Model Answers

B. Pharm. III SEMESTER

EXAMINATION, Dec 2013

Subject: Pathophysiology of common diseases

Subject Code: AS 2514

SECTION- A (Objective type questions)

12X2= 24

1. Inflammation is "A dynamic response of vascularised tissue to injury."
2. Margination, rolling, and adhesion to endothelium, Diapedesis (trans-migration across the endothelium), Migration toward a chemotactic stimuli from the source of tissue injury, Phagocytosis.
3. Atrophy in the partial or complete wasting away of body part and hypertrophy is the increase in the volume of an organ or tissue due to enlargement of its component cells.
4. Hypoxia is the condition in which the body or reduced oxygen or inadequate oxygenation of cell leading to ischemia, acid base imbalance, decrease oxidative phosphorylation, decrease ATP, increase free radical and cell death.
5. Functional and morphological changes are reversible in an injury if the damaging stimuli are removed like oxidative phosphorylation, ATP depletion and cellular swelling.
6. Free radicals are the reactive oxygen and nitrogen species which causes cellular injury.
7. It is the end volumetric pressure that stretches the right or left ventricles of the heart.
8. Insulin resistance is a physiological condition in which cell fails to respond to the normal action of hormone insulin.

9. Delusions, Hallucinations- Auditory, Visual, Olfactory, and Tactile, Losing Sense of Reality, Disorganization of Thought, Thought Blocking.
10. Sudden, severe, pressing chest pain starting substernal &radiate to left arm due to imbalance between myocardium oxygen requirement and oxygen supply.
11. Stomach : 3 Small intestine: 7.8
12. Know as heart attack occurs due to sudden stoppage of blood supply to the parts of the heat and the heart muscles is injured due to less O2 supply.

SECTION- B **14X4= 56**

2. Results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to damaging agents. Cell injury can be reversible or irreversible.

Reversible cell injury:

Functional and morphologic changes are reversible if the damaging stimulus is removed. The features are: decreased oxidative phosphorylation,ATP depletion and cellular swelling.

Irreversible injury and cell death:

- With continuing damage, injury becomes irreversible.
- Cells undergo morphologic changes recognisable as cell death.
- Cell death is of 2 types-necrosis and apoptosis.

Causes of cell injury:

- Oxygen deprivation.
- Physical agents eg:mechanical trauma, burns, deep cold, barotrauma, electric shock.
- Chemical agents & drugs eg: poisons, environmental pollutants, CO, asbestos, alcohol, narcotic drugs etc.
- Infectious agents-viruses, rickettsiae, bacteria, fungi, protozoa and helminths.
- Immunologic reactions-anaphylaxis, autoimmune disorders.
- Genetic derangements.
- Nutritional imbalances-PEM, obesity, specific vitamin deficiencies etc**.**

Mechanisms of cell injury:

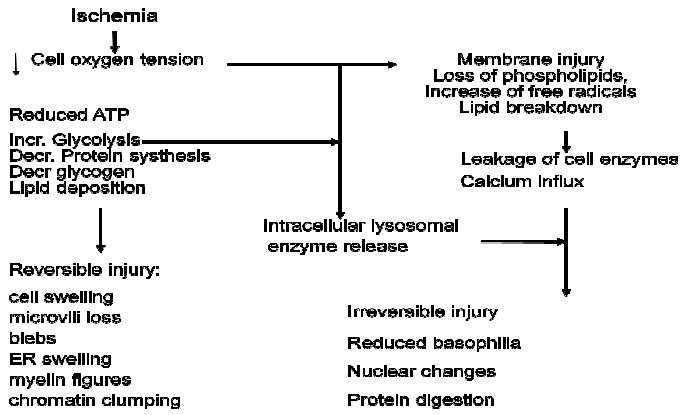
- Depletion of ATP-affects activity of Na,K-ATPase pump.This results in anaerobic glycolysis.
- Mitochondrial damage-leakage of cytochrome-C into cytosol,resulting in apoptosis.
- Influx of Ca & loss of Ca homeostasis, leading to activation of ATPases,phospholipases,proteases & endonucleases.

Free radical injury:

- Oxygen derived.
- Free radicals are chemical species that have a single unpaired electron in an outer orbit.
- Energy created by this unstable configuration is released through reactions with adjacent molecules.
- They initiate autocatalytic reactions.
- Absorption of radiant energy(u-v or ionising):Water is hydrolysed to(OH)&(H) free radicals.
- Enzymatic metabolism of exogenous chemicals or drugs ,eg:CCl_4 converted to CCl_3.
- Redox reactions in the cell: (O_2),(H_2O_2) &(OH).
- Transition metals like iron and copper.
- Nitrous oxide.

