PATHOLOGY
Study Guide

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National University of Health Sciences

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This publication is dedicated:

To the passing of my father.
To our mentors for inspiring us.
To our peers for collaborating & challenging us.
To our families for loving & supporting us.

NOTICE: the information contained within this study guide is written with the most current information available. While every attempt has been made to make this study guide as all-inclusive as possible, there may still be some omissions. The student is responsible for all materials presented, regardless of whether they appear in the book.

If any mistakes or relevant updates are discovered, please notify Dr. M. A. Khan in the Anatomy Department of the National University of Health Sciences.

Cell Pathology

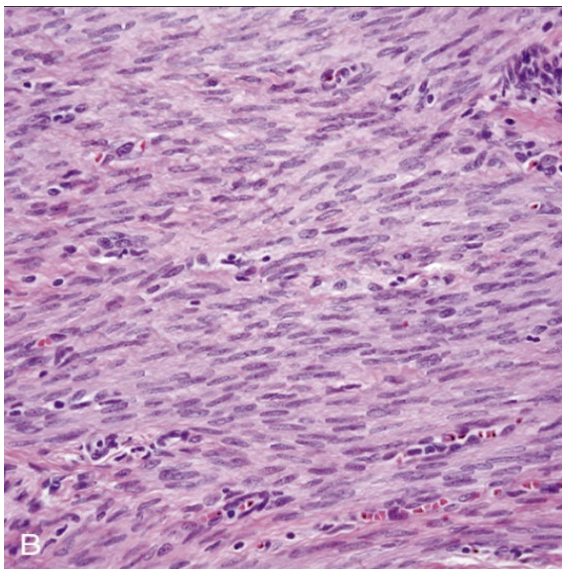
Adaptive Response

Cellular Adaptive Response to Injury

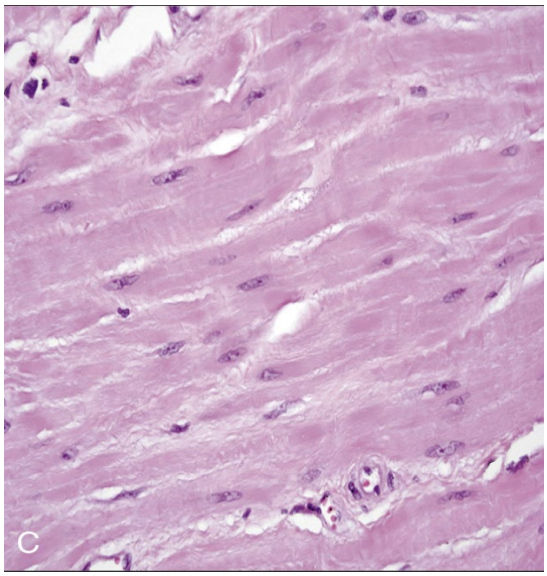
- Cellular adaptation is the result of persistent stress or injury
- Adaptive responses are potentially reversible once the stress has been removed but some adaptation may progress to malignancy

Hypertrophy

- Increases in cell size and function leading to enlargement of the tissues or organs
- In pure hypertrophy there are no new cells
- A response to increased demand, non-dividing cells undergo hypertrophy via stimulating resting (G0) cells to enter the cell cycle (G1) and then multiply
- Potentially reversible
- Physiological
  - Example: skeletal muscle hypertrophy with exercise
- Pathological
  - Example: left ventricular hypertrophy
- Increased mechanical demand:
  - Physiologically as seen in the striated muscle of the weightlifters
  - Pathologically as seen in the cardiac muscles in the hypertension
- Increased endocrine stimulation:
  - Puberty (by growth hormone, androgens or
  - estrogen)
  - Gravid uterus (estrogen) or lactating breast (prolactin and estrogen)
- Adaptive response:
  - In some organs e.g. heart, skeletal muscle, such adaptive responses are accomplished mainly by increased cell size
  - In other organs e.g. kidney, thyroid, cell numbers(hyperplasia), and cell size (hypertrophy) may both increase.



Robbins and Cotran Figure 2.25 B: Normal uterine tissue with spindle shaped smooth muscle cells. Courtesy of Robbin & Cotran (use only for educational purposes).



Robbins and Cotran Figure 2.25 C: Hypertrophic uterus with large plump cells taken from a gravid uterus. Courtesy of Robbin & Cotran (use only for educational purposes).

- End of heart hypertrophy
    - Cardiac hypertrophy eventually reaches a limit beyond which enlargement of muscle mass is no longer able to compensate for the increased burden
    - At this stage several regressive changes occur in the myocardial fibers, like lysis and loss of myofibrillar contractile elements
    - If the stress that triggered the hypertrophy does not stop, the organ will most likely proceed to failure, e.g. persistent hypertension can lead to ischemia, necrosis, and heart failure

Mechanism of Hypertrophy

- Hypertrophy & hyperplasia can be mediated by different stimuli like growth factors, cytokines that lead to cell hypertrophy (by stimulating adaptive cellular remodeling, increasing protein production, facilitate cell function and promote cell survival)
- Growth factor stimulation:
    - In many cases certain growth factors appear to be key initiators of hypertrophy, such Insulin Growth Factor-I (IGF-I) which is increased in load-induced muscle hypertrophy
- Neuroendocrine stimulation:
    - In some tissues, adrenergic or noradrenergic signaling may be important in initiating and/or facilitating hypertrophy
- Ion channels:
    - Ion fluxes may activate adaptation to increased demand
    - Calcium channel activity, in particular, may stimulate a host of downstream enzymes (e.g., calcineurin) to produce hypertrophy
- Other chemical mediators:
    - Factors such as nitric oxide (NO), angiotensin II, and bradykinin may support cell hypertrophic responses

- Resistance training like Olympic weight lifting mediates hypertrophy of skeletal muscle via IGF-1 & GH release.
    - These molecules act via a series of cellular intermediates and induce genetirc transcription or proteins such as eIF2.
    - Elongation factor eIF2 (Eukaryotic Initiation Factor) is a eukaryotic initiation factor
    - It is required in the initiation of translation and Protein kinase B (PKB), is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration
    - It targets the rapamycin (mTOR), a protein that in humans is encoded by the MTOR gene
    - mTOR = mammalian target of rapamycin. A serine/threonine protein kinase that was discovered in 1994 and regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription.
        - mTOR 1
        - mTOR 2
    - mTOR Simultaneously, increases eIF2 activity & activates transcription of genes that inhibit protein degradation
- Lack of oxygen supply, as in cases of cardiac muscle hypertrophy in ischemia
    - Angiogenesis is stimulated when a tissue oxygen deficit and may be an indispensable component of adaptive hypertrophy

Selective Hypertrophy

- As seen in steatosis (it is due to the accumulation of fat in the hepatocytes)
- Reversible cell injury
- Sometimes a subcellular organelle may undergo selective hypertrophy, like individuals treated with drugs such as barbiturates show hypertrophy of the smooth endoplasmic reticulum (ER) in hepatocytes
- This is an adaptive response that increases the amount of enzymes (cytochrome P-450 mixed function oxidases) available to detoxify the drugs

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Causes of Hypertrophy

- Hormonal causes:
  - Normal increase in estrogens at puberty or early in the menstrual cycle leads to increased numbers of endometrial and uterine stromal cells
  - Enlargement of the male breast, called gynecomastia, develops from estrogens used as therapy for prostate cancer
- Injuries, especially persistent injury like long-standing inflammation or chronic physical or chemical injury, may lead to hyperplasia
- Chronic inflammation of the bladder (chronic cystitis) often causes hyperplasia of the bladder epithelium
- Inappropriate hyperplasia can be harmful, and is seen in psoriasis, which is characterized by hyperplasia of the skin
- Increased functional demand like at high altitudes low atmospheric oxygen content leads to compensatory hyperplasia of erythrocyte

Hyperplasia and Hypertrophy

- Physiological - breast at pregnancy and puberty or hyperplasia and hypertrophy in pregnant uterus
- Pathological - endometrial hyperplasia
- Benign prostatic hyperplasia or myocardial hypertrophy

Summary Hyperplasia and Hypertrophy

- Physiologic:
  - Hormonal
  - Pregnant uterus
  - Female breast at puberty
- Compensatory:
  - After damage
  - Partial resection
- Pathologic:
  - Cancerous proliferation
  - Hormonal
  - Endometrium changes
  - Benign prostatic hyperplasia (due to androgen)
  - Growth factors
  - Wound healing
  - Viral infections

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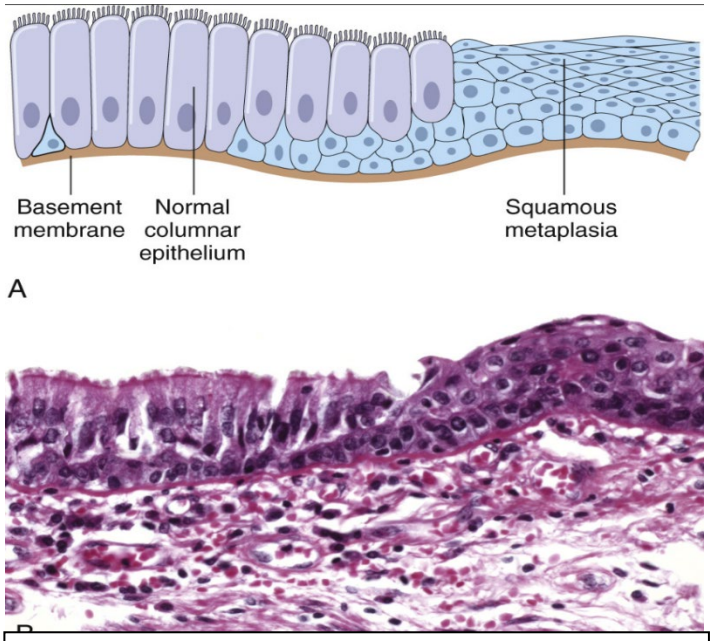
Metaplasia

- "Reversible change in which one adult cell type is replaced by another adult cell type" in response to environmental changes
- It can be physiological like squamous metaplasia of the endo-cervix at puberty
- Pathological like squamous metaplasia of the bronchial ciliated pseudostratified columnar epithelium due to smoking.
- Examples:
    - The ossification of cartilage to form bone
    - Myeloid metaplasia
    - The occurrence of myeloid tissue in extra medullary sites
    - If a patient has continuing heartburn, the esophagus cells will change to cells similar to the stomach and start excreting anti acid materials



Robbins and Cotran Figure 2.28: Histology depiction of metaplasia occurring within the bronchus. Note transition from columnar epithelium (left) to squamous epithelium (right). Courtesy of Robbin & Cotran (use only for educational purposes).

Dysplasia

- Disordered growth - abnormal proliferation of cells that is characterized by changes in cell size, shape, and loss of cellular organization, like cervical dysplasia
- Normal cervix under a microscope we see layers of cells
- The normal distribution is that the bottom layer is made of round young cells
- As the cells mature they rise to the surface and flatten out, so that on the surface the cells are flat.
- In cervical dysplasia there is a lack of this organized growth process
- In mild dysplasia (CIN I) only a few cells are abnormal
- In moderate dysplasia (CIN II) the abnormal cells involve about one-half of the thickness of the surface lining of the cervix

Anaplasia

- Anaplastic cells display marked pleomorphism.
- The nuclei are characteristically extremely hyper chromatic (darkly stained) and large

The nuclear-cytoplasmic ratio may approach 1:1 instead of the normal 1:4 or 1:6

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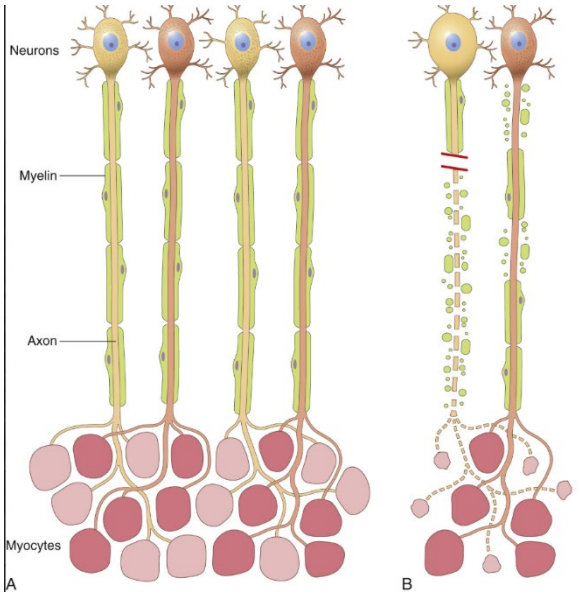
Atrophy

- Clinically, atrophy means decreased size or function of a cell or organ
  - Atrophied cells are smaller than normal, but are still viable
- Physiologic
  - Loss of endocrine stimulation- menopause
  - Shrinkage of uterus after birth
- Pathologic
  - Decreased workload - (disuse) - immobilization
  - Denervation - nerve damage
  - Diminished blood supply - ischemia
  - Inadequate nutrition - marasmus
  - Aging
  - Pressure by tumors or by any space occupying lesions
- Atrophy may be reversible or irreversible.
- For example, renewing physical activity to a disused limb may cause atrophic muscle cells to resume their usual size and function.
- By contrast, atrophy of the brain in Alzheimer disease is secondary to extensive cell death, the size of the organ cannot be restored



Robbins and Cotran Figure 27.2: (A) Designates a normal & healthy peripheral nerve. (B) Designates axonal injury & atrophy of denervated myofibers. Courtesy of Robbin & Cotran (use only for educational purposes).

Causes of Atrophy

Diseases	
Aging	Most common cause of atrophy
Chronic disease	Atrophy occurring in chronic disease as in cancer, congestive heart failure, chronic obstructive pulmonary disease, cirrhosis of the liver and AIDS
Ischemia	Arteriosclerosis or Hypoxia, decreased nutrient availability, renal artery stenosis.
Malnutrition	Generalized atrophy
Decreased functional demand	Limb immobilization, as in a fracture
Interruption of trophic signals	Denervation atrophy following nerve injury.
Increased pressure	Decubitus ulcers, passive congestion of the liver

Mechanism of Atrophy

- Not clear
- May be because of decreased protein synthesis or increased protein degradation
- The degradation of cellular proteins occurs mainly by the ubiquitin-proteasome pathway
- Ubiquitin is a small regulatory protein that has been found in almost all tissues
    - Protein degradation pathways are activated Proteasome (degradation and also leading to cancer, cachexia)

Ubiquitination

- In some cases, mutations in Ubiquitination (Ub) pathway are the primary causes of specific diseases
- For example: neurodegenerative diseases
- Mutations in parkin are implicated in the pathogenesis of Parkinson disease, in which undegraded parkin accumulates as Lewy bodies
- Regulation of ubiquitination may be important in tumor development like Human Papilloma Virus (HPV) strains are associated with human cervical cancer produce E6 protein, which inactivates the p53 tumor suppressor gene and lead to cervical cancer

Cell injury

- Cell injury can be reversible or irreversible
- In reversible injury, the structures will return to normal (this is called adaptations to stress)
- For example: If conditions like hypoxia or ischemia reduce the blood flow to the myocardium for 10 minutes and then are restored, myocardial function will become normal
- In irreversible, the stressor alters homeostasis past the point of cellular adaptation, cell cannot recover function, it will lead to irreversible cell injury.
- For example: Interruption of blood flow to the myocardium for about 1 hour – leading to irreversible injury (Necrosis).

Irreversible Cell Injury (Death)

- Necrosis:
  - Due to severe damage to the membranes, lysosomal enzymes enter the cytoplasm and digest the cell, which lead to leaking of cellular contents resulting in necrosis.
  - Necrosis is always a pathologic process.
- Apoptosis:
  - When the cell's DNA or proteins are damaged beyond repair, the cell kills itself by apoptosis, a form of cell death that is characterized by:
    - Nuclear dissolution
    - Fragmentation of the cell without complete loss of membrane integrity
    - Rapid removal of the cellular debris
  - Apoptosis serves many normal functions and is not necessarily associated with cell injury

Common Causes of Cellular Injury

- TIPS:
  - Toxins:
    - Chemical
    - Drugs (e.g. paracetamol)
    - Poisons (e.g. paraquat, cyanide, carbon mono oxide)
  - Infections:
    - Viruses (Coxsackie virus = HFM disease)
    - Bacteria (Rickettsia gram -)
    - Fungi (Aspergillus)
    - Parasites (Shigella)
    - Autoimmune diseases (SLE)
  - Physical injury
    - Mechanical
    - Chemical
    - Thermal
    - Burns
    - Freezing

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    - Serum deficit injury
        - Nutrition
        - Hydration
        - Oxygenation
    - Nutritional imbalances continue to be major causes of cell injury
        - protein deficiencies anemia
- Excess of cholesterol predisposes to atherosclerosis
- Obesity is associated with increased incidence of several important diseases
        - Diabetes
        - Cancer

Mechanism of Cell Injury

- Cell injury results when there is dysfunction of any of the following essential cellular systems:
    - Aerobic respiration
    - Membrane integrity
    - Protein synthesis
    - Cytoskeleton
    - Genetic apparatus
- Characteristics of cell injury are:
    - Irreversible mitochondrial dysfunction
    - Profound membrane dysfunction
- Irreversible mitochondrial damage due to:
    - Cytosolic Ca^{2+}
    - Oxidative stress
    - Lipid breakdown products (may damage mitochondria)
- Mitochondrial permeability leak cytochrome C which will triggers apoptotic mechanisms
- DNA is damaged by free radicals (free radicals are produced by ultraviolet radiation energy)
- Transition metals like iron and copper can produce free radicals
- Acute reversible injury:
    - Because of chemical and biological toxins or viral or bacterial infections, ischemia, excessive heat or cold, there is swelling of the cells which is called as hydropic swelling
        - Characterized by a large, pale cytoplasm and a normally located nucleus and the cisternae of the endoplasmic reticulum are distended by fluid
    - In some forms of acute injury, particularly ischemia, there is also swelling of the mitochondria. In the nucleus, reversible injury is reflected principally in nucleolar change.

