- Disruption of protein synthetic apparatus
- Detachment of ribosomes
- Decreased protein synthesis

7) **CA²⁺ activation of enzyme systems**

- Too much calcium in a system can do a lot of damage all at once
 - **Phospholipases:** breakdown of phospholipids
 - **Proteases:** breakdown of proteins
 - **ATPases:** breakdown of ATP
 - **Endonucleases:**
- Mitochondria are often damaged by increases in **cytosolic CA²⁺**
- Inner membrane permeability is increased
- **Loss of proton motive force** = death blow for the cell
- **Leakage of cytochrome C**
 - An integral component of the electron (e⁻) transport chair
 - Can trigger apoptotic death pathways in the cytoplasm

8) **Unfolded Protein Response** (Attempt to prevent protein denaturation)

9) **Protein denaturation starts**

10) **Damage to all membranes of all organelles**

11) **ER & other organelles swell**

12) **More changes in membrane permeability**

- With massive influx of CA²⁺
- This will likely be the final death blow to the cell

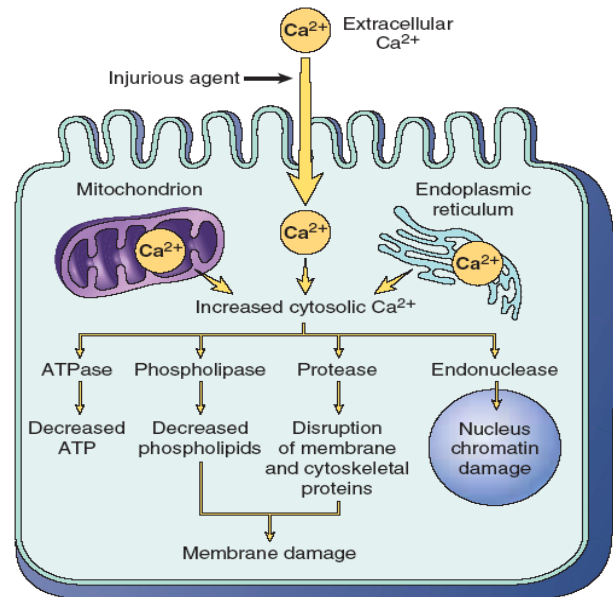
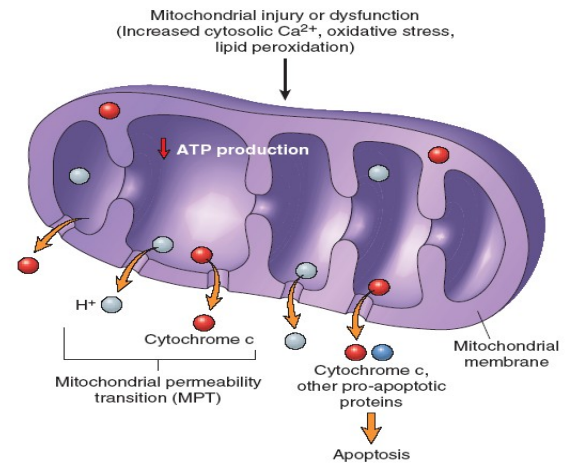



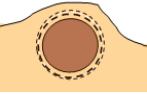




FIGURE 1-13 Sources and consequences of increased cytosolic calcium in cell injury. ATP, adenosine triphosphate.

25) List 5 characteristics of neoplasia & 2 hallmarks of neoplastic growth

- **Characteristics of neoplasm (5)**
 - 1) **Abnormal mass** of cells or tissue
 - 2) Growth rate exceeds normal; **rapid mitotic activity**
 - 3) Growth is uncoordinated with the body's needs &/or other tissue (**Autonomous**: self-controlled growth)
 - 4) Growth continues after the inciting cause is removed
 - 5) Progressive such that each generation of cells is further from normal until death

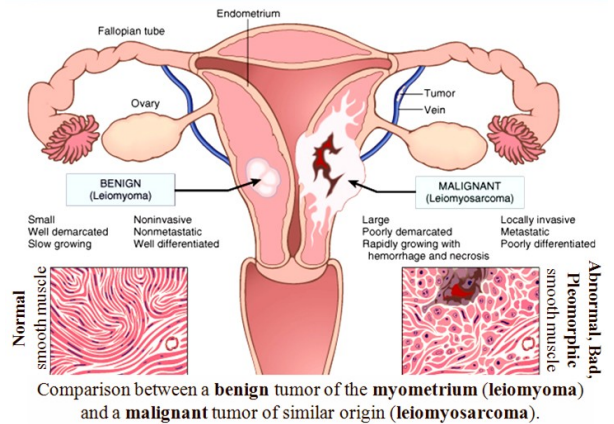
- **Hallmarks of malignant growth (2)**
 - 1) **Metastasis**: the **spread of a disease** process **throughout the body** by way of the **circulatory system** (blood &/or lymphatics)
 - 2) **Infiltrative growth**: difficult to remove 

26) List differences between benign & malignant tumors (gross & micro)

	Benign	Malignant
Growth rate	- Slower	- Faster
Growth progression	- Limited Growth - STOP or REGRESS - most will quit growing once a certain size is reached	- Unlimited growth - Progressive & grows until death - Each generation may grow faster
Interface with normal & adjacent tissue**	- Expansive growth - usually easy to remove - Sharp demarcation - often encapsulated 	- Infiltrative growth - Difficult to remove - "Dimple effect" anchored 
Growth on surface**	- Grows outward - Grows on a stalk - Has a with restricted base - becomes pedunculated 	- Sessile - broad base- growth - un-restricted base 
Recurrence	- Not expected	- Expected
Vascularization	- adequate blood supply (~ normal) - no necrosis -	- Inadequate blood supply - necrosis due to anoxia - infarction b/c tumor grows into itself - tumor outgrows supply
Metastasis	- No	- Yes
Anaplasia	- No anaplasia - normal, uniform population	- Yes – more anaplasia - more malignant
Nuclear chromatin	- Near normal	- Hyperchromatic - Polyploidy (several X #)
Nuclear/cytoplasmic ratio	- Small (normal)	- Large (b/c large nuclei)
Nucleoli	- normal	- Large, prominent , exaggerated - triploid  - bizarre
Mitotic figures	- Few or absent	- Numerous, Bizarre, abnormal looking
Overall cell size	- Normal & uniform	- Irregular & Pleomorphic (many shapes & sizes)
Invasion of vessels	- none	- yes
Tissue structure (architecture)	- Nearly normal	- Loss of normal tissue structure (more non- normal) - more malignant