Summary of Morphology Changes

- Basically 4 types of changes are seen morphologically:
  - Hydropic changes
    - Tiny vacuoles in cytoplasm
- Fatty changes
  - Accumulation of triglycerides in cell
  - Most common in liver (also heart, muscle, kidney)
- Necrosis= Cell death
  - Exogenous stimuli (ischemia, chemical injury)
- Apoptosis =Programmed cell death
  - Cell dies through activation of internally controlled suicide program

Channelopathies

- Channelopathies are group of diseases caused by disturbed function of ion channel subunits or the proteins that regulate them
- Channelopathies may be acquired as well as inherited
- Examples:
  - The voltage gated channelopathies causing inherited muscle diseases like the non-dystrophic myotonias and familial periodic paralyses
  - Cystic fibrosis an example of chloride channel dysfunction
  - Myasthenia Gravis due to ligand-gated sodium channel dysfunction

Chaperonopathies

- Defects in molecular chaperones have now been identified as etiologic causes in a number of disorders called “chaperonopathies”
- These have been implicated in certain disorders of
    - Development
    - Neuropathies
    - Dilated cardiomyopathy
    - Polycystic liver disease
    - Contributes to tumor formation
- Types:
    - Genetic chaperonopathies:
        - Example: some developmental disorders, neuropathies, dilated cardiomyopathy and polycystic liver disease
    - Acquired chaperonopathies:
        - Example: the stress response may be impaired, leading to inadequate amounts of chaperone proteins

Apoptosis and Necrosis

- Programmed cell death - “falling off”
- Apoptosis is characterised by death of single cells without an inflammatory reaction
    - Between 50 and 70 billion cells die each day due to apoptosis in the average human adult
    - For an average child between the ages of 8 and 14, approximately 20 billion to 30 billion cells die a day
- Excessive apoptosis causes atrophy, such as in ischemic damage
- Insufficient amount results in uncontrolled cell proliferation, such as cancer
- Apoptosis is required to ensure that there is a steady turnover of cells in tissues and in response to physiological stimuli like:
    - Shedding of menstrual endometrium
    - Involution of breast after weaning
    - Prostatic ‘atrophy’ after castration
    - Cell turnover in intestinal crypts

Apoptosis

- As a result of certain types of cell injury/ DNA damage, e.g. radiation, chemotherapy, and drugs
- Viral infections, e.g. viral hepatitis, AIDS
- Neurodegenerative disorders
- In tumours that regress or involute.

- Others including rejection of transplants
- Morphologic features of the apoptosis are:
    - Cell shrinkage
    - Chromatin condensation
    - Cytoplasmic blebs
    - Phagocytosis of apoptotic cells
    - Lack of inflammation (Important)

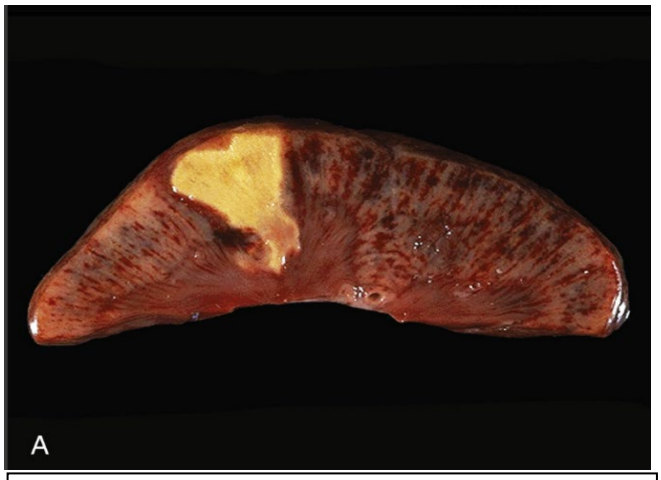
Necrosis

- Characterized by:
    - Initially by swelling of the cell and organelle
    - Followed by ATP depletion and increased plasma membrane permeability
    - Release of macromolecules from the cell eventually cell death
- Morphological changes are result from the leakage and denaturation of proteins and enzymatic digestion of cellular organelles
    - Leakage of proteins/enzymes out of the injured cell can be used clinically as a marker of cell death (e.g. raised serum levels of cardiac enzymes after an MI)
- Time to death with hypoxia:
    - Brain – < 3 minutes
    - Heart – 1-2 hours
    - Kidney – 2-3 hours
    - Skin fibroblasts – < 24 hours

- Etiology
    - Hypoxia
    - Physical injury like trauma, radiation
    - Chemicals
    - Biological toxins like endotoxins
    - Immunological reactions
    - Inborn genetic disorders
    - Nutritional
- Mechanism
    - Impaired oxidative phosphorylation
    - Membrane dissolution
    - Cytoplasmic changes Karyopyknosis (shrinking)
    - Karyolysis (dissolution of chromatin)
    - Karyorrhexis (fragmentation of chromatin)
    - Osmotic regulation
    - Nuclear degeneration like Chromatin clumping

Coagulative Necrosis

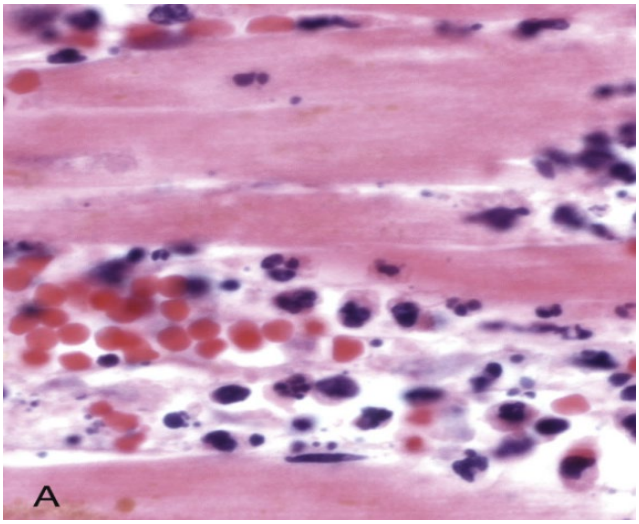
- Seen in myocardial or kidney infarction
- Protoplasm of the cells becoming fixed and opaque by coagulation of the protein elements, the cellular outline
- persisting for a long time
- Caused by ischemia, which results in decreased ATP, increased cytosolic Ca+ and free radical formation, which eventually cause membrane damage
- Macroscopically:
  - Cell's outline will be lost as a result of the coagulation of protein
  - Coagulative necrosis can be characterized by the forming of glassy eosinophilic appearance
- Microscopically nucleus will show:
  - Pyknosis
  - Karyolysis
  - Karyorrhexis



Robbins and Cotran Figure 2.7: Coagulative Necrosis of the kidney with yellow fatty infiltrate. Courtesy of Robbin & Cotran (use only for educational purposes).

Myocardium Necrosis (Infraction)

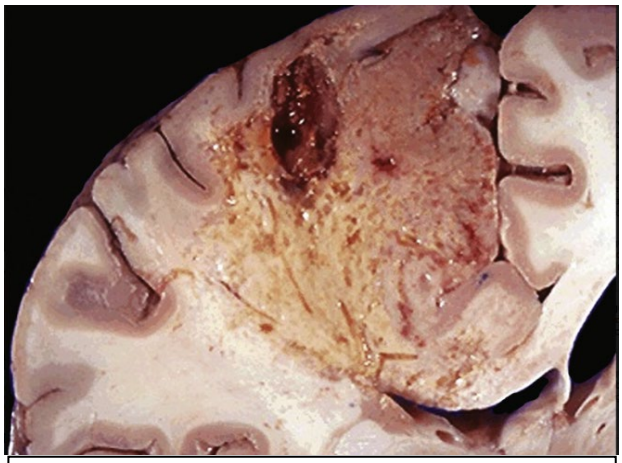
- A pale, whitish infarct is surrounded by a zone of
- hyperemia (vascular dilatation)
- The bluish areas on each side of the necrotic zone represent the granulation tissue response to the necrosis
- Granulation tissue is a part of the repair process



Robbins and Cotran Figure 3.6: Histological representation of an inflammatory reaction in the myocardium after ischemic necrosis (infarction). (A) demonstrates early neutrophilic infiltration and congestion of blood vessels. Courtesy of Robbin & Cotran (use only for educational purposes).

Liquefactive Necrosis

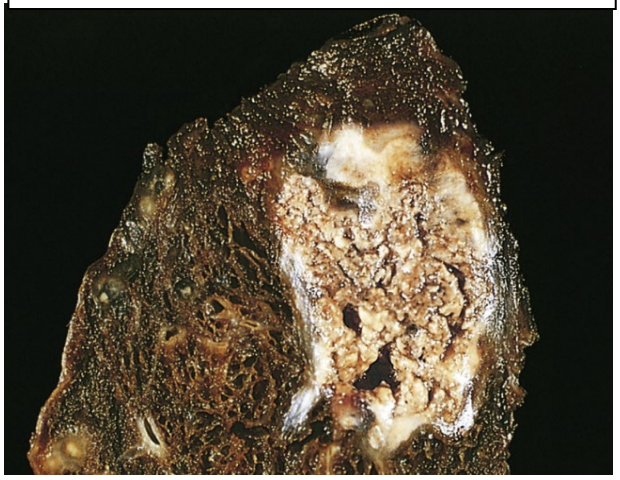
- Liquefactive necrosis in which the necrotic material becomes softened and liquefied
- This is usually seen in the CNS due to infarction
- Usually caused by focal bacterial infections, because they can attract polymorph nuclear leukocytes
- The enzymes in the polys are released to fight the bacteria, but also dissolve the tissues nearby, causing an accumulation of pus, effectively liquefying the tissue (hence, the term liquefactive)
- It can result from tissue digestion by phagocytes
- Macrophages liquefy and remove the necrotic tissue, leaving a fluid-filled cavity
- Cavity is filled with clear, watery fluid
- Microscopic characteristics
    - Loss of neurons and neuroglial cells and the formation of a clear space at the center left



Robbins and Cotran Figure 2.8: Liquefactive Necrosis of the Cerebrum. Courtesy of Robbin & Cotran (use only for educational purposes).

Caseous Necrosis

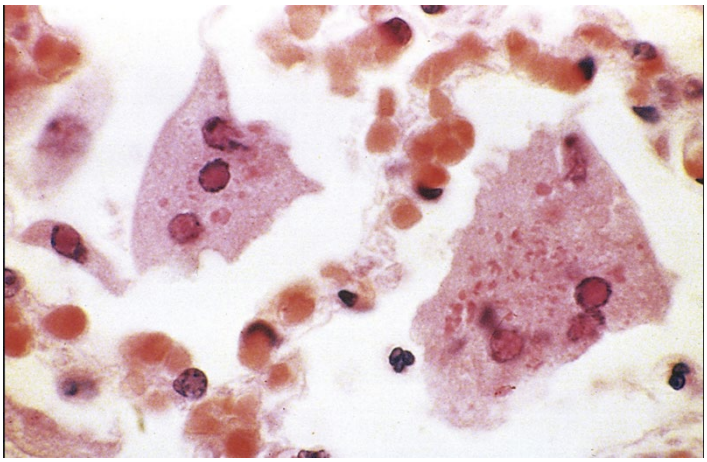
- Seen in Tuberculosis
- There are areas with eosinophilic, granular, and friable Cheese like cellular debris with necrosis
- Cavitation often occurs when phagocytes cause
- liquefaction and digestion of areas of caseous necrosis in the lung
- Other rare cause of caseous necrosis is fungal infection



Robbins and Cotran Figure 2.9: Caseous Necrosis of the lung. Courtesy of Robbin & Cotran (use only for educational purposes).

Giant Cell

- Large macrophage cells are characterized by an arc of nuclei toward the outer membrane
- The cell is formed by the fusion of epithelioid cells, which are derived from immune cells called
- macrophages
- Once fused, these cells share the same cytoplasm, and their nuclei become arranged in an arc near the outer edge of the cell



Robbins and Cotran Figure 8.7: Histological representation of multiple measles giant cells within pulmonary tissue. Note the large cell and nuclei being pushed to the outer membrane of the cell. Courtesy of Robbin & Cotran (use only for educational purposes).

Granuloma

- Focal collection of inflammatory cells at sites of tissue infection and includes
  - activated macrophages (epithelioid cells)
  - Langerhans' giant cells
  - Lymphocytes
- Examples:
  - Found in the tubercle, or primary focus of infection, in tuberculosis
  - Also seen in lesions of
    - Syphilis
    - Leprosy
    - Sarcoidosis - granuloma is composed of a collection of palisaded histiocytes in the periphery that may contain one or more benign multinucleate giant cells in the center
    - Fungal infections
- Exposure to beryllium lead to chronic allergic-type of the lung disease

Fibrinoid Necrosis

- Deposition of eosinophilic fibrin-like deposits or ground substance, in arterial walls
- It is seen with malignant HTN and periarteritis nodosa
- FN may also seen in
  - acute rheumatic fever
  - Sub-acute bacterial endocarditis
  - Peptic ulcers
  - Rheumatoid arthritis
  - Immune complex disease
  - Hepatitis B virus
  - Malignancy, Complement C2 deficiency
  - Henoch-Schönlein purpura, SLE, Collagen vascular diseases

Fatty Necrosis

- Acute pancreatitis leads to fatty necrosis
- During acute pancreatitis, lipase is released from pancreatic acinar cells
- This lipase hydrolyzes fat into fatty acids and glycerol.
- Free fatty acids bind with calcium to form soaps, which is a process known as saponification
- These appear grossly as the soft, chalky white areas as seen here on the cut surfaces

Gangrene

- Refers to the decay and death of tissue resulting from an interruption of blood flow to a certain area
- Gangrenous necrosis usually implies coagulative necrosis with superimposed bacterial infection
- Types:
    - Dry gangrene:
        - Usually develops slowly.
        - Characterized by dry skin ranging in color from brown to purplish-blue to black.
        - Occurs most commonly in people who have a blood vessel disease, such as atherosclerosis.
    - Wet gangrene:
        - If there's a bacterial infection in the affected tissue
        - Swelling, blistering and a wet appearance
        - Can develop after a severe burn, frostbite or injury
        - Often occurs in people with diabetes

- Gas Gangrene:
  - Usually caused by an infection by the bacteria Clostridium Perfringens, which develops in an injury or surgical wound that's depleted of blood supply
  - The bacterial infection produces toxins that release gas and cause tissue death
  - Typically affects deep muscle tissue
  - Surface of the skin may initially appear normal
  - As the condition progresses, skin may become pale and then evolve to a gray or purplish-red color
  - A bubbly appearance to skin may become apparent, and the affected skin may make a crackling sound when you press on it because of the gas within the tissue
  - Like wet gangrene, gas gangrene can become life-threatening
- Internal Gangrene:
  - Affecting one or more of the organs
  - Most commonly intestines, gallbladder or appendix

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
Physiological or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiological, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

Intracellular Accumulations

- Normal substance is produced at a normal rate, but metabolism cannot remove it (like fatty change in the liver), e.g. lipid accumulation in hepatocytes.

- These substances accumulate because of genetic or acquired defect in metabolism like storage diseases, e.g. alpha-1-AT deficiency or pigments due to inability of cell to metabolize or transport them (e.g., carbon, silica/talc).
- Causes of the accumulation of the fats are:
    - Alcohol
    - Toxins
    - protein malnutrition
    - DM
    - Obesity
    - Excess accumulation of triglycerides in the liver
- Morphology:
    - Liver may enlarge and become yellow
    - Eventually rupture and produce fatty cysts
- Atheroma - accumulation of cholesterol leads to atherosclerosis in intimal layer of aorta and large arteries filled with lipid vacuoles
- Xanthoma - accumulation of cholesterol within macrophages mostly hereditary problem
- Protein - Accumulation of protein like abnormal proteins may be toxic when they are retained within a cell
    - Examples:
        - Lewy bodies in Parkinson disease
        - Kidney filtration disorders (glomerulonephritis)
        - Protein folding disorders (cystic fibrosis, neurodegenerative diseases)
- Exogenous
    - Carbon in black lung disease in coal miners
- Endogenous
    - Lipofuscin, aging pigment - result of oxidative damage to lipid membranes

- Hemosiderin
    - Derived pigment which stores iron in cells like in cases of hemolytic Anemias
    - Ferritin forms hemosiderin when there is excess iron
    - Accumulation of hemosiderin is called hemosiderosis - usually not damaging to organs, but if it progresses to hemochromatosis then it is damaging.
- Due to abnormal deposition of calcium and iron
- Pathological Like Dystrophic Calcification. Occurs locally in dying tissue and is seen in damaged heart valves

- Metastatic Calcification
    - Occurs in viable tissue secondary to hypocalcemia
- Etiology:
    - PTH - parathyroid adenoma
    - Destruction of bone - primary tumors or metastatic disease
    - Vitamin D related disorders
    - Renal failure - retention of phosphate leading to secondary hyperparathyroidism

Aging

- "Progressive time related loss of structural and functional capacity of cells leading to death"
- Cellular ageing is the result of a progressive decline in cellular function and viability caused by genetic abnormalities
- The accumulation of cellular and molecular damage due the effects of exposure to exogenous influences leading to senile changes
- Factors affecting aging:
    - Genetic – fibroblasts
    - Diet
        - Malnutrition
        - Obesity
    - Social conditions
    - Diseases
        - Atherosclerosis
        - Diabetes
    - Werner's Syndrome

Cellular Mechanisms of Aging

- Decreased cellular replication
- Cross linking or mutation of DNA
- Accumulation of toxic by-products
- Ageing genes
- Loss of repair mechanism
- Free radical injury
- Cells have an average life span of 50-65 replications, then are killed off via Telomerase shortening

Aging Changes

- Gradual atrophy of tissues and organs. Dementia. Loss of skin elasticity. Graying and loss of hair
- Blood Vascular damage – atherosclerosis/bruising
- Loss of lens elasticity → opacity → vision. Lipofuscin pigment deposition – brown atrophy in vital organs

Werner's Syndrome

- Appear to age rapidly following puberty
- Increased risk of developing cancer and cardiovascular disease
- Symptoms:
    - Premature graying and loss of hair
    - Bilateral cataracts
    - Osteoporosis
    - Atherosclerosis
    - Diabetes
    - Scleroderma-like changes and ulceration of the skin

Case Questions: Part I

1. A 56-year-old man dies 24 hours after the onset of substernal chest pain radiating down his left arm to the ulnar aspect of his fingertips. Which of the following morphologic myocardial findings is an indicator of irreversible injury?
    A. Mitochondrial swelling
    B. Bleb formation
    C. Pyknotic nuclei