18) Be able to name benign & malignant neoplasms

Sarcoma Nomenclature Mesenchymal (Support Tissue) Origin			
	Prefix (cell of origin)	Benign (Suffix = oma)	Malignant (Suffix = sarcoma)
Fibroblasts	Fibr-	Fibroma	Fibrosarcoma
Bone	Oste-	Osteoma	Osteosarcoma
Cartilage	Chondr-	Chondroma	Chondrosarcoma
Striated muscle	Rhabdomy-	Rhabdomyoma	Rhabdomyosarcoma
Mast cell		--	Mast cell sarcoma
Lymphocytes	Lymph-		Lymphosarcoma or Lymphoma



Carcinoma Nomenclature Epithelial (glandular) Origin		
Prefix	Benign (Suffix = oma)	Malignant (Suffix = carcinoma)
Simple epithelium (Prefix = gland)		
Stratified squamous	Squamous papilloma	Squamous cell carcinoma
Urothelium	Transitional papilloma	Transitional cell carcinoma
Basal Cell	epithelioma	Basal cell carcinoma
Glandular epithelium (Prefix = gland + adeno)		
Mammary	Mammary adenoma	Mammary adenocarcinoma
Thyroid	Thyroid adenoma	Thyroid adencarcinoma

Breaking the nomenclature rules

- Adding malignant
 - Lymphosarcoma = malignant lymphoma
- "cyt" vs. "blast"
 - If a tumor has "cyt" in its name, it is not as malignant as one with "blast"
 - Astrocyte vs. astroblast (malignant astrocytoma << malignant astroblastoma)
- Melanocytic tumors
 - Benign = melanocytoma
 - Malignant = melanoma

27) Understand mechanisms of metastasis & paraneoplastic syndromes

Metastasis – the spread of a disease process throughout the body by way of the circulatory system (blood &/or lymphatics)

- Sarcomas: metastasize by way of venules (blood system); Look in the lung for secondary metastases (e.g. Osteosarcoma)
- Carcinomas: Metastasize by way of the lymphatics; Look for secondary METS in the (draining) lymph nodes; Look for tertiary METS in the lung (e.g. Mammary adenocarcinoma)
- **Methods of Tumor Spread**
 - o Direct Invasion (Expansive (benign) or Infiltrative (malignant) linear growth of Tumors into adjacent tissues)
 - o Transplantation (Fine needle aspirate; Organ transplantation)
 - o Implantation (Transfer of tumors from one adjacent surface to another by physical contact, especially in the thoracic & abdominal cavities where organs rub together; tumors prone this type of spread: Carcinomatosis, Ovarian cancer, Mesophilioma, Lung Tumors)
 - o Transmissible Venereal Tumors (TVT) (Tumor caused by a virus, spread by mating dogs)
 - o Spread along preformed ducts (Milk ducts in the mammary glands; salpinx; seminiferous tubules (Sertoli cell tumors))

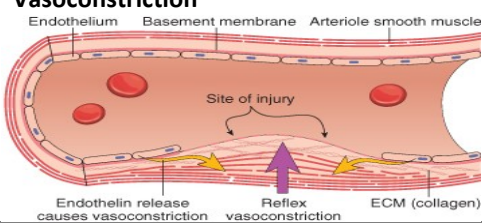
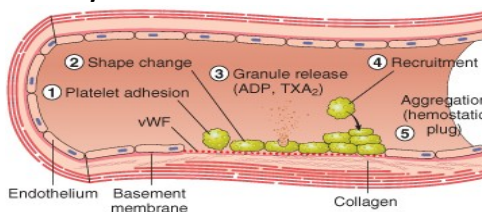
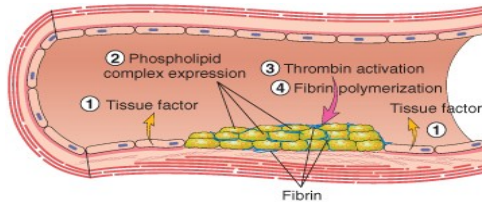
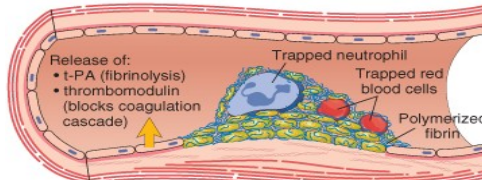
Paraneoplastic Syndrome: sets of clinical signs that are a side effect of neoplasia

- Usually due to secretion of hormones, metabolites, or other mediators that have an action on other organs
- ex. Feminization of male dogs with Sertoli Cell Tumors (sertoli cells stop producing sperm & start producing estrogen)
- ex. Lymphosarcoma (inappropriate secretion of hormones → calcium pulled from bone & deposited into blood → hypercalcemia → mineralization of soft tissues, vomiting, & irregular heartbeat)

28) Be able to briefly discuss basic aspects of the molecular basis of cancer

- Cancer is a **genetic disease**
- Damage to the cellular genome is a common feature for virtually all neoplasia, regardless of the tissue it is found in
- Many diverse agents can result in this damage, such as: Viruses; Mutagenic chemicals; Radiation
- The genetic damage is believed to be random & many mutations may be inconsequential
- Classes of **regulatory genes** that can be **affected** in the **development of abnormal cell growth**, eventually **resulting in neoplasia**
 - 1) **Oncogenes**
 - **growth-promoting** regulatory genes
 - 2) **Tumor suppressor genes**
 - **growth-inhibiting** regulatory genes
 - 3) **Apoptotic genes**
 - regulate "**programmed cell growth**"
 - 4) **DNA repair genes**
 - often considered to be another class of tumor suppressor genes