2. A 48-year-old woman has a malignant lymphoma involving lymph nodes in the para-aortic region. She is treated with a chemotherapeutic agent which results in the loss of individual neoplastic cells through fragmentation of individual cell nuclei and cytoplasm. Over the next 2 months, the lymphoma decreases in size, as documented on abdominal CT scans. By which of the following mechanisms has her neoplasm primarily responded to therapy?
    A. Coagulative necrosis
    B. Mitochondrial poisoning
    C. Phagocytosis
    D. Acute inflammation
    E. Apoptosis

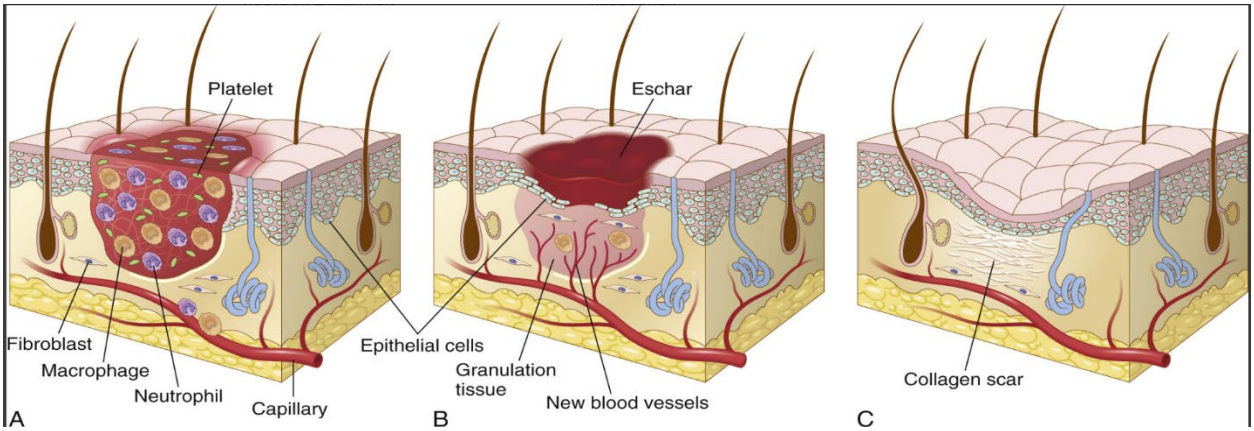
3. A 50-year-old chronic alcoholic presents to the emergency room with 12 hours of severe abdominal pain. The pain radiates to the back and is associated with an urge to vomit. Physical examination discloses abdominal tenderness. Laboratory studies show elevated serum amylase. Which of the following morphologic changes would be expected in the peri pancreatic tissue of this patient?
    A. Coagulative necrosis
    B. Caseous necrosis
    C. Fat necrosis
    D. Fibrinoid necrosis
    E. Liquefactive necrosis

4. Hyperplasia:
    A. Characterized by an increase in cell number
    B. Characterized by an increase in cell size, leading to an increase in organ size
    C. Characterized by smaller-than-normal cells which may undergo necrosis
    D. Always a pathologic process

5. Apoptosis:
    A. Usually a regulated, controlled process
    B. Plays a role in embryo-genesis
    C. Both

6. In histology, which term is used to designate a transition from columnar epithelium to squamous epithelium. As in cases of Barrett's esophagus.
    a. Metaplasia
    b. Dysplasia
    c. Anaplasia
    d. Hyperplasia

Tissue Renewal and Repair



Robbins and Cotran Figure 3.26: Depiction of the healing process and scar formation. Courtesy of Robbin & Cotran (use only for educational purposes).

The Concept of Healing

Healing is a

- Fibro-proliferative response which patches rather than restores a tissue
- The goal is to return tissue to original state
- Repair process begins early - sometimes within 24 hours

Stages of Healing

- Inflammation
- Granulation tissue (soft callus)
- Scar – Fibrosis (hard callus)
- Remodeling
- Wound strength
- Granulation tissue --(fibroblast deposition) and angiogenesis are characteristic of the repair process (IMP)

Tissue Repair Processes

- Regeneration of injured tissue
  - Refers to proliferation of cells and tissues to replace lost structures by parenchymal cells of the same type
- Repair
  - Restore some of the original structures but with deformities. Scar formation is the replacement by connective tissue (by Fibrosis or scarring)

Regeneration and Repair: Principles of cell Proliferation

- Occurs via the proliferative capacity of tissues and the role of stem cells in maintaining tissue homeostasis
- Lots of cells proliferate during tissue repair like vascular endothelial cells & fibroblasts
- Growth factors & cell-signaling mechanisms (Cell-Cycle) permit regulation & repair.
- Platelet-derived Growth Factor (PDGF) stimulates rebuilding of blood vessel walls
- Interactions between cells & ECM
- Vascular Endothelial Growth Factor (VEGF), stimulates endothelial cells to multiply and restore the endothelial lining

Growth Factors (GF's)

- Growth factors are very important in tissue repair
- These are polypeptides and found in secretions of body like -- sweat, saliva, urine, milk, plasma, intestinal fluids
- Actions:
    - stimulate cell division and proliferation
    - promote cell survival
- In healing wounds, EGF is produced by macrophages and other inflammatory cells
- Common GF's
    - EGF (Epidermal Growth Factor)
    - TGF (Tissue Growth Factor)
    - PDGF (Platelet Growth Factor)
    - HGF (Hepatocyte Growth Factor)

- GF's are produced by fibroblasts, most mesenchymal cells, endothelial cells, liver non-parenchymal cells
- Vascular Endothelial Growth factor (VEGF-B, C,D,)
    - Potent inducer of angiogenesis in tumors, chronic inflammation, wound healing
- Fibroblast growth factor (FGF) involved in:
    - Angiogenesis
    - Wound repair
    - Skeletal muscle development
    - Hematopoiesis
- Growth factors Cell Proliferation can also be stimulated by hormones like Endometrium growth by Estrogen
- TSH mediated replication of cells of thyroid during pregnancy
- Nodular Goiter by increased serum level of TSH (Pathologic)

Types of Cells

- Continuously dividing (labile) tissues
  - Cells are continuously proliferating
  - Easily regenerate after injury
  - Contain a pool of stem cells
  - Examples: bone marrow, skin, GI epithelium
- Stable tissues
  - Cells have limited ability to proliferate
  - Limited ability to regenerate (except liver)
  - Normally in G_0 but can proliferate if injured
  - Examples: liver, kidney, and pancreas
- Permanent tissues
  - Cells can't proliferate after birth
  - Can't regenerate (so injury always leads to scar)
  - Examples: neurons and cardiac muscle

Regeneration

- Occurs all the time in labile tissues
- Cells are constantly being lost and replaced
- If demand increases, supply increases easily
- Occurs in limited form in stable tissues

- Only occurs if residual tissue is intact
- Remove one kidney: the other one undergoes hypertrophy (compensatory hypertrophy)
- Remove half of the liver: it will grow back
- Trigger seems to by cytokines and growth factors

Extracellular Matrix

- ECM is the network that surrounds cells
- Secreted locally and assembles into network in spaces surrounding cells
- It is composed of Collagen which provides structural integrity and tensile strength.
- Without it, a human would be a clump of cells and neurons.
- Collagen is composed of a helix of 3 polypeptide (proline/lysine) chains
- There are 27 different types currently known
- Bottom line: ECM regulates proliferation, movement, and differentiation of the cells living in it

Scarring

- If injury is severe, regeneration cannot occur. In such cases, fibrosis (a scar) replaces the injured tissue
- Four components to scarring
    - New vessel formation (angiogenesis) = is the extension of existing vessels in close proximity (may also involve recruitment of stem cells, angioblasts from BM to form new vessels)
    - Fibroblast proliferation = growth factors and cytokines (IL-1, TNF) cause migration of fibroblasts to site of inflammation
        - Synthesis of collagen (scar formation)
        - Remodeling of scar

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Summary of Scar Formation

- By 24 hours:
    - Endothelial cells start proliferating
    - Fibroblasts emigrate
- By 3-5 days:
    - Granulation tissue present
- Weeks later:
    - Dense fibrosis (scar)

Healing by First Intention

- Occurs in small wounds that close easily
- Epithelial regeneration predominates over fibrosis
- Healing is fast with minimal scarring/infection
- Examples:
    - Paper cuts
    - Well-approximated surgical incisions
    - Replaced periodontal flaps

Healing Timeline

- By 24 hours
    - Clot forms
    - Migration of the Neutrophils.
    - Epithelium begins to regenerate

- By 3-7 days
    - Macrophages come in & granulation tissue is formed
    - New blood vessels form
    - Fibroblasts lay down collagen & begins to bridge incision
    - Epithelium increases in thickness
- Weeks later
    - Granulation tissue gone
    - Collagen is remodeled
    - Epidermis full, mature

Healing by Second Intention

- Occurs in larger wounds that have gaps between wound margins
- More inflammation
- More granulation tissues
- Fibrosis predominates leading to wound contraction
- More extensive loss of cells and tissue (ulcer)
- Wound strength - after 1 week, tissue strength is approximately 10% of normal
- At 3 months it is at 80% of normal and does not improve further
- Examples:
    - Infarction
    - Large burns and ulcers

Why do good wounds go bad?

- Extrinsic factors
  - Infection
  - Diabetes
  - Steroids
- Type of tissue injured
  (labile vs. permanent)
- Aberrant cell growth or ECM production produces
  - Keloid scars

Factors Affecting Healing

- Systemic
  - Nutrition
  - Vitamin deficiency
  - Age
  - Immune status
  - Comorbidities & chronic disease
- Local
  - Necrosis
  - Infection
  - Apposition
  - Blood supply
  - Mobility
  - Foreign body

- Complications
  - Inadequate formation of granulation tissue may lead to rupture or ulcer
  - Excessive accumulation of granulation tissue can form keloid scars.
  - Contracture can occur as an exaggeration of normal healing (burns)

Summary

- Healing – Proliferation & Differentiation
- Labile, Stable & Permanent cells
- Stages of Healing
- Healing by First or Second Intention
- Skin wound healing - bone healing
- Factors affecting healing – Local / Systemic

Disorders of Circulation

Intracellular

- Ions
- Ion specific gates in cell membrane
- Cellular proteins

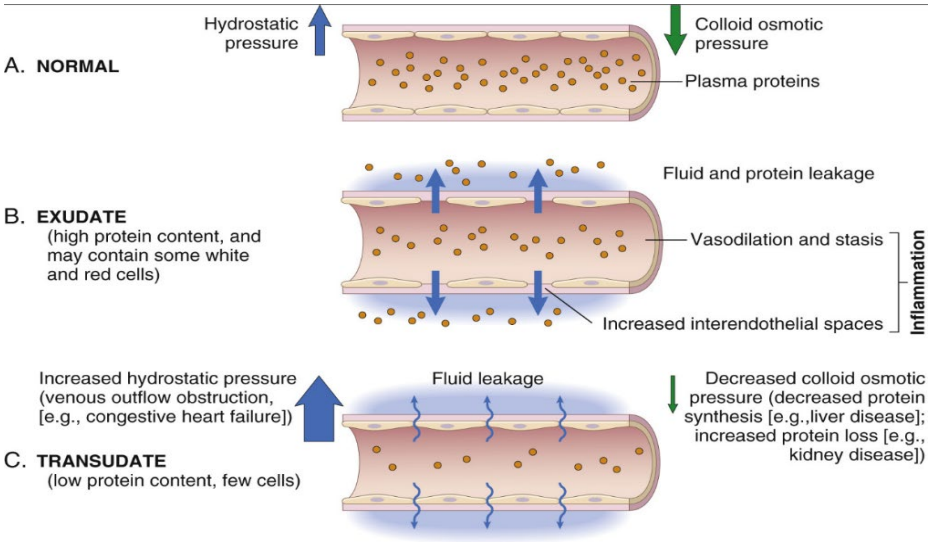
Extracellular

- Interstitial (between the cells)
- Intravascular
    - Blood
    - Lymphatic fluid

Terms

- Edema (increased fluid in the ECF)
- Anasarca is a term used to describe gross edema.
- Hyperemia (Increased flow)
- Congestion (Increased backup)
- Hemorrhage (extravasation)
- Hemostasis (keeping blood as a fluid)
- Thrombosis (clotting blood)
- Embolism (downstream travel of a clot)
- Infarction (death of tissues w/o blood)
- Shock (circulatory failure/collapse)
- Roughly 65%of the total blood volume resides in the venous system
- Microcirculation includes arterioles, capillaries and venules
- Cardiac output is the volume of blood pumped by each ventricle per minute and represents the total blood flow in pulmonary and systemic circuits.
    - Cardiac output is the product of heart rate and stroke volume (CO= HR X SV)
    - The sum of all regional flows equals the venous return, which in turn determines the cardiac output
- Peripheral vascular resistance is the sum of the factors that determine regional blood flow in each organ
    - Two thirds of the resistance in the systemic vasculature is determined by the arterioles
- In flow to the heart is called as preload and outflow is called as after-load

Transudate	Exudate
Specific gravity < 1.012	Specific gravity > 1.012
Protein content < 3 g/dl	Protein content > 3 g/dl
LDH low	LDH high
Glucose normal	Glucose low
No inflammatory cells	Inflammatory components such as leucocytes, fibrin are seen



Robbins and Cotran Figure 3.2: Visually distinction between exudate & transudate. Courtesy of Robbin & Cotran (use only for educational purposes).

Edema

- Edema is defined as a palpable swelling produced by excess accumulation of fluid in the extra vascular compartment
- Mostly in interstitial compartment
- Edema is a shift of fluid to the interstitial space
- Hydrothorax (in pleura)
- Hydropericardium
- Hydroperitoneum (Ascites)
- Localized edema: due to inflammation
- Generalized edema: due to systemic illness
- When massive and generalized this is called anasarca (which is usually caused by liver failure - cirrhosis of the liver) or renal failure/disease and severe malnutrition/protein deficiency

Examples of Edema

- Heart failure (left versus right failure)
- Pulmonary edema due to:
    - Left sided heart failure
    - Pulmonary infections
    - Hypersensitivity reaction
- Subcutaneous (“Pitting "or “Dependent”)
- Periorbital (Renal)
- Cerebral (closed cavity, no expansion)
- Lymphatic obstruction (like due to radiation) presents as non-pitting type of edema

Physiology of Edema

- Increased Hydrostatic Pressure
- Reduced oncotic Pressure
- Increase capillary permeability
- Lymphatic Obstruction
- Sodium/Water Retention

Normal

- What is hydrostatic pressure?
    - The pressure that the fluid exerts on the walls of its container-like capillaries. AKA the force of blood on the blood vessel walls.
    - what is the main cause of hydrostatic pressure in the Cardiovascular System
- What is osmotic pressure?
    - The pressure required to prevent the flow of water across a semipermeable membrane via osmosis
- What is the main cause of osmotic pressure in the Cardiovascular System?
    - Diffusion of water from a hypotonic solution to a hypertonic solution

Movement of Water in the Vascular System

- Hydrostatic, the pumping pressure
    - Heart
    - Skeletal muscle action
- Oncotic or osmotic, holds fluid in
    - Proteins such as albumin
    - Cellular elements such as RBCs

Hydrostatic Pressure

- If osmotic pressure is higher on the capillary side, then fluid will be pulled from the interstitial space into the capillary.

- At the venule side, osmotic pressure is higher than hydrostatic pressure
- Hydrostatic pressure in the arteriolar segment of the capillary (is 32 mm Hg)
- It is opposed by plasma oncotic pressure (26 mm Hg) (hydrostatic pressure as blood pressure which is higher in the artery side rather than the venule side)
- This drives the material out of the capillary, while the osmotic pressure brings the material back to the capillary

Hydrostatic pressure at the capillary physiology

- The capillary wall acts as a filtration "barrier"
- Most of the fluid within the capillaries is retained, but some filter will through pores between the cells, pushed by the pressure difference between the capillary blood and the Interstitial fluid
- Water and small solutes can pass freely through pores
- The net effect of the hydrostatic pressure alone is a net loss of water and solute from plasma to the Interstitial fluid
- The capillary wall (both cells and pores) are impermeable to the plasma proteins and lipids
  Under normal conditions the protein and lipids stay within the plasma
- Note that following injury, the capillaries can also leak protein

Hydrostatic Pressure Pathophysiology

- If the hydrostatic pressure at the venous end of the capillary system is elevated - reabsorption decreases (Interference of venous drainage)
- As long as the lymphatic can drain the surplus fluid - no edema results
- If capacity is exceeded - edema fluid accumulates
- Seen in:
  - Venous obstructions
  - Hepatic venous obstruction
  - Cardiac failure
  - Edema due to hemodynamic disturbances leads to transudate formation

Edema Pathophysiology

- Decreased oncotic pressure
- Nephrotic syndrome in which glomerular capillary walls become leaky and the patient will have lose proteins
- Reduced albumin synthesis in liver diseases (cirrhosis)
- Protein Malnutrition (Kwashiorkor) a malnutrition disease, chiefly of children, caused by severe protein and vitamin deficiency and characterized by:
    - Retarded growth and potbelly
    - Changes in pigmentation and anemia
    - Protein-losing gastroenteropathy
- Leaky vessels (Increase capillary permeability)
- Allows the fluid and protein to pass through endothelium in to the interstitial space
- Inflammation - exudate or allergic response burns or due to trauma

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Clinical Affects

- Subcutaneous tissue edema in cardiac or renal failure is important for diagnosis
- Edema can also impair wound healing or the clearance of infection
- It can also lead to infections as edema fluid is a good media for the growth of microorganisms
- Pulmonary edema can cause death by interfering with normal ventilatory function
- Brain edema is serious and can be rapidly fatal
- Brain edema can cause tonsillar herniations which is the extrusion of the brain through the foramen magnum causing the compression of vessels, nerves, and brain tissue

Hyperemia and Congestion

- Hyperemia and congestion both indicate a local increased volume of blood in a particular tissue
- Hyperemia is an active process by which there is increased inflow of blood into a tissue
- Hyperemia may be caused by an increased supply of blood from the arterial system (active hyperemia)
- Affected tissue is redder in color
- Congestion is a passive process (Chronic) is due to impaired outflow from tissue
- By impaired exit of blood through venous pathways
- The tissue has a blue-red color (cyanosis)
- May be Local (Isolated venous obstruction)
- May be systemic (Cardiac Failure)
- May be Acute or Chronic

Active Hyperemia

- Localized arteriolar dilatation as seen in inflammation
- Vasoactive materials released by inflammatory cells cause blood vessels to dilate; this contributes to the classic “tumor, rubor, and color” of inflammation
- In pneumonia - alveolar capillaries are engorged with erythrocytes
- Associated alveolar septal edema and/or focal intra-alveolar hemorrhage

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Pneumonia Pathology

- Major stages of Acute Lobar pneumonia
    - Congestion
    - Red hepatization
    - Grey hepatization
    - Resolution

Passive Hyperemia (Congestion)

- Engorgement of an organ with venous blood (obstruction of venous return or increased back pressure from congestive heart failure)
- Acute passive congestion is clinically a consequence of acute left ventricular failure - mitral stenosis or due to shock

- Chronic passive congestion is seen in failure of the right ventricle; the liver can become severely congested
- Generalized increase in venous pressure, typically from chronic heart failure, results in slower blood flow and a con-sequent increase in blood volume in many organs, including liver, spleen and kidneys.
- Congestive heart failure secondary to coronary artery disease, hypertension and right-sided failure due to pulmonary disease are now common

Pulmonary Edema

- Chronic left ventricular failure impedes blood flow out of the lungs and leads to chronic passive pulmonary congestion
- Pressure in alveolar capillaries increases and these vessels become engorged with blood
- It will lead to the thickening and fibrosis of the septa
- Microhemorrhages release erythrocytes into alveolar spaces, where they are phagocytosed and degraded by alveolar macrophages
- This will release iron, in the form of hemosiderin, (in macrophages which are then called “heart failure cells”)
- Therefore, the alveolar spaces may contain numerous hemosiderin-laden macrophages ("heart failure cells")

- Fluid is forced from blood into the alveolar air spaces especially at bases of the lungs
- The resulting pulmonary edema interferes with gas exchange in the lung
- Fibrosis increases in the interstitial space of the lung
- The presence of fibrosis and iron is viewed grossly as a firm, brown lung (brown induration)
- Pulmonary edema occurs only when the pulmonary capillary pressure rises to values exceeding the plasma colloid osmotic pressure, which is approximately 28 mm Hg in the human
- This effect is sometimes evident as Kerley- B lines, which are horizontal, pleural-based, peripheral linear densities
- Interstitial fluid will cause a perihilar "bat wing" appearance.

Cardiac Edema

- Congestive heart failure (CHF) is the condition in which heart is unable to maintain an output sufficient for the metabolic functions of the tissues and organs of the body
- Most of the cases are due to the fall of myocardial contractile function (systolic dysfunction)
- Example: Ischemic injury; pressure or volume overload; dilated cardiomyopathy
- CHF is characterized by diminished cardiac output (forward failure) or stagnation of blood in the venous system (backward failure) or both
- Influenced by gravity and is seen in the depending parts of the body (i.e. dorsum of the foot, ankle)
- Protein content of the edema fluid is low (2%)
- Heart failure cells are hemosiderin laden macrophages

Left-sided Cardiac Failure

- Left ventricular dysfunction causes blood to backup through left atrium and into pulmonary system
- Causes:
    - Systemic hypertension (most common cause)
    - Ischemic heart disease
    - Mitral or aortic valve disease
    - Primary myocardial disease
- Clinical presentation:
    - Due to obstruction to pulmonary vascular out-flow there is pulmonary congestion and edema
- Reduction of renal perfusion causes:
    - Ischemic acute tubular necrosis
    - Salt and water retention
    - Impairment of waste excretion causing azotemia (elevated levels of urea in blood)
    - Reduced perfusion of central nervous system causes hypoxic encephalopathy (irritability to coma)

Right-sided Cardiac Failure

- Most commonly followed by the left ventricular failure
- Intrinsic disease of lungs and pulmonary vasculature causing obstruction to right ventricular out-flow (Cor pulmonale)
- Pulmonary hypertension occurs when the back pressure from the pulmonary venous circuit is transmitted to the pulmonary arterial system. This may lead to right side heart failure and consequent generalized systemic venous congestion

- Pulmonary or tricuspid valve disease
- Congenital heart disease in which there is left-to-right shunt like patent foramen ovale; Patent ductus arteriosus and Interventricular septal defect
- Other causes:
    - Extra cardiac circulatory failure, for example hemorrhage; vasovagal syncope etc.
    - Impaired atrial filling by external compression, for example Constrictive pericarditis.

Clinical Presentation

- Note the color of skin, lips and nail beds.
- Inspect thorax, any visible pulsations, shifting of the apex beat, and distension of neck veins
- Right-sided cardiac failure leads to
    - Congestion and edema of portal and dependent peripheral sites:
        - Feet
        - Ankle
        - Sacrum
        - Effusions in pleura
        - Peritoneum (ascites)

- Hepatomegaly – hepatic veins empty into the vena cava immediately inferior to the heart so the liver is particularly vulnerable to acute or chronic passive congestion
- Increased venous pressure causes the central veins of hepatic lobules to dilate and is transmitted to hepatic sinusoids which dilate causing centrilobular hepatocytes to undergo pressure atrophy (nutmeg liver)
- Centrilobular necrosis due to chronic passive venous congestion may cause sinusoidal rupture with central hemorrhagic necrosis followed by:
    - Hemosiderosis
    - Central fibrosis
    - Cardiac sclerosis
- Congestive splenomegaly with sinusoidal dilation, focal hemorrhage followed by hemosiderosis and fibrosis.
- Renal congestion causes acute hypoxic tubular necrosis.
- Fate of the patients:
    - Patients die of progressive congestive heart failure or due to acute myocardial infarction or an arrhythmia (abnormal rhythm)

Renal Edema

- Nephritic edema in acute nephritis:
  - Edema is not extensive, but protein content is low
  - Edema is seen as puffiness of face and eyelids
  - This is due to the retention of Na+ and water due to oliguria resulting from damage of glomeruli
  - Na+ retention causes increased secretion of renin followed by angiotensin and aldosterone
- Nephrotic edema in nephrotic syndrome:
  - Hypoproteinemia due to massive proteinuria causes low osmotic pressure of plasma resulting in edema
  - Associated hyper-aldosteronism releases renin-angiotensin-aldosterone in the system causing edema

Cerebral Edema

- Localized to the site of injury (Example: abscess, neoplasm)
- Generalized example:
  - Encephalitis
  - Hypertensive crisis (greater than 180/120mmHg)
  - Obstruction to the venous outflow of brain
- Grossly, brain is swollen with narrowing of sulci and flattening of gyri due to pressure of swollen brain against the skull

Hemostasis and Thrombosis

- Normal hemostasis regulates blood in a fluid state (Clot-free in normal vessels)
- Normal endothelial cells maintain liquid blood flow by:
  - Inhibiting platelet adherence
  - Preventing coagulation factor activation
  - Lysing blood clots that may form
  - The pathologic form of hemostasis is thrombosis
  - Rapid formation of a localized hemostatic plug at the site of vascular injury

Mechanism of Hemostasis and Thrombosis

- Normal vascular wall(endothelium)
- Normal Platelets
- Coagulation cascade

- After an injury or inflammation endothelial cells are stimulated by direct injury or by various cytokines
- Results in formation of procoagulant proteins (e.g., tissue factor and vWF) that will start local thrombus formation
- Which will lead to:
    - Adherence of platelets
    - Exposure of tissue factor (factor III) &Thromboplastin
    - And local depletion of anticoagulant mechanisms (PGI2 & Plasminogen activators)

Thrombosis

- Aggregate of coagulated blood containing platelets, fibrin and entrapped cellular elements, within a vascular lumen
- Begin at sites of endothelial injury or turbulence
- Produced by platelet and coagulation activation
- Virchow's Triad
- Endothelial injury
- Stasis or turbulence of blood flow
- Blood hypercoagulability
- Thrombi can develop anywhere in the cardiovascular system cardiac chambers on valves, in arteries, veins, or capillaries
- Molecular Pathogenesis:
    - Homocysteinemia is associated with atherosclerotic coronary artery disease and cardiac ischemia
- Types:
    - May be white, red & mixed
    - May be arterial or cardiac thrombi
    - Arterial thrombi are frequently occlusive
    - Venous thrombi characteristically occur at sites of stasis
    - Venous thrombi extend in the direction of blood flow (thus both tend to propagate toward the heart)
    - Veins of the lower extremities are most commonly affected
    - Fragmentation lead to embolus

- Sites:
    - Arterial: Brain, heart, limbs, eyes
        - Occurring in heart chambers or in the aortic lumen are called mural thrombi
        - Common in aneurysms (localized dilations of the lumen) of the aorta and its major branches in which the distortion of blood flow combined with intrinsic vascular disease promotes thrombosis.
    - Venous: Legs
    - Capillary: DIC in septicemia

- Causes:
    - Abnormal myocardial contraction due to:
        - Arrhythmias
        - dilated cardiomyopathy
        - Myocardial infarction.
        - Endo myocardial injury caused by myocarditis, catheter trauma)
- Other causes:
    - Inflammatory vascular injury – vasculitis
    - Minor injury
    - Smoking
    - Radiation & Hypercholesterolemia

Fate of Thrombus

- Propagation
    - (Continue to form) causing vessel obstruction
- Embolization
    - Thrombi dislodge or fragment and are transported elsewhere in the vasculature
- Dissolution
    - Thrombi are removed by fibrinolytic activity
- Organization (fibrosis) and recanalization (revascularization)

Clinical Application

- Most venous thrombi occur in the deep veins of the leg. Superficial venous thrombi: saphenous system with varicosities
- Deep vein thrombosis: more serious - may embolize. Embolism to the lungs causes death.
- Arterial thrombi: embolize cause downstream tissue infarction. Tumor-associated procoagulant release is largely responsible for the increased risk of thromboembolic phenomena seen in disseminated cancers (called migratory thrombophlebitis, or Trousseau's syndrome).

Summary

- Arterial Thrombosis:
  - The primary cause of arterial thrombosis is rupture of an atherosclerotic plaque
  - This will lead to damage to the endothelium and release of constituents of the plaque into the lumen of the blood vessel
- Venous thrombosis:
  - Endothelium remains intact
  - Venous thrombosis can be triggered by several factors:
    - Abnormal blood flow (such as the absence of blood flow)
    - Altered properties of the blood itself (thrombophilia)
    - Alterations in the endothelium

Embolus

- Detached intravascular solid, liquid, or gaseous mass that is carried by blood to a site distant from its point of origin
- Embolism is passage through venous or arterial circulations of any material that can lodge in a blood vessel and obstruct its lumen

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- Types of Emboli
  - Thrombo-embolism – mostly in atherosclerosis, 99% of emboli- broken off from atherosclerosis plaque
  - Fat - long bone fractures, liposuction
  - Tumor – cancers
  - Gas – 'Caisson disease' Divers bends, IV leakage
  - Liquid – Amniotic fluid in new born, during childbirth or postpartum
- Result of emboli
  - Leads to development of collateral circulation:
  - Ischemia
  - Infarction
  - Gangrene
  - Hemorrhage

Pulmonary Thromboembolism

- 95% of cases - venous emboli originate from deep leg vein thrombi
- Occlude the main pulmonary artery, impact across the bifurcation (saddle embolus), or pass out into the smaller branching arterioles
- Multiple emboli
- Most pulmonary emboli (60%-80%) are clinically silent
- They can lead to sudden death, right ventricular failure (Cor pulmonale), or cardiovascular collapse
- Embolic obstruction of medium-sized arteries can cause pulmonary hemorrhage but usually not pulmonary infarction because the lung has a dual blood supply
- Many emboli occurring over a period of time may cause pulmonary hypertension

Systemic Thromboembolism

- Most (80%) arise from intra cardiac mural thrombi
- Are associated with left ventricular wall infarcts or with dilated left atria (e.g., secondary to mitral valve disease)
- May originate from aortic aneurysms, thrombi on ulcerated atherosclerotic plaques, or fragmentation of valvular vegetations
- Paradoxical emboli: very small fraction of systemic emboli appear to arise in veins but end up in the arterial circulation, through interventricular defects (congenital)

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Fat Embolism

- After bone fracture (femur)
- Microscopic fat globules can be found in the circulation
- This pathology is further exacerbated by free fatty acid release from the fat globules, causing local toxic injury to endothelium.
- It may lead to:
    - Pulmonary insufficiency
    - Neurologic symptoms
    - Anemia
    - Thrombocytopenia

Air Embolism

- Gas bubbles within the circulation can obstruct vascular flow
- Air may enter the circulation during obstetric procedures or as a consequence of chest wall injury
- Decompression sickness:
    - Individuals who are exposed to sudden changes in atmospheric pressure like deep-sea divers and underwater construction workers
    - During descent, large amounts of inert gas (nitrogen or helium) dissolve in bodily fluids
    - When the diver ascends, this gas is released from solution and exhaled
    - If the diver then ascends too rapidly, the nitrogen expands in the tissues and bubbles out of solution in the blood to form gas emboli that can induce focal ischemia in a number of tissues like brain & heart
- Treatment: place patient in a compression chamber to increase barometric pressure and force the gas bubbles back into solution

Amniotic Fluid Embolism

- Grave complication of labor and the immediate postpartum period
- Patient may have sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma
- Patient may develop disseminated intravascular coagulation (DIC) due to release of thrombogenic substances from amniotic fluid

Bone Marrow Embolism

- Bone marrow emboli to the lung
- Occasionally occur after fractures of long bones.
- Tumor emboli are occasionally seen in the lung during hematogenous dissemination of cancer

Infarction

- Localized area of ischemic necrosis caused by occlusion of the arterial supply or the venous drainage in a particular tissue
- Nearly 99% of all infarcts result from thrombotic or embolic events
- Factors Influencing Infarct Development:
    - Nature of vascular supply
    - Dual supply, collaterals
    - Rate of development of occlusion

    - Time to open new or existing collaterals
    - Vulnerability to hypoxia
    - Metabolic demands of tissues
    - Oxygen content of the blood
    - Anemic or cyanotic patient more vulnerable

- Infarcts are classified on the basis of their color
    - Red infarcts- hemorrhagic infarcts:
        - Occur with venous occlusions
        - Occur principally in organs with a dual blood supply (ex: lung) or those with extensive collateral circulation (ex: small intestine and brain)
        - Sharply circumscribed, firm, and dark red-purple
        - reestablishment of circulation in previous zone of ischemia
    - Pale infarcts, ischemic:
        - White infarcts occur with arterial occlusions or in solid organs (such as heart, spleen, and kidney)
        - On gross examination, 1 or 2 days after the initial hyperemia, an infarct becomes soft, sharply delineated, and light yellow.
    - Septic infarction
        - Results when the necrotic tissue of an infarct is seeded by pyogenic bacteria and becomes infected

- Morphology:
    - Typically wedge shaped with occluded artery at the apex, tissue at the base
    - Initially ill-defined and slightly hemorrhagic
    - Ischemic coagulative necrosis
    - Inflammatory response in 1-2 days
    - Reparative process in the preserved margins- some parenchymal regeneration
    - Mostly scarring (Fibrosis)

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Hemorrhage

- Hemorrhage — extravasation of blood because of vessel rupture
- Capillary bleeding can occur under conditions of chronic congestion
- Hemorrhagic diatheses — variety of clinical disorders with increased tendency to hemorrhage from usually insignificant injury
- Rupture of large artery or vein is usually due to vascular injury such as trauma, atherosclerosis, erosion
- Hematomas may be insignificant, such as a bruise, or may result in death, such as massive retroperitoneal hematomas
- Petechial — 1- to 2-mm hemorrhages into skin, mucous membranes, or serosal surfaces
- Typically associated with locally increased intravascular pressure, low platelet counts(Thrombocytopenia), platelet function defects, clotting factor deficits

Disseminated Intravascular Coagulation (DIC)

- condition in which blood clots form throughout the body's small blood vessels
- These blood clots can reduce or block blood flow through the blood vessels, which can damage the body's organs
- Disseminated intravascular coagulation is a serious disorder in which the proteins that control blood clotting become overactive.
- It is also called as consumption coagulopathy
- Risk factors for DIC include:
    - Blood transfusion reaction
    - Cancer, especially certain types of leukemia
    - Inflammation of the pancreas (pancreatitis)
    - Infection in the blood, especially by bacteria or fungus
    - Liver disease
    - Pregnancy complications (such as placenta that is left behind after delivery)
    - Recent surgery or anesthesia
    - Severe tissue injury (as in burns and head injury)
    - Sepsis

- Symptoms of DIC:
    - Bleeding, from many sites in the body
    - Blood clots
    - Bruising
    - Drop in blood pressure
- Tests:
    - Complete blood count with blood smear exam
    - Fibrin degradation products
    - Partial thromboplastin time (PTT)
    - Prothrombin time (PT)
    - Fibrinogen blood test

Shock

- Depressed vital functions due to decreased circulating blood volume
- A condition characterized by systemic hypo-perfusion by reduced cardiac output or circulating blood volume.
- Leading to Hypotension (low B.P.) → Impaired tissue perfusion → Hypoxia
- Initially the hypoxic effects are reversible, but eventually the effects are irreversible and death results
- Types:
    - Hypovolemic – True/Vasovagal
    - Cardiogenic – Heart failure, MI
    - Obstructive – Pulmonary embolism
    - Anaphylactic – Vasodilation due to allergy
    - Septic – Capillary damage by infection
    - Neurogenic – Loss of vascular tone and peripheral pooling of blood
    - Due to anesthetic accident or spinal cord trauma

Septic Shock

- Most commonly Gram Negative but may be due to Gram Positive Bacteremias
- Results from spread of a local infection (ex: abscess, peritonitis, pneumonia) into the blood stream
- 20% mortality rate
- Most common cause of death in intensive care units.
- Bacterial wall has lipopolysaccharides(LPS) which binds to:
    - Leukocytes (especially monocytes)
    - Macrophages
    - Endothelial cells

- Leading to systemic vasodilation widespread endothelial injury and ARDS(Lungs) activation of coagulation system (DIC)
- Non-progressive phase:
    - Compensatory reflex mechanisms are activated- perfusion to vital organs is maintained
    - Tachycardia
    - Peripheral vasoconstriction
    - Renal conservation of fluid
    - Compensatory mechanisms include:
        - Baroreceptors
        - Catecholamines activation of renin-angiotensin system ADH released causing sympathetic response

- Progressive Phase:
    - Tissue hypoperfusion - metabolic and circulatory acidosis
    - Anaerobic glycolysis becomes dominant and lactic acidosis occurs dulling the vasomotor response:
        - Arterioles dilation
        - Peripheral pooling
        - Endothelial hypoxia
        - DIC
    - Eventually organ failure and decreased urinary output as well as mental confusion.