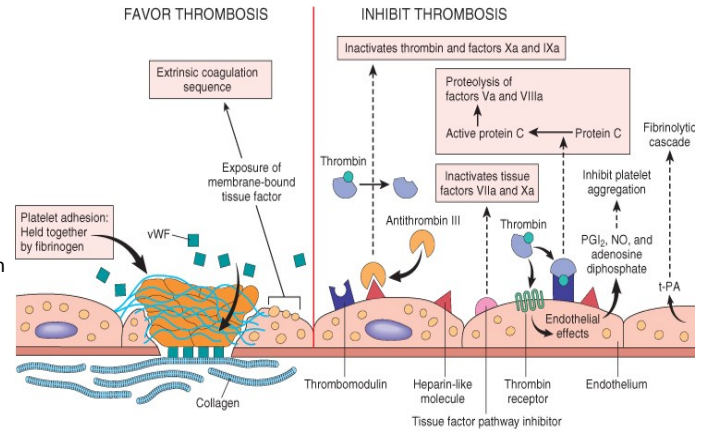
32) Understand the sequence of events that follow vascular injury

Sequences of Events Following Vascular Injury	
<p>1) Vasoconstriction</p> 	<ul style="list-style-type: none"> - Transient arteriolar vasoconstriction after initial endothelial injury that exposes collagen of the subendothelial matrix (ECM) - Vasoconstriction due to local nerve reflex & release of endothelin by endothelial cells - Vasoconstriction helps immediately limit escape of RBCs & proteins from damaged areas - Basement membrane is not completely intact, which is why collagen escapes
<p>2) Primary Hemostasis</p> 	<ol style="list-style-type: none"> (1) Platelets adhere to exposed ECM via von Willebrand factor (2) Platelets undergo activation (change shape) (3) Platelets release secretory granules that contain ADP & thromboxane A₂ → vasoconstriction & promote further platelet aggregation (4) Form primary hemostatic plug (5) vWF is released immediately from adjacent endothelial cells → aids platelet binding to collagen that is exposed below
<p>3) Secondary Hemostasis & Reorganization & Formation of a permanent "Plug"</p> 	<ul style="list-style-type: none"> - Local activation of the coagulation cascade <ul style="list-style-type: none"> ○ Tissue factor (thromboplastin) is secreted by adjacent endothelial cells ○ Thromboplastin initiates the clotting cascade - Secondary hemostasis → fibrin polymerization & "cementing" platelets into a definitive secondary plug
<p>4) Counter-Regulatory Mechanisms (Thrombus & Antithrombic Events)</p> 	<ul style="list-style-type: none"> - Must know when to stop clotting - Release compounds that limit the hemostatic process to the site of the injury <ul style="list-style-type: none"> ○ Fibrinolytic tissue type plasminogen activator (t-PA) ○ thrombomodulin interferes with the clotting cascade & actually stops the clotting cascade when it gets to a certain point

33) Be able to list properties of endothelial cells & platelets that induce & control formation of thrombi

Endothelia Cell Properties

- **Endothelium** = cells that line blood vessels
- **Prothrombotic** properties of Endothelium
 - Injury or activation of endothelial cells can
 - procoagulant phenotypes that augment local clot formation
- **Antithrombotic** properties of Endothelium
 - Normally acts as a barrier b/w blood & subendothelial collagen
 - Block platelet aggregation
 - Interfere with coagulation cascade
 - Actively lyse clots



1) Antiplatelet effects

- **Inhibit platelet aggregation**
- Intact endothelium prevents platelets & coagulation factors from meeting the highly thrombogenic subendothelial ECM
- Non-active platelets do not adhere to the uninjured endothelium
- Activated platelets are inhibited from adhering to surrounding uninjured endothelium by endothelial prostacyclin (PGI₂) & nitric oxide (NO)
 - Potent vasodilators & inhibitors of platelet aggregation
- Endothelial cells also express **ADPases** (ADP is needed for platelet aggregation)

2) Anticoagulant effects

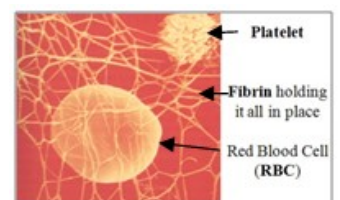
- Inhibit blood coagulation
- Heparin-like molecules (**cofactors**) from endothelium act indirectly with & inactivate several coagulation factors (thrombin, factors IXa...)
- Thrombomodulin from endothelium also acts indirectly, binding to thrombin & converting it from a procoagulant to an anticoagulant
- Major source for tissue factor pathway inhibitor
 - a cell surface protein that complexes with & inhibits several proteins of the clotting cascade (tissue factors VIIa & Xa)
 - Makes sure that clots form & stay in the damaged area where they are needed

3) Fibrinolytic effects

- Endothelial cells synthesize tissue-type plasminogen activator (t-PA)
- promote fibrinolytic activity & clears fibrin deposits from endothelial surfaces

Platelet Properties

- They're not cells; Membrane-bound smooth discs with no nucleus (when non-activated) & are the **Smallest components** of mammalian blood (diameter 2-4 μm)
- Originate from bone marrow megakaryocytes as the end products of cytoplasmic & membrane protrusions
- Their surface has several glycoprotein receptors called integrins that bind to exposed collagen
 - vWF acts as a bridge between integrins and exposed collagen → process called adhesion
- **After vascular injury**, platelets encounter ECM constituents normally sequestered beneath an intact endothelium
 - Constituents include: Collagen (most important); Proteoglycans; Fibronectin; & Other adhesive glycoproteins



- On contact with ECM, platelets undergo 3 **general reactions**:

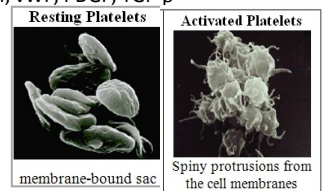
- 1) **Adhesion & shape change**
- 2) **Secretion** (release reaction)
- 3) **Aggregation**

- Contain 2 types of granules

- **Alpha granules** : Express the adhesion molecule P-selectin; contain fibrinogen, fibronectin, factor V, factor VIII, vWF, PDGF, TGF-β
- **Dense bodies**: (a.k.a. delta (δ) granules) they contain ADP, ATP, ionized Ca, histamine, serotonin, epinephrine

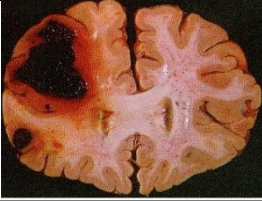




- **Platelet Activation**

- Activated platelets undergo change in shape (exact process remains unknown)
- **Secrete granule contents** (release reaction) & express surface phospholipid complex
- **Aggregate** (with help of thromboxane A₂) & form **reversible primary hemostatic plug**
 - Thrombin (from coagulation cascade) binds to surface receptors & binds fibrinogen to integrins on surface
- **Contract irreversibly** to form **secondary hemostatic plug**
 - Thrombin converts fibrinogen to fibrin & Fibrin "mortars" in place



- **Thrombocytopenia**: Lack of platelets (Thrombo=platelet, Penia = deficiency of)

34) Recognize & define hematoma, petechiae, ecchymoses, purpura, suffusive hemorrhage

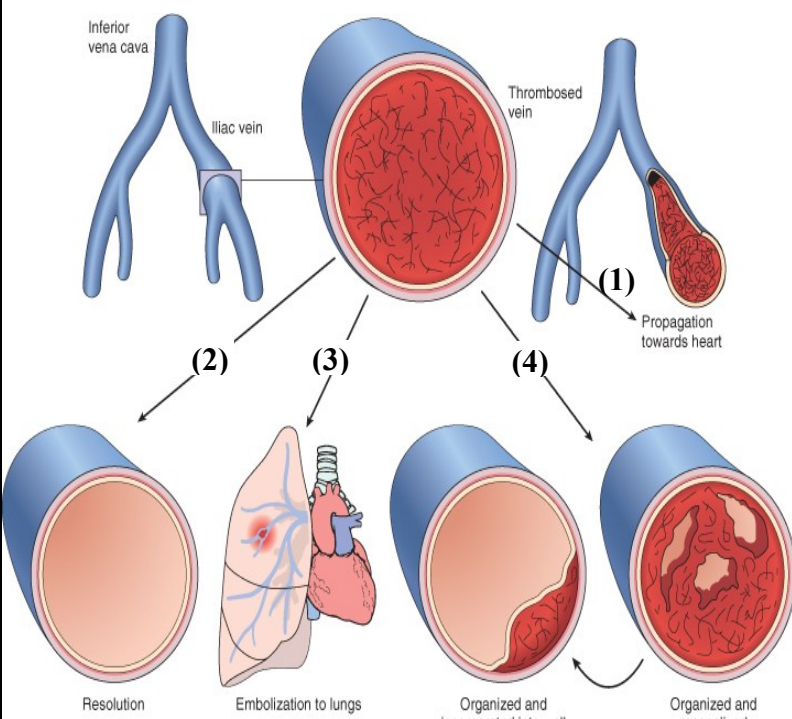
Types of Hemorrhages				
Hematoma	Petachiae	Ecchymoses	Purpura	Suffusive
				
Enclosed accumulation of blood in tissue - bulging, rounded area - severity ranges from insignificant (bruise) to fatal (intracranial hematoma)	1-2 mm hemorrhage Found in the skin, mucosa membranes, or serosal surface of an organ	2mm – 1 cm SQ hemorrhage Found in the skin, mucosa membranes, or serosal surface of an organ	> 1 cm hemorrhage Found in the skin, mucosa membranes, or serosal surface of an organ	"paintbrush" Occurs along a natural plane
	Associated with... - local ↑ intravascular pressure - thrombocytopenia - defective platelet function - clotting factor deficits	Associated with... - trauma - same as Petachiae H.	Associated with... - trauma - same as Petachiae H.	Associated with... - trauma - local vasculitis - ↑ vascular fragility - same as Petachiae H.

Multifocal to coalescing petechial to ecchymotic hemorrhages on the epicardial surface of the heart.



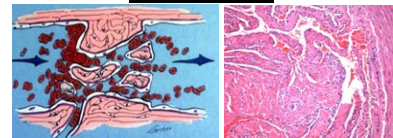
35) List & explain 4 possible outcomes of thrombosis

4 Possible Outcomes of Thrombosis



- (1) **Propagation**
thrombus may accumulate more platelets & fibrin leading to vessel obstruction
- (2) **Dissolution / Resolution**
thrombi may be removed by **fibrinolytic activity** (drugs available for this)
- (3) **Embolization**
thrombus may dislodge & travel to other sites, forming **thromboemboli**
- (4) **Organization & Recanalization**
induce inflammation & fibrosis (organization) & may eventually become recanalized

Recanalization



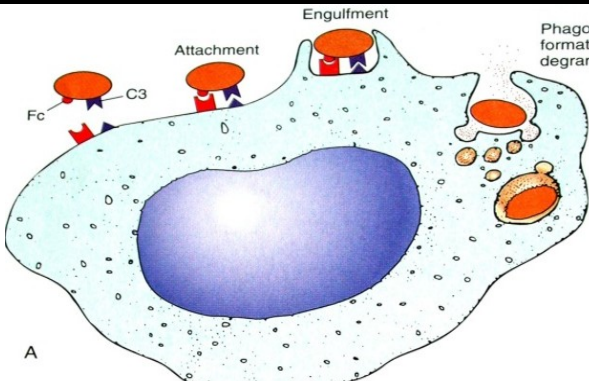
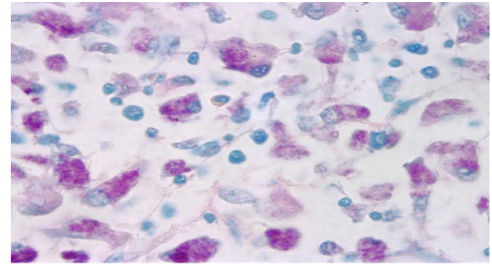
Re-establish blood flow or be incorporated into a thickened vascular wall
Thrombus converted to fibrous connective (scar) tissue & May contract over time

36) **Recognize the basic functions & major features of the leukocytes, erythrocytes, & platelets**

37) **Explain (in basic terms) what role endothelial cells play in inflammation**

38) **Understand & explain the events surrounding how leukocytes (especially neutrophils) leave the vascular in acute inflammation**