- Irreversible Phase:
    - Severe tissue and cellular injury with vital organ shut down (Multiple organ failure)
    - Brain- ischemic encephalopathy
    - Liver- Fatty change and central hemorrhagic necrosis
    - Lung - in septic shock- diffuse alveolar damage
    - Adrenals- cortical cell lipid depletion
    - Renal failure (due to tubular necrosis) leading to death

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Clinical Features of Shock

- Hypotension
- Tachycardia
- Weak, rapid pulse, cold clammy, cyanotic skin
- Rapid shallow respiration (Tachypnea)
- Septic shock: the skin may be initially warm and flushed
- Drowsiness, confusion, irritability
- Multi organ failure
- Compensatory mechanisms:
    - Adrenaline → cold, clammy skin
- Complications: Ischemic damage leading to necrosis if not treated

Shock Management

- Keep blood pressure to normal by Fluids, electrolytes or blood transfusion
- Stimulants – ammonia inhalation
- Pregnancy - Optimization of perfusion in the mother is the treatment of choice for the fetus.
- Pediatric - Compensatory mechanisms may be quite effective in children. Hypotension is a late finding and represents significant hemorrhage.
- Geriatric - Medications and underlying diseases may modify responses to cause or even therapy.

Inflammation "itis"

Introduction

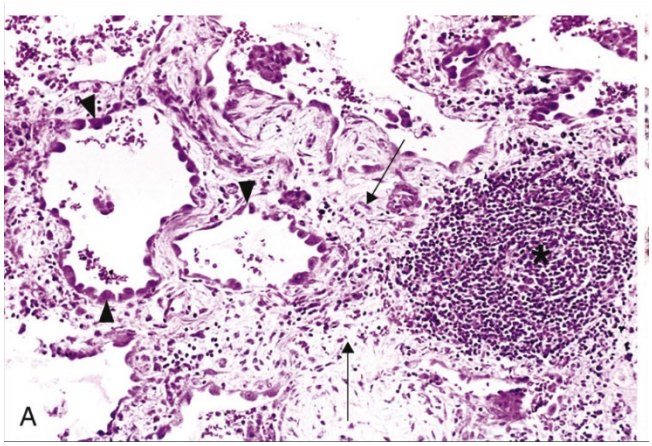
- What is it?
  - Series of reactions ("dynamic response of vascularized tissue to injury")
  - It is natural processes
  - Initial phase of healing
  - May be microbial or non-microbial like chemical or autoimmune
  - It serves to bring defense & healing mechanisms to the site of injury by destroying or diluting injurious agent by:
    - Vasoconstriction is lasting about 30 seconds followed by vasodilatation
    - Stasis slowing of blood flow
    - Hyperemia
    - Accumulation of leukocytes
    - Exudation of fluid
    - Deposition of fibrin
    - Processes of repair – production of new capillaries and fibroblasts organization
- What is the purpose?
  - Defend against the foreign substance
  - Dispose of dying material
  - The second line of defense or inflammatory response is activated when the first line of defense is inadequate
  - Inflammation can be induced by immune recognition of infection or tissue damage

Clinical signs of Inflammation

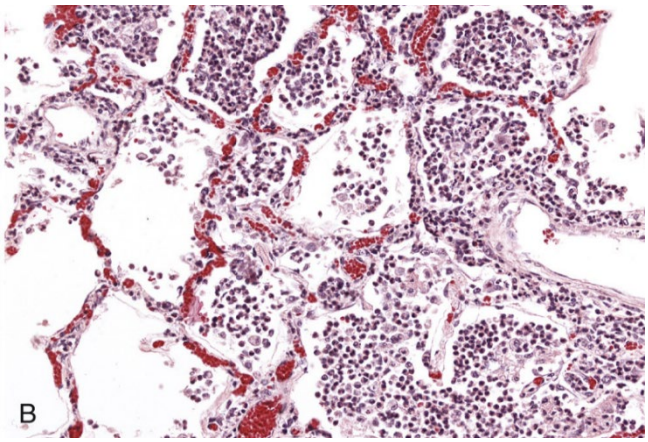
- Rubor: Redness – Hyperemia
- Color: Warm – Hyperemia
- Dolor: Pain – Nerve, Chemical
- Tumor: Swelling – Exudation
- Loss of Function: Virchow added a fifth – loss of function

Time Course

- Acute inflammation: (Hours to days)
  - Influx of white blood cells and fluid from blood
  - to fight infection and aid tissue repair
- Chronic inflammation: Greater than 48 hours (weeks, months, years) Leads to tissue damage and loss of tissue function (joint destruction, lung fibrosis, etc.)



Robbins and Cotran Figure 13.8 A Chronic Inflammation: Histology of pulmonary destruction that is visualized by alveoli being replaced by cuboidal epithelium (arrowheads) and tissue fibrosis (arrows). Courtesy of Robbin & Cotran (use only for educational purposes).



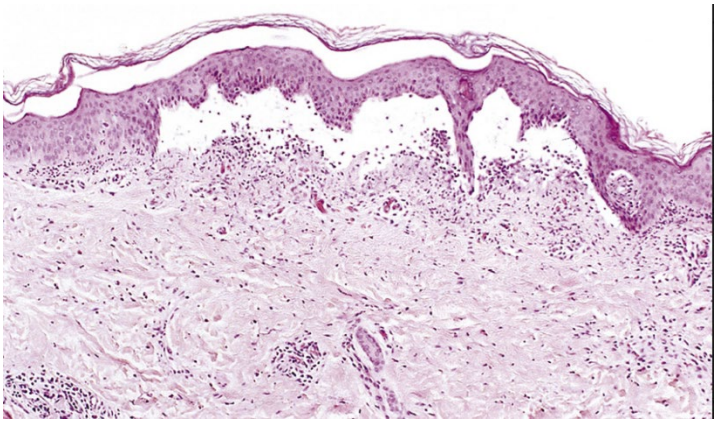
Robbins and Cotran Figure 3.18 B Acute Inflammation: Histology acute bronchopneumonia that is characterized by the saturation of neutrophils in alveolar spaces and blood vessels congestion. Courtesy of Robbin & Cotran (use only for educational purposes).

Cell Type

- Acute inflammation: Polymorphonuclear leukocyte (PMN)
- Chronic inflammation: Mononuclear cells (Macrophages, Lymphocytes, Plasma cells)

Morphological Types

- Acute: Exudative inflammation: excess fluid
  - Suppuration/Purulent – Bacterial - neutrophils
  - Fibrinous – pneumonia – fibrin
  - Serous – excess clear fluid – Heart, lung
  - Hemorrhagic – Blood vascular damage – anthrax
- Chronic inflammation: fibrosis with healing.
  - Granulomatous – clusters of epithelioid or giant cells (e.g. TB, fungus, foreign body)



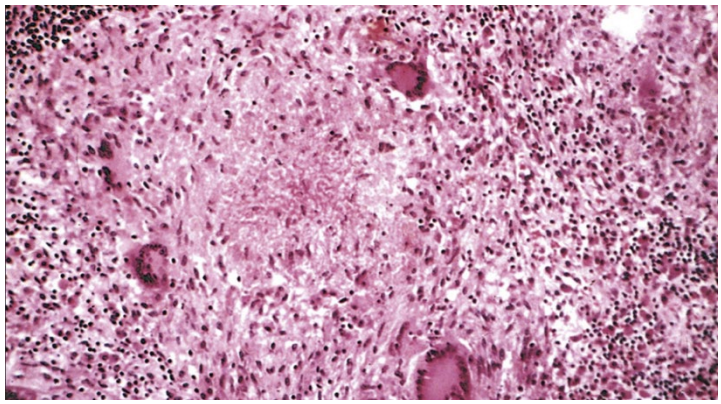
Robbins and Cotran Figure 3.13 Serous Inflammation: Histology of a skin blister within the epidermis that is characterized by tissue separation and effusion. Courtesy of Robbin & Cotran (use only for educational purposes).

Monocytes and Macrophages

- Monocytes leave the circulation then enter the tissue and differentiate into macrophages
- They are highly mobile and actively phagocytic
- Activate lymphocytes to mount an immune response

Neutrophils

- Important cells in acute inflammation
- They contain azurophilic granules
- These granules will give
- Myeloperoxidase
- Phospholipase A2
- Lysozyme
- Acid hydrolases
- Elastase
- Defensins
- Bactericidal permeability increasing protein (BPI)



Robbins and Cotran Figure 3.22 Granulomatous Inflammation: Pictured is the histology of tuberculous granulomas. This is characterized by multiple areas of central necrosis that are surrounded by Langhans-type giant cells. Courtesy of Robbin & Cotran (use only for educational purposes).

Eosinophilia

- Type of white blood cell produced in the bone marrow
- Eosinophils make up about 1-3% of a healthy person's white blood cells
- These cells, which are normally found in the bloodstream and gastrointestinal tract produce proteins that help the body fight against infections from parasitic organisms
- Eosinophilia is a condition that develops when there are too many eosinophils in the bloodstream or body tissues
- Causes of Eosinophilia.
    - Parasitic infections (ex: hookworm schistosomiasis)
    - Allergic conditions (ex: asthma and hay fever)
    - Immune disorders (like Churg-Strauss syndrome), Hodgkin's disease, or Addison's disease
    - Drug reactions

Basophils (Mast Cells)

- Characteristics and function
  - Binds IgE molecules
  - Contains electron-dense granules
- Primary inflammatory mediators
  - Histamine
  - Leukotrienes (LTC, LTD, LTE)
  - Platelet-activating factor
  - Eosinophils chemotactic factors
  - Cytokines (e.g. TNF-alpha, IL-4)

Endothelial Cells

- Characteristics and functions
  - Maintains vascular integrity
  - Regulates platelet aggregation
  - Regulates vascular contraction and relaxation
  - Mediates leukocyte recruitment in inflammation

- Primary inflammatory mediators
  - Von Willebrand factor
  - Nitric oxide
  - Endothelins
  - Prostanoids

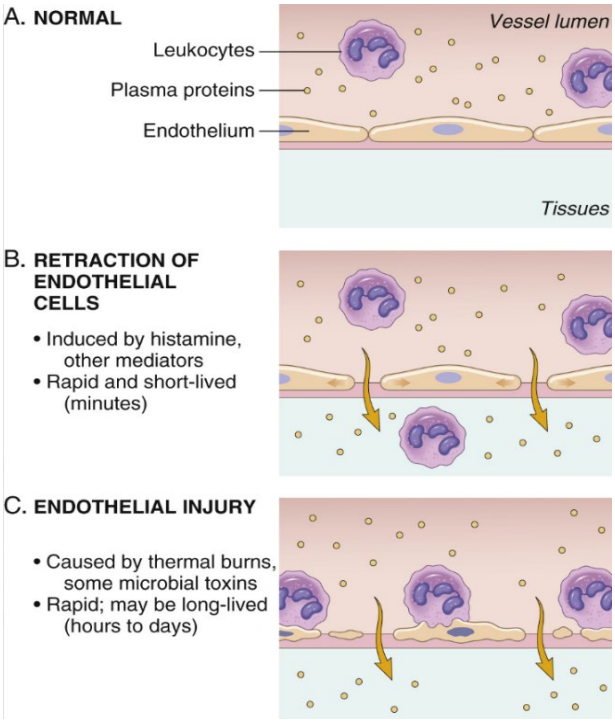
Platelets

- Upon damage to blood vessels endothelium platelets:
  - With the help of von Willebrand factor (VWF) adhere to collagen
  - Stimulated by thromboxane A2
  - Stick to exposed collagen fibers and form a platelet plug

The release of serotonin and ADP attract more platelets. The platelet plug is limited to the immediate area of injury by prostacyclin

Inflammatory Response to Injury

- Chemical mediators and cells are released from plasma following tissue injury
- Vasodilatation and vascular injury lead to leakage of fluid into tissues (edema)
- Platelets are activated to initiate clot formation
- Increase via histamine release
- Vascular endothelial cells contribute to clot formation, by retracting which increases vascular permeability. This bring circulating neutrophils via their adhesion molecules.



Robbins and Cotran Figure 3.3: Depiction of increased vascular permeability. Courtesy of Robbin & Cotran (use only for educational purposes).

- Microbes (red rods) initiate activation of the complement cascade, which, along with soluble mediators from macrophages, recruit neutrophils to the site of tissue injury
- Neutrophils eliminate microbes and remove damaged tissue so that repair can begin

Property	**Exudate**	**Transudate**
Contents	Cells, proteins and fluid	Fluid
Mechanism	Change in vascular permeability	Hydrodynamic changes
Specific gravity	>1.020	<1.020
Occurs in	Inflammation	Hypoproteinemia, venous or lymphatic obstruction

Acute Inflammatory Phase

- Acute phase proteins are produced early in inflammation especially by liver like Interleukin-6
- Responses are:
  - Fever
  - Increased sleep
  - Decreased appetite
  - Release of neutrophils in to circulation
  - Release of ACTH
  - Vascular changes leading to hypotension and shock
  - Endothelial response chemotaxis via cellular adhérence and cellular migration
  - Fibroblast effect
  - Leukocyte effects

Possible Outcomes of Acute Inflammation

- Complete resolution
  - Little tissue damage
  - Capable of regeneration
- Scarring (fibrosis)
  - In tissues unable to regenerate
  - Excessive fibrin deposition and development of fibrous tissue.
  - Abscess formation occurs with some bacterial or fungal infections. Progression to chronic inflammation

Inflammatory Mediators

- Lipids and Proteins (cytokines/chemokines)
- Cytokines are soluble protein mediators secreted by immune cells (mostly) that act on other cells to regulate their activity, many are called “interleukins” (IL-1, IL-2, etc.)
- Subfamily of cytokines primarily functions in directing migration of cells, these are called chemotactic cytokines or chemokines
- TNF (tumor necrosis factor): main function is to induce inflammation
- Mediators of pain are Bradykinin and Prostaglandin (E2)
- Mediators of Fever are Cytokines IL-l IL-6, TNF-a and Prostaglandins

Leukocyte Recruitment to Site of Inflammation (Cellular Response)

- Vascular response: the cellular response is regulated by chemical mediators
- Three major inflammatory mediators
    - chemotaxis
    - cellular adherence
    - cellular migration
- Leukocytes leave the vasculature routinely through the following 4 steps:
    - Margination, rolling, and adhesion
    - Diapedesis (transmigration across the endothelium)
    - Migration toward a chemotactic stimulus
    - Phagocytosis

Phagocytosis

- Recognition and Attachment of the injurious agents to be ingested by Leukocytes:
    - Leukocyte expresses mannose receptors on its surface to bind and ingest particles
    - Phagocytic cells move into the area of invasion by chemotaxis
    - These cells will attach to bacteria with the help of either antibodies or complement such as C3b
    - These Opsonin such as C3b coat the surface of microbes, allowing recognition by the neutrophil C3b receptor
    - This process is called opsonization (soluble immune recognition elements tag a particle for phagocytosis. These cells are now called phagosomes.

- Engulfment:
    - Extensions of the cytoplasm flow around the particle to be engulfed resulting in complete enclosure of the particle
    - Engulfed particles fuse with lysosomal membrane discharging its contents Killing mechanisms:
        - NO
        - Proteases
        - Anti-microbial peptides
    - Genetic defects in phagocyte oxidase components: chronic granulomatous disease

Defects of Leukocyte Function

- Defects of adhesion:
  - Leukocyte adhesion deficiency (LAD) is a rare autosomal recessive disorder
  - It is characterized by immunodeficiency resulting in recurrent infections
  - Leukocyte adhesion deficiency is divided into at least two subtypes, LAD-1 and LAD-2
  - Defects in adhesion are also seen in Diabetes mellitus or Corticosteroid use or in Acute alcohol intoxication
- Defects of chemo-taxis/phagocytosis:
  - Chediak-Higashi Syndrome is an inherited autosomal recessive genetic disorder that leads to defects in microtubule assembly leads to impaired locomotion and lysosomal degranulation
  - Characterized by partial albinism, abnormal granules in the white blood cells, and marked susceptibility to bacterial infections
- Deficiency of NADPH oxidase (nicotinamide adenine dinucleotide phosphate-oxidase) that generates superoxide. Therefore no oxygen-dependent killing mechanism causing condition like chronic granulomatous diseases

Abscess or Pus Formation

- Dead neutrophils and bacteria are referred to as Pus.
- Inflammatory exudate due to leukocidins which will kill the neutrophils
- Viral infections desquamated tissue, and dead cells may accumulate in the fluid filled vesicles
- Pus anywhere in the body must be drained

Anti-inflammatory Therapies

- NSAIDs: inhibitors of inflammation and fever (block prostaglandin synthesis)
- Glucocorticoids are also potent anti-inflammatory drugs; natural systemic anti-inflammatory mechanism
- Agents that block TNF are effective in treating rheumatoid arthritis, Chron's disease, etc.
- Agents that block IL-1 are less effective for these diseases but are useful for some genetic inflammatory diseases

Summary: Bacterial vs. Viral Infections

- Presence of pus- most likely bacterial infection
- Constant fever - Most likely bacterial infection
- Biphasic illness - Likely to be viral
- Malaise and fatigue disproportional to other symptoms Most likely to be viral
- Lab:
    - In Bacterial- mostly Neutrophils are increased
    - In Viral or chronic infections- mostly Lymphocytes or monocytes are increased
    - In Parasitic - Eosinophils are increased

Chronic Inflammation

- Time course: greater than 6 months.
- Chronic inflammation arises in various organs in 1 of 3 ways
    - Following acute inflammation
    - After repeated bouts of acute inflammation (pneumonia)
    - Without prior acute inflammation (Tb, viruses, silica, asbestos, rheumatoid arthritis

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- Cells involved are:
    - Lymphocyte, macrophage, plasma cell (mononuclear cell)
    - Continuous recruitment and activation of Macrophages
    - Tissue destruction by inflammatory cells
    - Attempts at repair with fibrosis and angiogenesis (new vessel formation)

Ethology of Chronic Inflammation

- Persistent infection
    - T.B. Syphilis, viruses, fungi, parasites
    - These organisms have low toxicity & evoke delayed hypersensitivity (Immune reaction – specific-granulomatous reaction)
- Prolonged exposure to toxic agents (Exogenous or Endogenous)
    - Silica, Atherosclerosis, asbestosis.
- Autoimmunity
    - RA, Lupus, Hashimoto
    - Cell Mediated (Type-IV hypersensitivity initiated by antigen activated T Lymphocytes)
    - Delayed hypersensitivity reaction mediated by CD4 T-helper 1 cells
    - Direct Cell cytotoxicity mediated by CD8 T-helper 2 cells