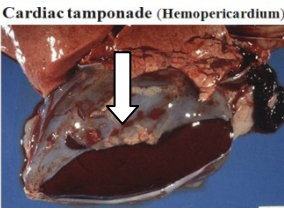

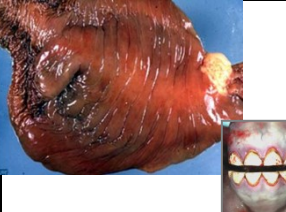

39) Understand the process of phagocytosis

Phagocytosis	
an Active cellular process where by cells engulf, kill, &/or remove offending substances	
Process of Phagocytosis	Phagocyte-mediated tissue damage
 <p>(1) Recognize & Attach</p> <ul style="list-style-type: none"> - Surface attachment of the leukocyte to the particle & recognition - Aided by <i>opsonization</i>: antibodies, C3b, fibronectin <p>(2) Engulf</p> <ul style="list-style-type: none"> - Extension of pseudopodia around object - Fusion of membrane → phagosome <p>(3) Phagosome / Lysosome fusion</p> <ul style="list-style-type: none"> - expulsion of lysosomal contents into phagolysosome (degranulation) <p>(4) Respiratory burst</p> <ul style="list-style-type: none"> - → production of reactive oxygen species (bactericidal) - Superoxide hydrogen peroxide, hydroxyl radical, hypochlorous acid <p>(5) Extrusion of debris (inconsistent)</p>	<ul style="list-style-type: none"> ▪ Neutrophils are short-lived in tissues & are sloppy eaters <ul style="list-style-type: none"> - This leads to variable degrees of tissue damage caused by the inflammatory response. ▪ Neutrophils tend to undergo phagosome/lysosome fusion prior to phagosome closure <ul style="list-style-type: none"> - Results in regurgitation of lysosomal enzymes & reactive oxygen species into surrounding tissue ▪ Frustrated phagocytosis occurs when the particle is too large to be engulfed <ul style="list-style-type: none"> - The neutrophil discharges its enzymes, etc. in an attempt to destroy ▪ Suicide – phagocyte dies at the site of inflammation & releases lysosomal enzymes into the surrounding tissue  <p style="text-align: center;">Phagocytosis</p>
<p>Phagocytosis → ↑ enzyme levels in & numbers of lysosomes, ↑ mitochondria, ↑ endocytosis, & ↑ killing ability Can be down-regulated (deactivated) by TGF-b (TGF-b also stimulates fibrosis)</p>	

40) Causes of ischemia/embolism/thromboembolism

	Ischemia	Embolism	Thromboembolism
Definition	Loss of blood supply, Oxygen, & metabolic substrates (like Glucose)	Detached intravascular solid, liquid, or gaseous mass that is carried by the blood away from its site of origin to cause blockage elsewhere	Thromboembolism = Dislodged thrombus (clot) Almost all emboli are thrombic in origin
Causes	<ul style="list-style-type: none"> - Impeded arterial flow - Impeded venous drainage - Pressure - Vascular Constriction - Thrombi - Thromboembolism 	<ul style="list-style-type: none"> - Tumor cells (Neoplastic emboli) - Bacterial (Septic) emboli - Ruptured intervertebral discs (Fibrocartilagenous emboli) - Bubble of air or nitrogen (Benz disease) - Atherosclerotic debris (cholesterol debris) - Bits of Bone Marrow - Fat Droplets - Foreign objects (bullets) 	<p>Thrombosis is caused by abnormalities in ...</p> <ul style="list-style-type: none"> - blood composition (hypercoagulability) - quality of vessel wall (endothelial cell injury) - Nature of blood flow (hemostasis) - High altitudes

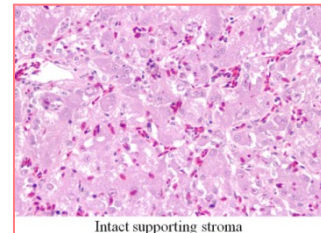
41) Be able to explain the **phases** & types of shock, as well as the clinical consequences

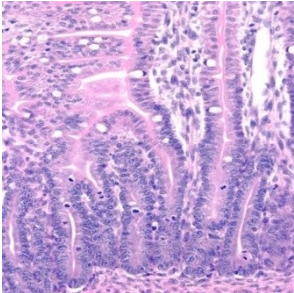
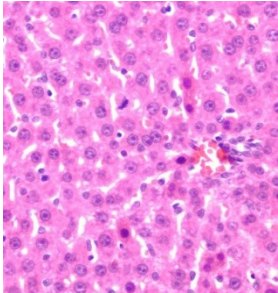
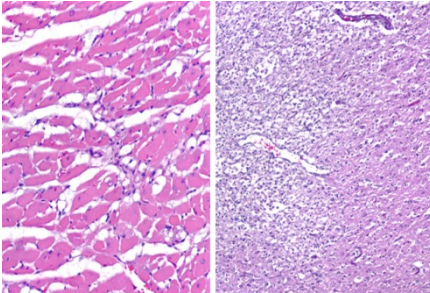
Shock				
Description	<ul style="list-style-type: none"> - Shock is also known as "cardiovascular collapse" - Failure of the circulatory system to adequately perfuse vital organs - Characterized by Hypoperfusion (low systemic blood flow) due to: ↓ cardiac output & ↓ circulating blood volume - End results are hypotension followed by impaired tissue perfusion & cellular hypoxia - Shock is classified based on the primary general cause of the shock 			
Types	Cardiac Shock	Hypovolemic Shock	Septic Shock	Anaphylactic Shock
	 <p>caused by insults that ↓ cardiac output (↓ hearts ability to pump blood) Cardiac Tamponade: compression of the heart due to collection of blood or fluid in the pericardial sac</p>	 <ul style="list-style-type: none"> • Dog; HBC; ruptured spleen • Liver is pale • there is a large clot around the spleen <p>- Caused by sudden & severe loss of blood volume</p> <ul style="list-style-type: none"> - Acute hemorrhage (¼ to ½ blood volume) - ↑ Vascular permeability 	 <p>Caused by a bacterial infection in which large amounts of endotoxins are released into circulation</p> <ul style="list-style-type: none"> - Lipopolysaccharide (LPS) are toxic molecules 	 <p>A severe type of allergic reaction that involves two or more body systems (e.g., hives and difficulty breathing).</p> <ul style="list-style-type: none"> - Systemic manifestation of acute hypersensitivity (allergic) response - Eventually causes collapse of the cardiovascular system
Phases				
Clinical Consequences	<ul style="list-style-type: none"> ○ Biggest problem → oxygen does not get to cells (anoxia) → multiple organs will eventually fail <ul style="list-style-type: none"> ● myocardial damage ● kidney damage ○ Endothelial injury – increased vascular permeability and loss of intravascular fluid <ul style="list-style-type: none"> ● Further aggravate hypovolemia & anoxia (deplete blood volume and decrease cardiac output) ● Activate platelets and coagulation cascade (thrombosis) ● depletion of clotting factors ● hemorrhage with thrombosis (DIC) ○ Decreased kidney function & muscle perfusion results in metabolic acidosis <ul style="list-style-type: none"> ● Results in even further suppression of cardiac output ○ Decreased perfusion of heart muscle causes anoxic injury to myocytes <ul style="list-style-type: none"> ● Results in even further decrease in cardiac output 			
Cardiovascular & Systemic Responses to Shock	<ul style="list-style-type: none"> ○ The body responds by attempting to increase cardiac output by shunting blood to vital organs (brain, heart, kidneys) ○ If these adjustments fail and inciting cause is not corrected, uncompensated shock results ○ Microvasculature is unresponsively dilated (<u>end stage vasodilatory shock</u>) ○ Death is the outcome <ol style="list-style-type: none"> Cardiac support <ul style="list-style-type: none"> - epinephrine and norepinephrine from adrenal medulla to increase heart rate - aldosterone from adrenal cortex to retain sodium & water, thereby increasing blood volume Vascular support <ul style="list-style-type: none"> - Epinephrine and norepinephrine stimulate vasoconstriction - Renin-angiotensin system produce angiotensin II which stimulates vasoconstriction 			