Chronic Inflammation Mediators

- Lymphocytes- Gamma Interferon -activates macrophages
- Macrophage derived-
    - Enzymes: proteases, elastase, lipase
    - Plasma proteins- Complement components
    - Oxygen radicals
    - Eicosanoids- prostaglandins
    - Cytokines like IL1 and TNF
    - Growth factors - Fibroblast Growth factor (FGF), angiogenesis factor

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Chronic Inflammation Events

- Continuous recruitment and activation of Macrophages
- Change of macrophages to the epithelioid and giant cells
- It will lead to granuloma formation
- Involvement of Lymphocytes, mast cells or eosinophils
- Fibroblastic response- fibrosis

Chronic Granulomatous Inflammation

- Activation of T cell-activated macrophages which engulf and surround indigestible foreign bodies (such as mycobacteria, H. capsulatum, silica)
- Resemble squamous cells, therefore called epithelioid granulomas
- TB is characteristic example of granulomatous inflammation.
- It is also seen in sarcoidosis, leprosy, syphilis, cat scratch- disease, lymphogranuloma inguinale, brucellosis, berylliosis or autoimmune disease (Crohn disease – IBD)

Clinical Patterns of Acute and Chronic Inflammation

- Serous
    - Watery, protein-poor effusion (e.g., blister)
- Fibrinous
    - Fibrin accumulation
- Suppurative
    - Presence of pus (pyogenic staph)
    - Often walled-off if persistent
    - Ulceration
- Hemorrhagic – blood vascular damage – anthrax

Clinical Patterns of Inflammation

- Purulent:
    - Large amounts of pus or purulent exudates
    - Consisting of neutrophils, necrotic cells, edema.
    - Abscesses may form if deep enough.
    - Examples are Acute Appendicitis inflammation of brain and myocardium

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- Ulceration
    - Surface excavation of surface of an organ or tissue due to sloughing of dead tissue.
    - Seen in mucosa of mouth, stomach, intestines, genitourinary tract, subcutaneous tissue of lower extremity

Outcome of Chronic Inflammation

- Resolution/regeneration/restitution of normal structure
- Repair/organization/healing by connective tissue/fibrosis/scarring
- It can continue indefinitely--some disease processes are capable of continuing indefinitely such as rheumatoid arthritis

Summary of Inflammatory Process

- Vasodilatation and Exudation of fluid from blood vessels
- Attraction of leukocytes to the site of injury
- Activation of chemical mediators
- Proteolytic digestion of extra cellular debris
- Restoration of injured tissues

Summary of Main Chemical Mediators of Inflammation

- Histamine & serotonin
- Bradykinin
- Complement fractions C3a, C5a
- Prostaglandins (Fever)
- Mediators of Fever: Cytokines IL-l IL-6, TNF-alpha and Prostaglandins
- Mediators of Pain: Bradykinin and Prostaglandin (E2)
- Leukotrienes- C4, D4 & E4
- Oxygen metabolites
- Nitric oxide (released by Macrophages and endothelial cells)

- Mediators vasodilate and permeabilize the blood vessels, which results in the net distribution of blood plasma from the vessel into the tissue space leading to increased collection of fluid into the tissue causes swelling (edema)
- Chemo attractants/Chemotactic factors
- C5a
- Leukotriene B4
- Platelet activating factor
- Interleukin 1(IL 1) and Tumor necrosis factor (TNF)
- Chemokines

- The complement system, when activated, creates a cascade of chemical reactions that promotes opsonization, chemotaxis, agglutination, and produces the MAC
- The kinin system generates proteins capable of sustaining vasodilation and other physical inflammatory effects
- The coagulation system or clotting cascade which forms a protective protein mesh over sites of injury
- The fibrinolysis system which acts in opposition to the coagulation system to counterbalance clotting and generate several other inflammatory mediators

Clinical Markers

- Plasma levels of ICAM-1 and E-selectin may serve as molecular markers for atherosclerosis and the development of Chronic heart diseases.
- Higher levels of E-selectin and ICAM-(Inter-cellular adhesion molecule 1 also known as CD54) are observed in patients with chronic heart diseases
- Absence of CR3, Macrophage-1 antigen, an immunological cell surface receptor for a complement component results in reduced binding and ingestion of Mycobacterium tuberculosis (in mice)

Case Questions: Part II

1. Which of the following is the most characteristic of inflammation?
    A. Tissue destruction
    B. Increase vascular permeability
    C. Connective tissue replacement
    D. All of the above

2. By definition, opsonization is which of the following?
    A. Membrane attack complex lysing a bacterium by making a hole in its membrane
    B. When complement causes inflammation to occur
    C. When the nine complement factors cascade in order
    D. Coating of a bacterium with antibody to make it more susceptible to phagocytosis

3. Mrs. Brown presents to your clinic. He burned the tattoo off with his lighter. Clinical signs and symptoms of the lesion on his thumb include which of the following?
    A. Rubor (redness)
    B. Tumor (swelling)
    C. Color (heat)
    D. Dolor (pain)
    E. All of the above

4. Continuing from pervious question: a week later, the patient presents to your clinic. The wound looks worse in that it is much more erythematous and more painful to touch. Upon culture, numerous pathogenic Staphylococcus aureus organisms grow. The most important system for the killing of bacteria processed by X's PMNs (assuming they are normal) is which of the following:
    A. Oxygen dependent, myeloperoxidase independent system
    B. Oxygen dependent, myeloperoxidase dependent system

5. Continuing from pervious question: Several days later he shows up again. This time the lesion is bulging and quite warm to touch. You suspect an abscess has formed, foul-smelling purulent debris is exuded. You take some of the debris, smear it out on a slide, and stain it. You expect to see mostly which of the following:
    A. Lymphocytes, plasma cells, and macrophages.
    B. Proliferation of fibroblasts and small blood vessels
    C. PMNs and necrotic debris
    D. Collections of histiocytes and giant cells

6. Clinical study is performed of patients with pharyngeal infections. The most typical clinical course averages 03 days from the time of onset until the patient sees the physician. Most of these patients experienced fever and chills. On physical examination, the most common finding is a pharyngeal purulent exudate. Which of the following types of inflammation did these patients most likely have?
    A. Granulomatous inflammation
    B. Acute inflammation
    C. Abscess formation
    D. Chronic inflammation

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Environmental and Nutritional Pathology

Personal Exposures

Tobacco Use

- Most common exogenous cause of lung cancer (90%) most smoking
- Includes: Cigarettes, Cigars, Pipes, & Snuff, Chewing.
- One of the largest cause of mortality and morbidity.
- Most preventable cause of death in USA.

Cigarette Smoking:

- 440,000 premature deaths/yr. related to smoking (Lung Cancers; Cerebrovascular disease, COPD) in USA
- Synergistic with other environmental exposures (asbestos)
- Mortality from lung cancer, almost all of which is related to cigarette smoking, exceeds that from cancers of the breast and prostate, which are among the most common cancers in the United States
- Contains numerous carcinogenic chemicals:
    - Initiators and promoters (Carcinogenesis in Neoplasms)
    - Tar
    - Cadmium
    - Lead
    - hydrogen cyanide
    - Arsenic
    - Nitrogen oxides
    - Benzopyrene
    - Carbon monoxide
    - Vinyl chloride
    - Acetaldehyde
    - Polycyclic aromatic hydrocarbons (PAHs)

- Person who smokes two packs of cigarettes a day at the age of 30 years will live an average of 8 years less than a non-smoker
- Individuals who have smoked for 1 year have a two-fold greater probability of dying than a nonsmoker
- Those who have smoked for more than 15 years have more than a three-fold greater probability of dying
- Smoking precipitates initial myocardial infarction, increases the risk for second heart attacks

Pathological Effects of Smoking

- Cancers of the lip, tongue and buccal mucosa.
- Cancer of the larynx: white male smokers have from 6 to 13 times greater a death rate from laryngeal cancer as non-smokers
- Cancer of the esophagus
- Cancer of the bladder is twice as frequent a cause of death in cigarette smokers as in non-smokers
- Carcinoma of the kidney is increased 50% to 100% among smokers
- Cancer of the pancreas has shown a steady increase in incidence
- Cancer of the uterine cervix is significantly increased in women smokers
- Smokers are at higher risk for diseases like chronic bronchitis and emphysema
- Due to smoking, there is:
    - ↓ Ciliary clearance to 3 mm/min (normal= 10 mm/min)
    - Surfactant (Alveoli are lined by) is denatured
    - Alveolus hypo ventilate (Retention of more CO2) and collapse (Atelectasis)
    - ↑ Mucus secretion gland hypertrophies → more Mucus, narrowed Bronchi airways
    - Cause of Chronic bronchitis (COPD)

- Fetal Tobacco Syndrome:
    - 20-40% incidence of low birth weight of newborns
    - Perinatal mortality shows → 40% increase among smokers
    - Increased incidence of Placenta (Placenta in front of Fetus in Utero), with Uterine bleeding, Premature rupture of membranes
    - Impairment of Physical, Cognitive, Emotional development of children at older ages
- Smoking also impairs female reproductive functions
- It also exacerbates osteoporosis in women
- Peptic ulcer disease is 70% more common in male cigarette smokers
- Thyroid diseases are linked to cigarette smoking

Alcohol (Ethanol)

- 15-20 million alcoholics in US- responsible for 100,000 deaths/yr.
- Toxic effects include:
    - Liver- Alcoholic steatosis (Fatty- change)
    - Increased Triglycerides
    - Glutathione depletion
    - Mitochondrial injury, cytokine release is directly hepatotoxic
    - Hepatitis, Cirrhosis with Portal Hypertension
    - Heart: Hypertension, Cardiomyopathy caused by direct injury of ethanol
    - Alcoholic cardiomyopathy leads to low-output congestive heart failure
    - CNS - Thiamine deficiency which causes degeneration of nerves, atrophy of cerebellum (Wernicke -Korsakoff syndrome) with Ataxia, disturbed cognition, and ophthalmoplegia
    - Peripheral Neuropathy
    - Gastritis, pancreatitis
    - Muscles: Rhabdomyolysis

    - Fetal Alcohol Syndrome-1 drink/day during pregnancy has been linked with FAS- microcephaly, facial disfiguration
    - Most commonly preventable cause of mental retardation

Health Effects of Particulate Matter (PM) Air Pollution

- Respiratory: Shortness of breath, coughing, chest pain, fatigue
    - Increase in asthma attacks
    - COPD exacerbations
    - decreased lung function, bronchitis (Chronic), and more allergic sensitization
    - Allergic-like irritation of eyes and throat
- Cardiovascular:
    - Increased risk of heart attack
    - Rhythm disturbances (Arrhythmia)
    - Vascular changes
    - For every 10 points increase in PM 2.5, carotid arteries were 4% narrower
    - For women over 60, every 10 points increase led to more than 15% narrowing
    - The above data suggest increased risk for stroke with increased PM2.5 exposure
- Cancer—increased risk of lung cancer

Indoor Air Pollution

- Carbon monoxide (CO)
    - Nonirritating, colorless, tasteless, odorless gas
    - Product of imperfect oxidation (wood smoke)
    - Affinity of CO to Hb is 200x higher than that of O_2 – carboxy hemoglobin is formed, leading to systemic hypoxia
- Toxic effects on humans:
    - Low-level: cardiovascular and neurobehavioral
    - High-level: headaches/nausea/fatigue to possible death.
    - Oxygen deficient people esp. vulnerable (anemia, chronic heart or lung disease, high altitude residents, smokers)
    - Concern in homes especially - Install CO monitor
    - >70 ppm lead to flu-like symptoms (w/out fever)
    - 150-200 ppm lead to disorientation, drowsiness, and vomiting
    - >300 ppm lead to unconsciousness and brain damage and death
    - 500 Americans die/year from unintentional CO poisoning

- Treatment: fresh air and oxygen therapy

Asbestos Fibers

- Homes and public buildings built prior to 1970 have asbestos
- Used mainly for insulation and fire protection
- Not a problem until exposed during construction or deterioration
- Associated with mesothelioma (Pleural malignancy) and lung cancer
- Mesothelioma is a rare Cancer arising in lung pleura related to exposure to asbestos- 50% have history of asbestos exposure
- Latent period of 25-40 years.
- Combination of cigarette smoking and asbestos- about 90% chance for some form of lung ca.
- Metastasis is rare

Lead

- Lead Paint (prior to 1978).
- Dust, Soil
- Water
- Industry
- Hobbies
- In Batteries, alloys, red paint (Exterior), ammunition
- By inhalation, G.I. tract

Burns

- Any burn exceeding 50% of total body surface, whether superficial or deep is potentially fatal
- The rule of nines assesses the percentage of burn and is used to help guide treatment decisions including fluid resuscitation
- First-degree burns, e.g., a mild sunburn:
    - Vasodilation (Increase vascular permeability) leading to edema and pain
- Second-degree burns.
    - necrosis of the epithelium
    - blisters (separation of epidermis from dermis)
- Third-degree burns.
    - necrosis of epidermis and dermis, and the tissues under the skin
    - no pain
    - Complications:
        - excessive fluid loss that leads to hypovolemic shock

Hyperthermia

- Abnormal elevation of body temperature above 104 F
- Exertional heat stroke:
  - Hot/dry skin and cessation of sweating
  - Rhabdomyolysis
  - Myoglobinemia and Myoglobinuria
  - Acute tubular necrosis (30% of cases)
  - Disseminated intravascular coagulation (DIC)
- Classic heat stroke:
  - At risk persons: very young or elderly people, chronically ill patients, alcoholics, obese
  - Associated with febrile illnesses and hot humid weather
  - Characteristics:
    - Hot/dry skin; respiratory alkalosis
    - blood moves to the skin → hypotension → dec. perfusion of CNS → fainting → coma

Hypothermia

- Decrease in body temperature below 95 F
- Generalized hypothermia:
  - Acute immersion in water (39.2-50 F):
    - Dec perfusion of brain-mental confusion
    - After 30 min.:
      - Body temp drops below 95 F- decrease respiratory rate, heart rate, and BP
      - cardiac arrhythmias leading to sudden death
      - temp. < 82.4 F results in coma
- Focal thermal alterations
  - Local reduction in body temperature - local vasoconstriction
  - If freezing occurs slowly - crystallization of water (frostbite)
    - vasoconstriction - Inc. permeability: edema, blisters, and inflammation
    - Endothelial cell injury, thrombosis, and gangrene

Nutritional Pathology

Malnutrition

- CDC defines micronutrients as essential vitamins and minerals needed in small amounts for various physiological functions, but cannot be made in the body
- Nutrition deficiency: Infectious diseases including diarrhea often coexist with micronutrient deficiencies which contribute to one third of deaths in children worldwide
- Marasmus: "wasting" (lack of energy-providing foods)
- Kwashiorkor: Protein malnutrition → hypo - albuminemia, pitting edema, and enlarged liver

Affluent Malnutrition

- "In an affluent, industrialized, fast-paced society, the purpose of eating is not for survival
- malnutrition includes:
    - Highly processed foods are deficient in vitamins and minerals
    - High in synthetic food compounds, refined sugars, and saturated fat
    - Deficient in fiber
    - High in calories

Vitamin A

- Maintains the health and well-being of "the epithelial tissues of the body"
- These are generally the tissues that line the openings, Skin, and Mucous membranes
- All glands and their duct systems come under the protection of vitamin A

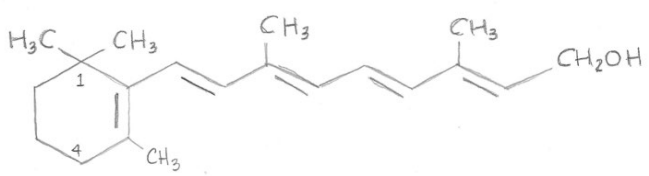

Figure 1: Hand drawn structural formula for All-trans retinol which is found within plasma as the precursor to Vitamin A.

- Deficiency:
    - Cause of blindness in children worldwide night blindness, color blindness and dry eyes (Xerophthalmia) and Keratomalacia
    - Epithelial cell metaplasia (of columnar to squamous) and cancer
    - Dry skin (keratinization and Hyperkeratosis)
    - Infections of Respiratory and urinary tracts
    - Kidney stones
    - Immune deficiency
    - Toxic effects due to hypervitaminosis

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Vitamin D

- Vitamin D maintains normal serum level of calcium and phosphates
- Prevent bone disease
- Deficiency:
  - Tetany
  - Rickets = malformation of bones due to decreased deposition of calcium phosphate
  - Osteomalacia (in adults) = skeletal demineralization in spine, pelvis, and lower extremities
  - Restlessness and poor sleep

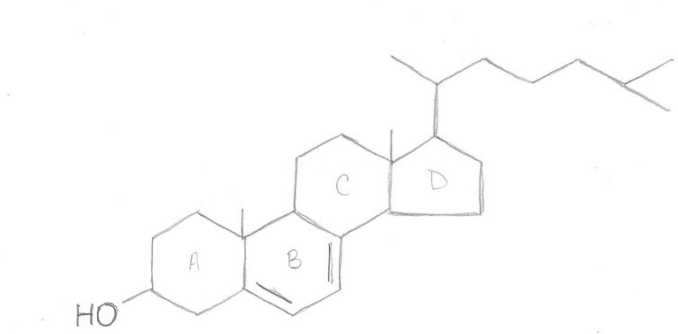

Figure 2: Hand drawn molecular schematic for 7-dehydrocholesterol which is located within the skin

- Causes of deficiency
  - Altitude and season – both influence the amount of UV light reaching the skin
  - The ageing process – thinning of the skin reduces the efficiency of this synthetic process
  - Skin pigmentation: the presence in the skin of darker pigments interferes with UV light reaching the appropriate layer of the skin.
  - Clothing – virtually complete covering of the skin for medical, social, cultural, or religious reasons leaves insufficient skin exposed to sunlight
  - Sunscreen use – widespread and liberal use of sun-blockers reduces skin damage by the sun but also deleteriously affects synthesis of vitamin D

Vitamin E

- Main fat-soluble anti-oxidant
- prevents lipid peroxidation - free radicals steal electrons from cell membrane and cause damage
- Deficiency:
  - Premature infants- Hemolytic anemia caused by excessive free radicals killing off RBC's
  - Adults- disruption of myelin
  - Oxidative damage
  - Impaired neuro exam
  - Lipid malabsorption

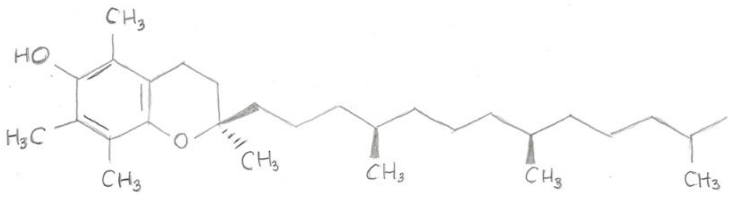

Figure 3: Hand drawn structural formula of Vitamin E which belongs to an 8 membered family of compounds known as tocopherols and tocotrienols.