42) Know the 2 consistent characteristics of chronic inflammation & be able to give 6 possible causes/stimuli of chronic inflammation

43) Be able to list the requirements for regeneration & know the types of cells capable of undergoing regeneration. Be able to explain why permanent cells are unable to undergo regeneration.

- Cellular Requirements for Regeneration:
 - o Cells of the injured tissue must be **capable of dividing**
 - **Labile** cells: **continually dividing** (stem cells)
 - **Stable** cells: **not normally dividing**, but can be induced
 - o **Intact Supporting stroma**, especially of the basement membrane (BM)



Types of Cells Capable of Undergoing Regeneration		Cells <u>NOT</u> capable of Regeneration
Labile cells	Stable cells	Permanent cells
		
<ul style="list-style-type: none"> - constantly proliferating throughout life - Epidermis - Mucosal epithelial cells - bone marrow 	<ul style="list-style-type: none"> - retain the capacity to replicate, but have very low turn over rate - All glandular parenchymal cells - Mesenchymal cells - Endothelial cells 	<ul style="list-style-type: none"> - no practical capacity to replicate - Neurons - Cardiac muscle -

44) Be able to list at least 4 possible hindrances to regeneration

1) Destruction of original supporting stroma / architecture

- Chaotic proliferation of parenchymal cells
- Replacement of original stroma with fibrous connective tissue

2) Excessive exudation / infection

- Tissue destruction by leukocyte or bacterial enzymes
 - PMNs secrete numerous proteases (collagenases, elastases)
 - Which digest the basement membrane & supporting connective tissues
 - Bacteria often have similar enzymes & / or toxins which may kill the parenchymal or inflammatory cells

3) Excessively large defects

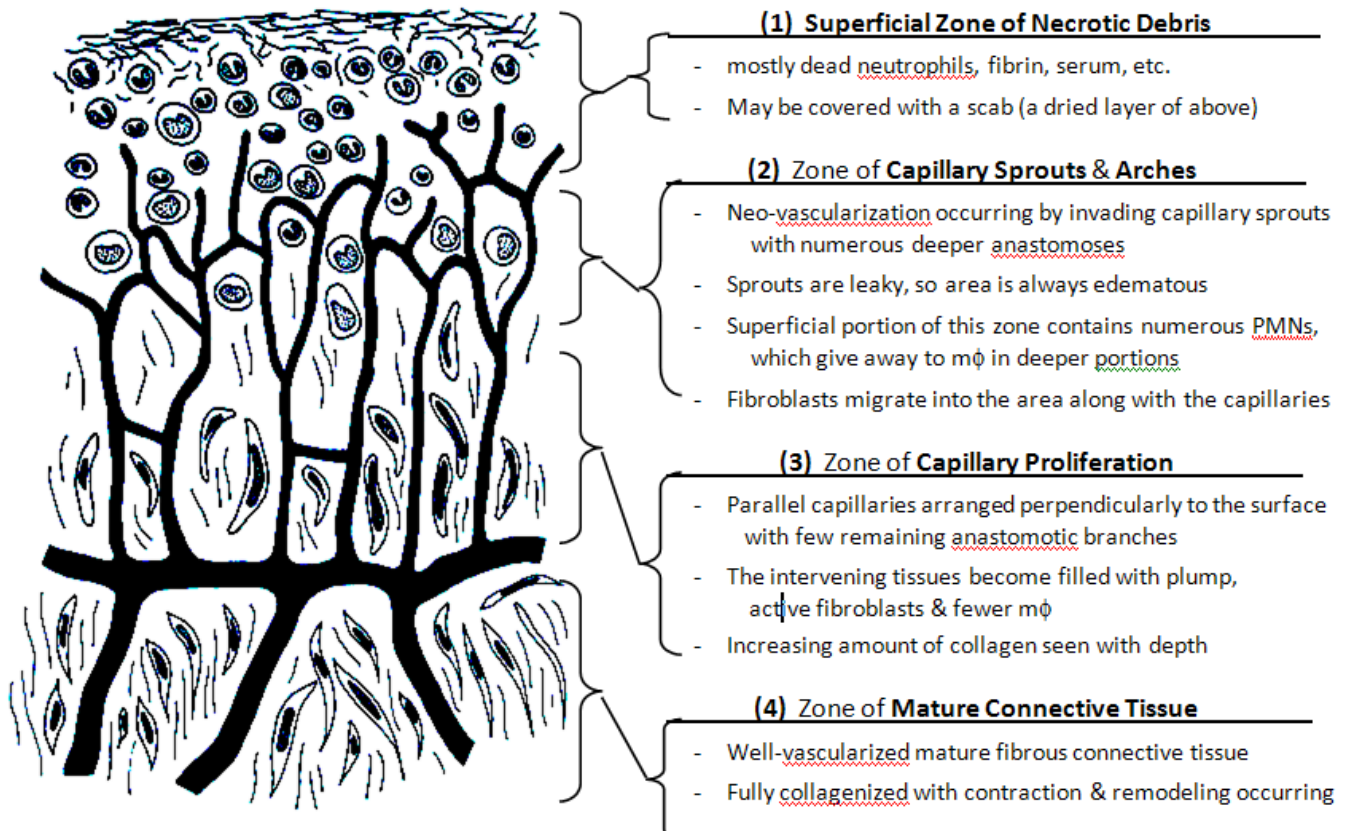
- Stroma will not remain exposed indefinitely before fibrovascular proliferation is initiated
- Large deficits must be filled with granulation tissue before stromal cells can regrow

4) Permanent cells

- Cannot effectively proliferate, so MUST heal by fibrous tissue replacement

45) Understand & be able to explain the steps associated with organization of granulation tissue

Organization of Granulation Tissue

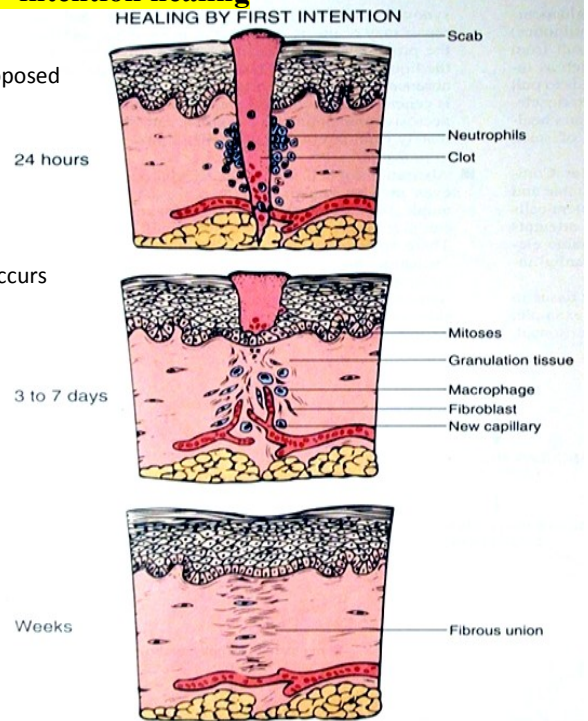


46) **Be able to recognize the differences between 1st, 2nd, & 3rd intention healing**

o **First Intention Healing**

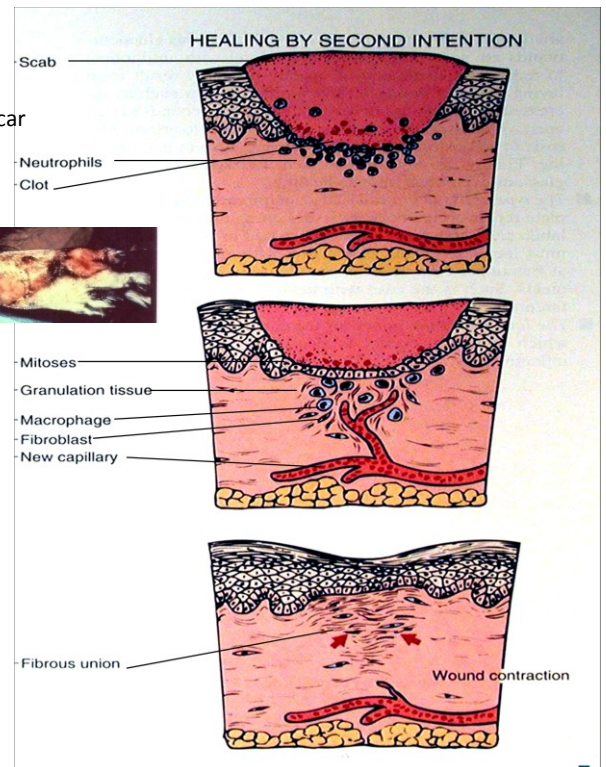
- occurs when there is minimal tissue damage & edges are closely opposed
- Goal of surgical procedures
- Epithelial continuity can be restored as early as 48 hours
- Clean edges closely apposed by sutures
- Allows epithelium to migrate across defect before it fills with granulation tissue (can occur as early as 48 hrs)
- About 10 days before any significant collagenization of the wound occurs

1. Wound fills with blood clot
2. Acute inflammation
3. Simultaneous proliferation of endothelial cells, fibroblasts, & epithelial cells at periphery of wound
4. Endothelial cells & fibroblasts grow across wound & epithelium grows over surfaces
5. Clot and fibrin removed
6. Granulation tissue matures by deposition of collagen, contraction, & remodeling to form scar.
 - About 20% original strength is restored within 3 weeks
 - reaching a maximum of 70% original strength in months



o **Second (third) Intention Healing**

- occurs when tissue gap is large or when a wound is contaminated
- Same process as 1st intention but takes longer & produces more scar
- Defect must fill in from edges and base with granulation tissue before re-epithelialization can proceed
- Some references refer to third intention healing in infected wounds—still same process



o **Nervous System**

- **CNS:** healing is by replacement with astroglial scar (fibrous astrocytes)
- **Peripheral nervous system:** nerves can regenerate if axon tube is properly aligned & intact--**SLOW**

o **Remodeling & Scaring**

- Inflammation subsides
- Decreased fibroblasts & EC
- Myoid differentiation of fibroblasts leading to wound contraction
- Crosslinking of collagen into thicker bundles → proteolysis → further contraction → further crosslinking...