Vitamin K

- Plants synthesize phylloquinone which is also known as vitamin K1
- Bacteria synthesize a range of vitamin K forms designated
- Vitamin K Deficiency
- Infancy – "Hemorrhagic disease of the Newborn"
    - Due to poor transport across the placenta and sterile gut
    - Newborns are given a Vitamin K shot immediately after birth to prevent this
- Easy bleeding in kids – nose bleeds
- Adults- decreased bone density

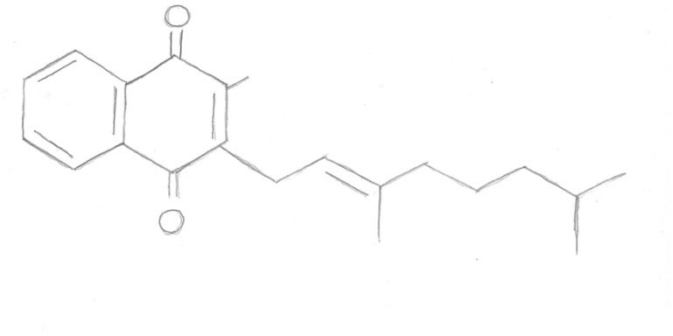

Figure 4: Hand drawn structural formula for Vitamin K1 which known as Phylloquinone. This molecule was discovered by H. Dam & E. Doisy in 1943.

Vitamin B1 (Thiamine)

- Maintains normal nerve conduction
- Deficiency seen in:
    - South Asians
    - Chronic alcoholics
    - Chronic illness
    - Pregnancy (heavy vomiting)
- Major targets of deficiency
    - Peripheral nerves
    - Heart
    - Brain
- Beriberi= "I can't, I can't" patients are unable to do anything
- Dry beriberi, polyneuropathy, and muscle wasting are caused by inactivity
- Wet beriberi: Congestive Heart Failure, edema starting in feet progressing upward caused by severe physical exertion and high carbohydrate intake
- Neuro symptoms caused by greatly decreased utilization of carbs for energy. When B1 is deficient, the body uses ketones instead which damages neurons in brain.

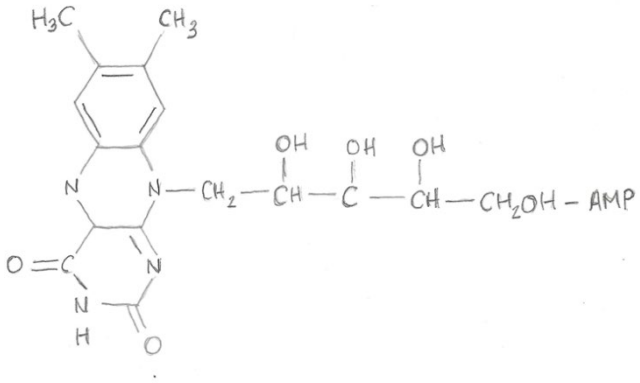

Figure 5: Hand drawn structural formula for Vitamin B1 "Thiamine". This molecule was isolated from rice bran in 1929 by Christiaan Eijkman who deemed it a vital amine, which gave rise to the term vitamin that is used today.

- Weakness and palpitations caused by decrease in conversion of pyruvate to acetyl CoA in Krebs cycle
- Wernicke-Korsakoff Syndrome (mental confusion, anorexia, muscle weakness, palpitations) consists of two separate syndromes:
    - A. short–lived and severe condition called Wernicke's encephalopathy
    - B. and a long–lasting and debilitating condition known as Korsakoff's psychosis

Vitamin B2 (Riboflavin)
Riboflavin Deficiency

- Deficiency: In developing countries, alcoholics, and with deficiency of other vitamins
- Cheilosis: Begins with pallor at the angles of mouth and then with cracks & fissures and possibility of infections
- Glossitis: Atrophy of mucus membrane with red-blue coloration and cyanotic
- Eyes: Keratitis- Early Superficial layers of Cornea with increased capillaries, then inflammation, corneal ulcerations, and opacities
- Dermatitis and Bone marrow hypoplasia (Esp. RBC)

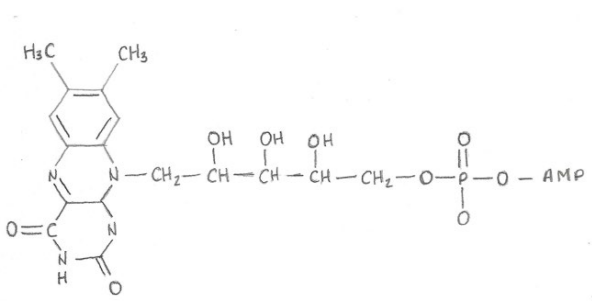

Figure 6: Hand drawn schematic of Flavin mononucleotide (FMN) bound to AMP. The molecule Riboflavin was isolated in 1938 by Richard Kuhn and is a constituent of coenzyme FAD.

Vitamin B3 (Niacin)

- For metabolism of proteins & carbs (NADH)
- Where: animal sources, esp. meats
- Deficiency:
    - Pellagra (rough skin) = 3D's
    - Dermatitis (redness, thickening, and roughness)
    - Dementia (degeneration of neurons, brain, and spinal cord tracts)
    - Diarrhea (atrophy of mucus membrane)
- Overdose:
    - Acanthosis Nigricans:
        - Characterized by skin thickening and hyperpigmentation of the skin in flexural areas.
            - Posterior neck, groin, umbilicus.

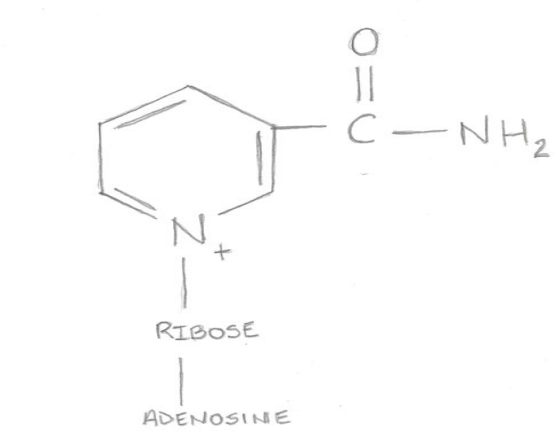

Figure 6: Hand drawn structural formula of Nicotinamide bound to sugar bases which yield NAD.

Vitamin B6 (Pyridoxine) Deficiency

- Deficiency is seen in:
  - Long term use of drugs (ex: Isoniazid or estrogens)
  - Alcoholics
  - Pregnancy
- Associated with high levels of Homocysteine (risk factor for atherosclerosis)
- Sign and symptoms:
  - Dermatitis
  - Cheilosis
  - Glossitis
  - PN
  - Convulsions

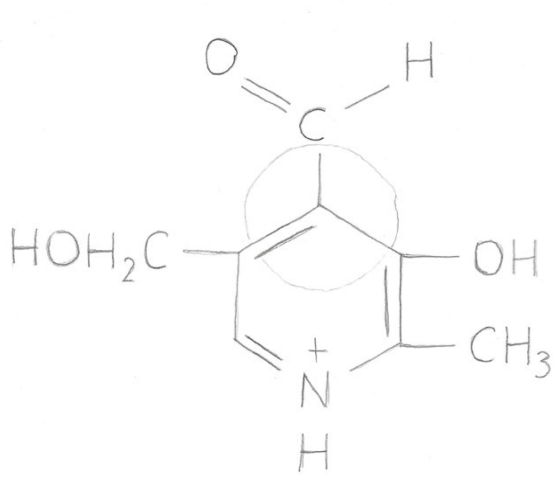

Figure 7: Hand drawn structural formula for Pyridoxal (PL). The functional group designated by the circle is classified as an Aldehyde. This molecule also exists in alcohol (PN) and amino (PM) form.

Vitamin C

- Vitamin C which is required for the synthesis of collagen in humans
- Protects against:
  - Immune system deficiencies
  - Cardiovascular disease
  - Prenatal health problems
  - Eye disease
  - Skin wrinkling
- Extreme deficiency of vitamin C will lead to scurvy
  - More common in pirates
  - Infants: scurvy is sometimes referred to as Barlow's disease
  - Scurvy is a disease that affects the blood vessels, skin, and the body's healing process, resulting in anemia, hemorrhaging of the skin, and gum disease (gingivitis)
- Other symptoms are:
- fatigue, weakness, muscle cramps, aching joints
- Decreased immune function
- Decreased glucose tolerance
- Adrenal fatigue
- While a cup of orange juice or a half-cup of red pepper would be enough to meet your RDA for Vitamin C, here are all the foods and beverages you'd need to consume to reach 500 milligrams (mg):
- Orange juice, 1 cup: 97 mg, Broccoli, cooked, 1 cup: 74 mg, Red cabbage, 1/2 cup: 40 mg, Green pepper, 1/2 cup, 60 mg, Kiwi, 1 medium: 70 mg, Tomato juice, 1 cup: 45 mg

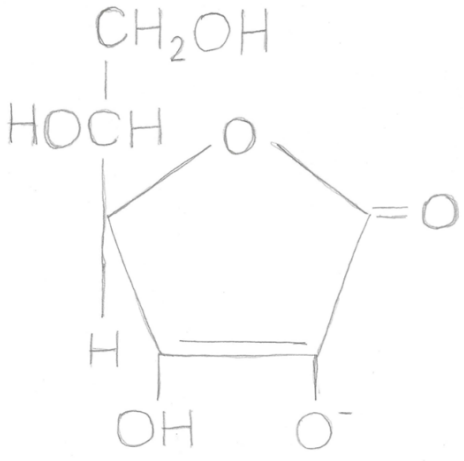

Figure 9: Hand drawn structural formula for Vitamin C "L-ascorbate". In 1928, A.S. Gyorgyi and W. Haworth isolated a substance from adrenal glands & oranges. This six-carbon molecule was named "ascorbic acid".

B12 Cobalamin and Folate Deficiency

- Deficiency: results in Megaloblastic (Macrocytic Anemia) due to reduced nuclear activity of RBC, WBC, and pernicious anemia due to lack of intrinsic factor to absorb B12 due to Gastric Atrophy
    - Progressive peripheral neuropathy
    - Fatigue
    - Depression
    - Macrocytes
    - Giant platelets
    - Subacute combined degeneration of the spinal cord and peripheral nerves
    - CNS symptoms are irreversible
    - Abnormal sensations (tingling and numbness)
    - Weakness of the legs, arms, or other areas
    - Unsteady gait and loss of balance
    - Beefy tongue and Cord

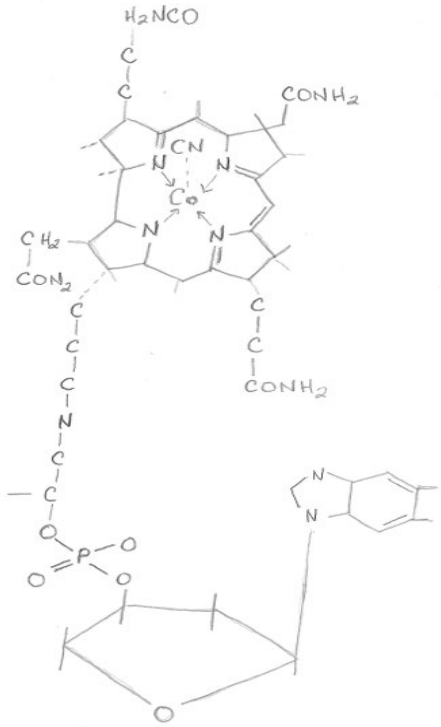

Figure 8: Hand drawn structural formula for Vitamin B12 "Cobalamin".

Subacute Combined Degeneration

- Blood tests including:
    - Complete blood count (CBC)
    - Vitamin B12 blood level
    - Methylmalonic acid blood level is used to diagnose anemia or vitamin B12 deficiency
- Optic neuritis: eye exam may show damage to the optic nerve
- Untreated: the disorder results in progressive and irreversible damage to the nervous system
- Immediate treatment: received within a few weeks complete recovery usually occurs
- Delayed treatment: longer than 1 or 2 months then recovery isn't as complete

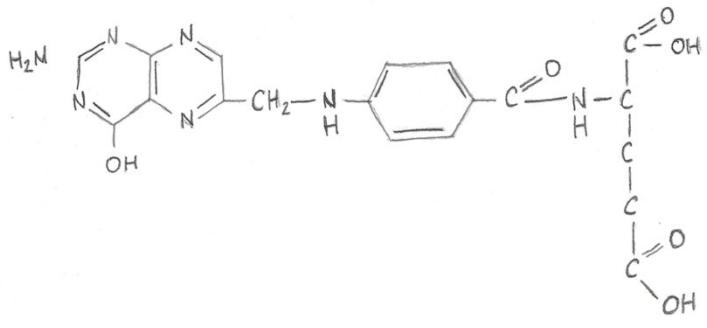

Figure 9: Hand drawn structural of Folate. This molecule was isolated in the 1930's and is also known as vitamin B9.

Hyper-Vitaminosis

- Vitamin overdose, or hyper- vitaminosis, is a phenomenon caused by excessively high levels of vitamin(s) that causes toxic effect in the body
- Water-soluble hyper-vitaminosis includes vitamins C and B-complex groups
    - Overdose from these vitamins are generally not very toxic as the body easily removes them successfully by dilution and elimination through urine
    - Certain water-soluble vitamins such as vitamin C will have laxative effect upon overdose, and can cause some gastrointestinal problems
- Fat-soluble hyper-vitaminosis includes vitamins A, D, E, and K
    - More likely to be toxic, as it cannot be eliminated easily like the water-soluble vitamins
- Vitamin A overdose generally causes visual and neurological problems
- Vitamin D overdose tends to cause imbalance of calcium levels and heart conditions
- Vitamin E poisoning induces GI problems such as nausea and diarrhea

Neoplasia

- mass of tissue that grows excessively and keeps growing even if you remove the stimulus that started it off
- Benign tumor = innocent acting tumor
- Malignant tumor = evil-acting tumor
- Derived from cells that normally maintain a proliferative capacity
- Mature neurons and cardiac myocytes do not give rise to tumors

Benign Tumors ("-oma")

- Small
- Slow-growing
- Non-invasive
- Well-differentiated
- Stay localized
- Can lead to serious problems such as:
    - The erosion of a benign tumor of smooth muscle can lead to serious hemorrhage.
    - Benign intracranial tumor of the meninges (meningioma) can kill by exerting pressure on the brain
- Tend to be histologically and cytologically similar to their tissues of origin

- Adenoma – benign tumor arising from glandular cells
- Leiomyoma – benign tumor arising from smooth muscle cells
- Chondroma – benign tumor arising from chondrocytes
- Enchondroma – chondroma located entirely within the bone
- Papilloma – has finger-like projections
- Polyp – projects upward, forming a lump
- Cystadenoma – has hollow spaces (cysts in ovaries) inside
- Benign tumors that arise from germ cells and contain derivatives of different germ layers are labeled teratoma
- These tumors occur principally in the gonads and occasionally in the mediastinum and may contain a variety of structures:
    - Skin
    - Neurons and glial cells
    - Thyroid
    - Intestinal epithelium
    - Cartilage

Malignant Tumors

- Large
- Fast-growing
- Invasive
- Poorly-differentiated
- Metastasize
- Certain types of malignant tumors are so indolent that they pose no threat to life
- Carcinomas – arise in epithelial tissue.

- Histological appearance classification:
    - Adenocarcinoma (glandular pattern)- malignant tumor of glandular cells
    - Squamous cell carcinoma – malignant tumor of squamous cells
- Sarcomas – arise in mesenchymal tissue
    - Chondrosarcoma – malignant tumor of chondrocytes
    - Angiosarcoma – malignant tumor of blood vessels
    - Rhabdomyosarcoma – malignant tumor of skeletal muscle cells.

Tumors

- Papillary describes a frond-like structures
- Medullary signifies a soft cellular tumor with little connective tissue stroma
- Whereas scirrhous or implies a dense fibrous stroma
- Colloid carcinomas secrete abundant mucus in which islands of tumor cells float

Colorectal Polyps

- Mostly benign tumors are capsulated
- Un-capsulated such as:
    - Papilloma's
    - Polyps of the visceral organs
    - Hepatic adenomas
    - Endocrine adenomas
    - Hemangiomas
- Colorectal polyps are often classified by their behavior (i.e. benign vs. malignant)
- They can be small or large and flat (sessile) or mushroom shaped and attached to a stalk (pedunculated)
- The larger a polyp = the greater the likelihood of cancer

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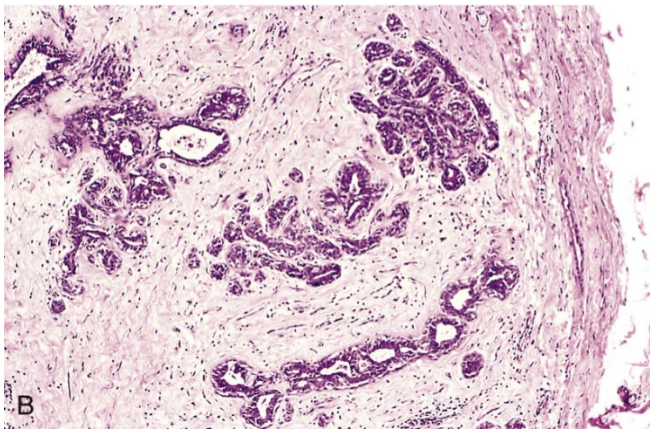
Histological Features that Favor Malignancy

- Cytologic evidence of anaplasia includes:
  - Variation in the size and shape of cells and cell nuclei (pleomorphism)
  - Enlarged and hyper chromatic nuclei with coarsely clumped chromatin and prominent nucleoli
  - Increase nuclear cytoplasmic ratio
  - Atypical mitoses
  - Bizarre cells including tumor giant cells
- Mitotic activity:
  - Abundant mitoses are characteristic of many malignant tumors
- Growth pattern:
  - Malignant neoplasms often exhibit a disorganized and random growth pattern, which may be expressed as uniform sheets of cells, arrangements around blood vessels, papillary structures, whorls or rosettes appearance
- Invasion:
  - Malignancy is proved by the demonstration of invasion, particularly of blood vessels and lymphatic
- Metastases:
  - The presence of metastases identifies a tumor as malignant

Mixed Tumors

- Mixed tumors show divergent differentiation
- Examples:
  - Pleomorphic adenoma – glands + fibromyxoid stroma
  - Fibroadenoma – glands + fibrous tissue
- Not to be confused with teratomas
- Teratoma = tumor arising from more than one germ
- layer (ecto, endo, and meso) variety of parenchymal cell types all grouped together (skin, muscle, fat, tooth)
- Most commonly seen in ovaries



Robbins and Cotran Figure 7.11B Fibroadenoma of Breast: Histology presentation of a fibrous capsule (upper right) that separates the tumor from surrounding tissue. Courtesy of Robbin & Cotran (use only for educational purposes).

Terminology

- Malignant tumors that sound benign
  - Lymphoma
  - Mesothelioma
  - Melanoma
  - Seminoma
- Non-tumors that sound like tumors
  - Hamartoma – mass of disorganized indigenous tissue
- Other Names
  - Nevus
  - Leukemia
  - Hydatidiform mole
  - A hydatidiform mole is a pregnancy/conceptus in which the placenta contains grapelike vesicles (small sacs)

Lymphoma

- Hodgkin and non-Hodgkin lymphomas
- Burkitt Lymphoma
- The cellular debris is cleared by macrophages, whose scattered appearance imparts a “starry sky” pattern

Neoplasia II

Tumor Characteristics

Dysplasia and Anaplasia

- Dysplasia= disorderly changes in non-neoplastic epithelial cells
- Disordered (atypical) growth seen only in epithelial cancers
- Hyperchromatic = large nuclei
- Does not necessarily progress to cancer

Differentiation

- Anaplasia (lack of differentiation) = undifferentiated- hallmark of malignancy
- Pleomorphism- variation is size and shape of cancer cells
- Abnormal nuclear morphology- dark staining, abundant DNA
- Hyperchromatic = large nuclei
- Bizarre nuclear shapes, distinct nucleoli
- Large numbers of mitoses
- Disturbed orientation of cells
- Presence of tumor giant cells

Carcinoma-in-situ

- Dysplastic changes involve the entire thickness of epithelium
- Lesion remains confined to normal tissue
- Basement membrane is intact
- No tumor cells in subepithelial stroma

Rate of Growth

- Malignant tumors grow faster than benign ones
- Poorly-differentiated tumors grow faster than well-differentiated ones
- Age of tumor:
    - High GF = early on (subclinical)
    - Low GF = later (clinically detectable) =
- Type of tumor:
    - High GF = Leukemia's, lymphomas, small-cell lung cancer
    - Low GF = Breast and colon cancer
- Important for treatment
    - High GF tumor = treat with chemotherapy/radiation
    - Low GF tumor = treat by de-bulking
- Growth is dependent on:
    - Blood supply
    - Hormonal factors
    - Emergence of aggressive sub-clones

Local Invasion

- Benign tumors
    - localized
    - Most can't invade or metastasize
    - Usually encapsulated
- Malignant tumors
    - Infiltrate, invade, destroy surrounding tissue
    - Then metastasize to other parts of body
    - Not capsulated

Local Affects

- All benign tumors grow as cohesive expansible masses
- Develop a rim of compressed connective tissue called a capsule which separates from normal tissue
- Keeps the neoplasm as a discrete, palpable, and movable mass
- Local affects like Pressure on blood vessels and nerves

Metastasis

- 30% of newly diagnosed pts. already have metastasis
- Development of secondary tumor implants in distant tissues
- Metastasis depends on:
    - Type of tumor
    - Size of tumor
- Only cancers which cannot metastasize are gliomas and basal cell carcinomas of the skin
- Ways the tumors metastasize are:
    - Direct extension
        - Damages the organ involved and adjacent tissues
        - Extend directly beyond the confines of that organ to involve adjacent tissues
        - Direct extension of malignant tumors within an organ may also be life threatening because of their location
        - Common example is the intestinal obstruction produced by cancer of the colon
        - Squamous carcinoma of the cervix frequently grows beyond the genital tract to ureters
    - Seeding
        - Malignant tumors that arise in organs adjacent to body cavities (e.g., ovaries, gastrointestinal tract and lung) may shed malignant cells into these space
        - Like implant on peritoneal surfaces or pleural cavities
        - Example: Ovarian cancer
    - Lymphatic spread
        - Tumor spreads to local lymph nodes
        - Tumors arising in tissues that have a rich lymphatic network (e.g., the breast) often metastasize by this route
        - Moves through thoracic duct and empties into subclavian vein

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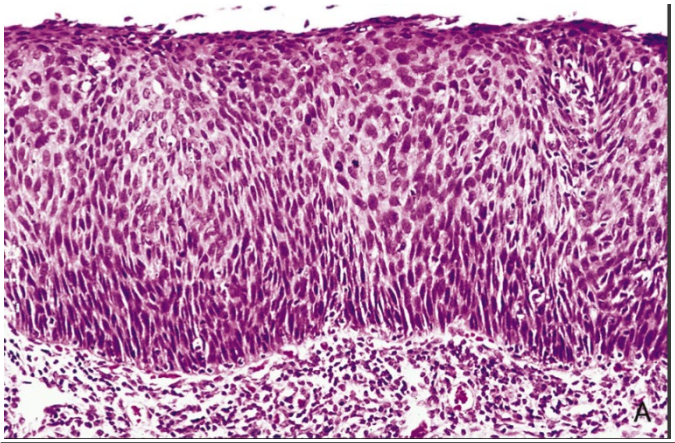
        - Hematogenous spread
            - Cancer cells commonly invade capillaries and venules whereas thicker-walled arterioles and arteries are relatively resistant
            - Abdominal tumors seed the portal system, they lead to hepatic metastases
            - Tumors penetrate systemic veins that eventually drain into the vena cava and hence to the lungs
        - Tumor cells may traverse the liver and produce pulmonary metastases
        - prostate → bone
        - most lung cancers → adrenals and brain

Grading and Staging

- Commonly used criteria include:
    - Tumor size
    - Extent of local growth = within or out of organ
    - Presence of lymph node metastases
    - Presence of distant metastases
    - Useful for determining treatment and prognosis
- Grading (differentiation):
    - Tells you how nasty the tumor looks
    - Pathologic evaluation of tumor (use microscope)
    - Mitoses, pleomorphism, and necrosis
    - Somewhat useful
    - Well-differentiated tumors are referred to as low grade, whereas poorly differentiated neoplasms are regarded as high-grade
- Staging (progression):
    - Tells you how far the tumor has spread
    - Clinical evaluation of patient (use imaging, surgery)
    - TNM system
    - Useful

- TNM system:
  - T= primary tumor
  - N= regional lymph node involvement
  - M= metastases
- T1-4 describes increasing size of primary lesion:
  - T0= carcinoma in situ
  - Tis – in situ tumor
  - T1 – small tumor
  - T2 – larger tumor
  - T3 – larger or invasive tumor
  - T4 – very large/very invasive
- N0-3 indicate progressively advancing node involvement:
  - N0 – no lymph node involvement
  - N1 – a few regional nodes
  - N2 – lots of regional nodes
  - N3 – distant nodes
- M0-1 reflects absence or presence of distant metastases:
  - M0 – no metastases
  - M1 – metastases
- T1N1M0: Means primary tumor is within the organ but cancer cells have spread to local lymph nodes =no metastasis
- T3N0M0: Means tumor has spread beyond primary organ but has not spread to lymph nodes or other sites



Robbins and Cotran Figure 7.10A Carcinoma in Situ: Histology presentation of epithelial replacement with atypical dysplastic cells. Courtesy of Robbin & Cotran (use only for educational purposes).

Cryptologic Grading

- Example of the cryptologic grading of squamous cell carcinoma of the lung:
  - Well-differentiated (grade 1) squamous cell carcinoma
    - The tumor cells bear a strong resemblance to normal squamous cells and synthesize keratin as evidenced by epithelial pearls
  - Poorly differentiated (grade 3) squamous cell carcinoma
    - The malignant cells are difficult to identify as being of squamous origin

Gene Factors

- Gene was defined as the unit of heredity
- Mutations are comparable to genetic changes that contribute to disease
    - Proto-oncogene = a normal gene whose product promotes cell growth
    - Oncogene = mutated proto-oncogene! Causes cell to grow autonomously
    - Oncoprotein = the product of an oncogene

Chemical Carcinogenesis

- Chemicals:
    - highly reactive groups bind to DNA
    - Important targets: RAS and p53
    - Directly cause DNA damage
- Direct acting compounds- directly damage DNA carcinogenic
    - Like chemotherapy drugs, cause secondary malignancies (e.g., leukemia)
- Indirect acting compounds- - most common form of chemical carcinogenesis are:
    - Hydrocarbons (in tobacco, charred meats)
    - Aflatoxin B (from Aspergillus-infected grains, nuts)
    - Nitrites (food preservative) or agents do not create DNA damage such as hormones, cytokines, or growth factors

Role of p53 Gene

- Nickname for p53: “guardian of the genome”
- Known as TP53 or tumor protein is a gene that codes for a protein that regulates the cell cycle and hence functions as a tumor suppression
- Important for cells in multicellular organisms to suppress cancer
- Name is due to its molecular mass: it is in the 53 kilodalton fraction of cell proteins
- Located on the seventeenth chromosome
- If a cell’s DNA is damaged, p53 causes a pause in the cell cycle via RB = DNA can be repaired
- If DNA damage is irreparable = p53 causes the cell to die
- Defective p53 could allow abnormal cells to proliferate = resulting in cancer
- As many as 50% of all human tumors contain p53 mutants.

Radiation

- Ionizing radiation:
  - Causes chromosome breakage, translocations.
  - Examples:
    - Unprotected miners: lung cancer
    - Atomic bomb survivors: leukemia, other cancers
    - Therapeutic radiation of head/neck: thyroid cancer.

- UV light:
  - Causes formation of pyrimidine dimers.
    - UVA- longer wavelength, deeper penetration (tanning rays)
    - UVB- shorter wavelength, effecting superficial skin (burning rays
  - Examples: squamous cell carcinoma, melanoma.

Carcinogenic Agents (Viral and Microbial)

- HTLV-1: T-cell lymphoma
- HPV: Cervical cancer
- EBV: various lymphomas
- HBV and HCV: Hepatocellular carcinoma
- H. pylori: Gastric cancer and lymphoma
- Herpes virus 8- Kaposi Sarcoma

Tumor Markers

- Carcinoembryonic antigen (CEA)- normally produced in embryo
- Positive in 60-90% of Colorectal Ca, 50-80% pancreatic Ca, 25-50% of gastric/breast Ca.
- Human Chorionic gonadotropin (HCG)- pregnancy test hormone, Associated with testicular Ca.
- Alpha-fetoprotein (AFP) = substance naturally produced by the fetus's liver
- The level of AFP in the mother's blood increases steadily during pregnancy
- An abnormally high AFP level can be a sign of a neural tube defect and associated with liver carcinoma and testicular Ca.
- AFP and HCG are also associated with germ cell tumors of ovaries
- Prostate specific antigen- indicates inflammation of prostate, but extreme elevations usually cancer
- BRCA2 and BRCA1 about 55-65 % of woman who inherit these mutations will develop breast cancer

Insensitivity to Growth-Inhibitory Signals

- Transit from one phase to another of the cell cycle is regulated at checkpoints
- Tumor-suppressor genes: normal genes whose products act as “brakes” on the cell cycle
- Mutate these genes, and you lose the brakes!
- Loss of both copies of the gene to cause tumors.
- Example: RB gene
- RB gene product stops cells at G1 checkpoint
- Mutant RB is inactive; lets cells pass through G1!
- Patients with two mutant RB genes have: increased risk of retinoblastoma and others like sarcomas

Retinoblastoma

- Mutation on chromosome 13, called the RB1 gene in children with the heritable genetic form of retinoblastoma
- Inherited form of retinoblastoma is born with a germ line mutation in one allele of the retinoblastoma gene located on the long arm of chromosome 13
- Second somatic mutation in the retina leads to the inactivation of the functioning Rb allele and the subsequent development of a retinoblastoma
- Rapidly developing cancer which develops in the cells of retina
- Treatable cancer
- Most common and obvious sign of retinoblastoma is an abnormal appearance of the pupil = leukocoria
- Other less common and less specific signs and symptoms are:
    - Deterioration of vision, a red and irritated eye
- Diagnosis:
    - Screening for retinoblastoma
    - Part of a "well baby" screening for newborns during the first three months of life
    - Macroscopically = viable tumor cells are found near blood vessels while zones of necrosis are found in relatively avascular areas
    - Microscopically = appear as collections of small round cells with hyperchromatic nuclei

Oncogene Activation by Chromosomal Translocation

- Pathogenesis of Chronic myelogenous leukemia there is translocation of the c-abl proto-oncogene on chromosome 9 to the breakpoint region (bcr) of chromosome 22
- The result is the Philadelphia chromosome = Ph1

- Hereditary Non-polyposis Colon Cancer Syndrome
- inherit one mutation – acquire the other
- Xeroderma Pigmentosum
- Small sun exposure leads to skin cancers
- Approximately 50% of affected individuals demonstrate acute sun sensitivity from early infancy, acquiring severe sunburn with blistering or persistent erythema on minimal sun exposure
- XP = inherited in an autosomal recessive manner

Sustained Angiogenesis

- In order to grow beyond about 2 mm in diameter, tumors need additional nutrients and oxygen supply
- Tumor cells need blood
- Can't grow >1-2 cm without new vessels
- Tumor cells eventually learn how to stimulate angiogenesis
- Lots of cytokines involved (i.e., VEGF)
- VEGF is a major mediator of tumor angiogenesis and is made by most tumor cells
- Tumor vessels are abnormal
- Anti-VEGF antibody is in widespread use as an anti-neoplastic agent for a variety of tumors

Paraneoplastic Syndromes

- Occur in 10% of malignancies
- Endocrinopathies are common result is ectopic hormone production
- 50% of patients with these endocrinopathies have lung carcinoma (Oat Cell Bronchogenic Carcinoma)
- Hypercalcemia is seen in para-neoplastic syndrome
- Osteolysis induced by cancer
- Production of calcemic humoral substances (calcium) by tumor cells
- Acanthosis nigricans- grey-black patches on the skin.

Case Questions: Part III

1. A 48-year-old woman goes to her physician for a routine physical examination. A 4 cm diameter non-tender mass is palpated in her right breast. The mass appears fixed to the chest wall. Another 2 cm non-tender mass is palpable in the left axilla. A chest radiograph reveals multiple 0.5 to 2 cm nodules in both lungs. Which of the following classifications best indicates the stage of her disease?
    A. T1 N1 M0
    B. T1 N0 M1
    C. T2 N1 M0
    D. T3 N0 M0
    E. T4 N1 M1

2. Study is performed to analyze characteristics of malignant neoplasms in biopsy specimens. The biopsies were performed on patients who had palpable mass lesions on digital rectal examination. Of the following microscopic findings, which is most likely to indicate that the neoplasm is malignant?
    A. Pleomorphism
    B. Invasion
    C. Increased nuclear/ cytoplasmic ratio

3. Child is born with a single functional allele of a tumor suppressor gene. At the age of five the remaining normal allele is lost through a point mutation. As a result, the ability to continue the transition from G1 to the S phase of cell cycle is lost. Which of the following neoplasm is most likely to arise via this mechanism?
    A. Infiltrating ductal carcinoma of breast
    B. Small cell anaplastic carcinoma of the lung
    C. Retinoblastoma of eye
    D. Cerebral astrocytoma

4. Which nutritional deficiency is associated with macrocytic anemia
    A. Vitamin B12 – Cobalamin
    B. Vitamin K – Phylloquinone
    C. Vitamin D – 7 Dehydrocholesterol
    D. Vitamin E – Alpha Tocopherol

5. An overdose of which nutrient is associated with Acanthosis Nigricans which is a pathological condition associated by thickening and hyperpigmented skin lesions that are localized to flexor regions of the body.
    A. Vitamin B3 – Nicotinic Acid
    B. Vitamin B2 – Riboflavin
    C. Vitamin B6 – Pyridoxine
    D. Vitamin B1 – Thiamine

6. The nutritional deficiency of which molecule, that was discovered in 1929, is associated with Wernicke Encephalopathy, which is a pathological condition associated with brain dysfunction and is characterized by mental confusion, muscle weakness, and heart palpitations
    A. Vitamin B1 – Thiamine
    B. Vitamin C – Ascorbic Acid
    C. Vitamin B9 – Folic Acid
    D. Vitamin B5 – Pantothenic Acid

Case Question Answers

Case Questions Part I

- Question 1 - C
- Question 2 - E
- Question 3 - C
- Question 4 - B
- Question 5 - C
- Question 6 - A

Case Questions Part II

- Question 1 - B
- Question 2 - D
- Question 3 - E
- Question 4 - B
- Question 5 - C
- Question 6 - B

Case Questions Part III

- Question 1 - E
- Question 2 - B
- Question 3 - C
- Question 4 - A
- Question 5 - A
- Question 6 - A

Thank you to Elsevier for helping advance the education of healthcare students around the world.

References

1) Kumar V, Abbas A K, Aster J C, Perkins J A. 2015. Robbins and Cotran: Pathological Basis of Disease. Elsevier Saunders Publishing Incorporated. 1600 John F. Kennedy Blvd; Ste 1800, Philadelphi PA (190103-2899).
    a. Figure 2.25 B/C
    b. Figure 2.28
    c. Figure 2.7
    d. Figure 2.8
    e. Figure 2.9
    f. Figure 3.2
    g. Figure 3.22
    h. Figure 3.26
    i. Figure 3.3
    j. Figure 7.10 A
    k. Figure 7.11 B
    l. Figure 8.7
    m. Figure 13.13
    n. Figure 13.8 A/B
    o. Figure 27.2

The document is a study guide on cell pathology, covering topics such as cellular responses to injury, types of cell adaptations, inflammation, neoplasia, and related physiological and pathological processes.