47) Be able to list the 5 classes of cytokines as well as the 5 types of cytokines

Types of Cytokines (What they are)	5 Classes of Cytokines (What they Do)
- Interleukins (IL)	1) Cytokines that regulate lymphocyte function : IL-2, IL-4, IL-5, IL-10, TGF- β
- Interferons (IFN)	2) Cytokines involved with innate immunity : TNF- α , IL-1, IFN- α & β , IL-6
- Chemokines	3) Cytokines that activate inflammatory cells (m ϕ): IFN- γ , TNF, IL-5, IL-10, IL-12
- Growth Factors (GF)	4) Chemokines : IL-8, eotaxin, (others)
- Colony Stimulating Factors (CSF)	5) Cytokines that stimulate hematopoiesis : IL-13, IL-7, GM-CSF, M-CSF, G-CSF, stem cell factor

48) Know which mediators are responsible for the acute phase reaction

- **Permeability Mediators**
 - **Vasoactive amines**
 - Histamine (m ϕ)
 - Serotonin (platelets)
 - **Complement**
 - C3a, C5a (blood)
 - **Bradykinin**
 - (blood) also a major pain inducer (*dolor*)
 - **Leukotrienes**
 - LTC₄, LTD₄, LTE₄ (leukocytes)
 - **Platelet-activating factor (PAF)**
 - EC, leukocytes
 - Important in cytoskeletal reorganization
 - **Cytokines** (IL-1, TNF) - m ϕ

49) Be able to describe ways with which the body inhibits, reduces, or suppresses immune reactions.

- **Inhibitors, Reducers, & Suppressors of the Inflammatory Process**
 - Non-specific Methods
 - **Dilution** - mediator concentration is important
 - **Natural Instability** - spontaneous degeneration
 - **Inactivators** - both specific & nonspecific
 - **Proteinases** - continue to chew on peptides
 - **Kininases** - breakdown bradykinin
 - **Antiproteinases** - prevent formation of more active compounds & deactivate existing compounds
 - **Specific Inhibitors**
 - **Inhibitors of cell response** - corticosteroids, epinephrine
 - **Antagonist cytokines** - switch inflammatory cells off (TGF β , IL 4, IL10, IL13)
 - **Competitive antagonist**
 - compete for receptor – IL-1ra
 - compete for cytokine - soluble receptors

The process of disseminated intravascular coagulation.

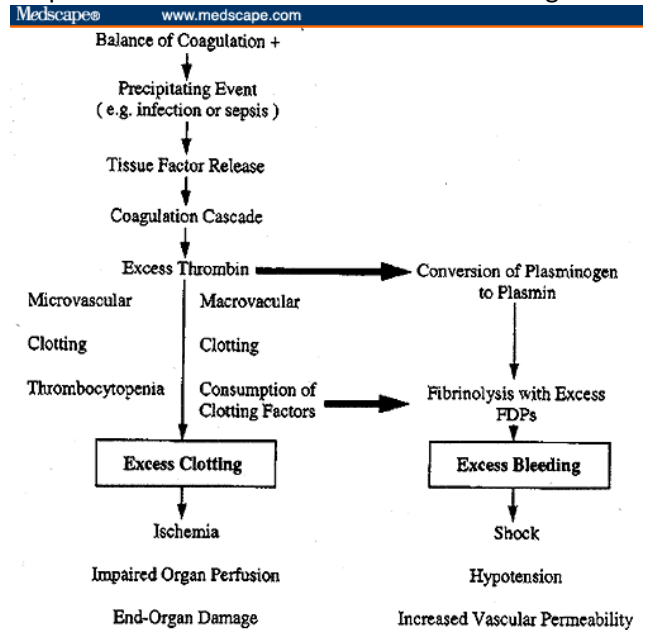
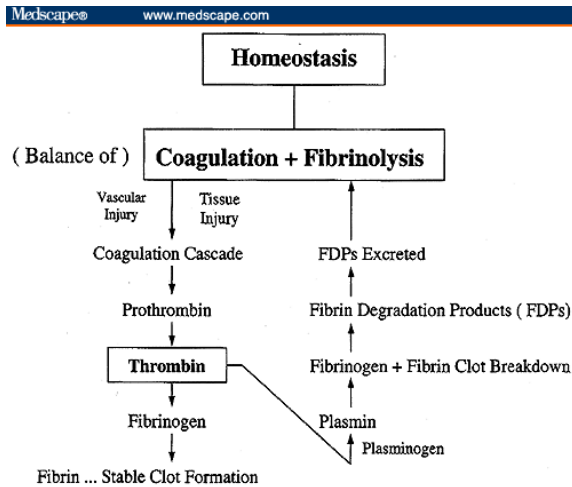
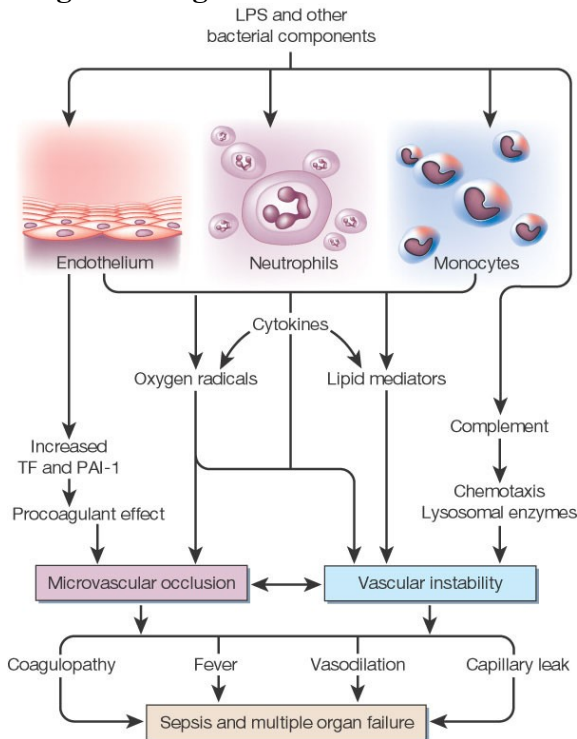


Fig.3. Pathogenetic networks in shock.



Sepsis disturbs the normal homeostatic balance between procoagulant & anticoagulant mechanisms