Effects of free radicals:

- Lipid peroxidation of membranes.
- Oxidative modification of proteins.
- Lesions in DNA.



3. **Rheumatoid arthritis** is an autoimmune disease in which the normal immune response is directed against an individual's own tissue, including the joints, tendons, and bones, resulting in inflammation and destruction of these tissues. The cause of rheumatoid arthritis is not known. Investigating possibilities of a foreign antigen, such as a virus.

Symptoms:

- In the initial stages of each joint involvement, there is warmth, pain, and redness, with corresponding decrease of range of motion of the affected joint
- Progression of the disease results in reducible and later fixed deformities
- Muscle weakness and atrophy develop early in the course of the disease in many people

A person shall be said to have rheumatoid arthritis if he or she has satisfied 4 of 7 criteria, with criteria 1-4 present for at least 6 weeks

Stages:

1. Mild
2. Moderate
3. Severe
4. End stage

Diagnosis:

a. Morning stiffness
b. Arthritis of 3 or more joints
c. Arthritis of hand joints
d. Symmetric arthritis
e. Rheumatoid nodules
f. Serum rheumatoid factor
g. adiographic changes

Treatment:

- Medications
  - NSAIDS - Usually, only one such NSAID should be given at a time. Can be titrated every two weeks until max dosage or response is obtained. Should try for at least 2 to 3 wk before assuming inefficacy.

- Slow acting - Generally, if pain and swelling persist after 2 to 4 mo of disease despite treatment with aspirin or other NSAIDs, can add a slow-acting or potentially disease-modifying drug (eg, gold, hydroxychloroquine, sulfasalazine, penicillamine) Methotrexate, an immunosuppressive drug is now increasingly also used very early as one of the second-line potentially disease-modifying drugs.
- Corticosteroids – offer the most effective short-term relief as an anti-inflammatory drugs. Long-term though improvement diminishes. Corticosteroids do not predictably prevent the progression of joint destruction, although a recent report suggested that they may slow erosions. Severe rebound follows the withdrawal of corticosteroids in active disease.
- Immunosuppressive drugs These drugs (eg, methotrexate, azathioprine, cyclosporine) are increasingly used in management of severe, active RA. They can suppress inflammation and may allow reduction of corticosteroid doses. Major side effects can occur, including liver disease, pneumonitis, bone marrow suppression, and, after long-term use of azathioprine, malignancy.

- Surgery:
  - Removal of inflamed synovium
  - Arthroplasty
  - Physical therapy

4. (A) Chemical substances synthesised or released and mediate the changes in inflammation.

Histamine by mast cells - vasodilatation.

Prostaglandins – Cause pain & fever.

Bradykinin - Causes pain.

These are chemical mediator that acts on blood vessels, inflammatory cells or other cells to contribute to an inflammatory response.

General principles:

o Originate from plasma or cells; when in plasma, are in an inactive state and must be activated and when in cells, they are often within granules and need to be secreted or they are synthesized in response to a stimulus.

a. Production of active mediators is triggered by microbial products or host proteins (eg cytokines).
b. Some have direct enzymatic activity; most require binding to specific receptors on target cells for biologic activity.
c. One mediator can stimulate the release of other mediators by target cells (ie provide amplification).
d. Chemical mediators may have different effects on different cells.
e. Chemical mediators are interactive and redundant, guaranteeing amplification and preservation of the response even if one or more components of the response are deficient.
f. Most are short-lived and have the potential to be harmful.

The mediators are:

Vasoactive Amines

Histamine and **serotonin** are believed to be the primary mediators in the immediate active phase of increased permeability. Vasoactive amines cause **vasodilation** and increased **vascular permeability** by causing endothelial cells to round up, increasing intercellular gaps, and also increasing vesiculovacuolar transfer of fluids. Vasoactive amines are stored within cells for immediate release.

Histamine

is extensively distributed in tissues, the main source being the mast cells that are normally present in the perivascular connective tissue; it is preformed and stored in granules with heparin.

- It is also present in granules of basophils and in platelets (some species).
- Histamine is important mainly in early inflammatory responses and in type 1 hypersensitivity reactions.
- Histamine is important in the immediate active phase of increased vascular permeability.

- It is also important in allergic reactions as it promotes contraction of extravascular smooth muscles in the bronchi and stimulates stromal cells to synthesize and release eotaxins (chemotaxins for eosinophils).

The following agents can stimulate release of histamine from mast cells:

o Ag (eg pollen) binding to IgE on mast cells

o Anaphylotoxins (C3a and C5a)

o Physical injury, mechanical trauma, heat, chemical agents

o Snake venoms, toxins, bile salts, ATP

o Histamine-releasing factors from neutrophils, monocytes, and platelets

o Cytokines (IL-1, IL-8)

o Neuropeptides, like substance P

Serotonin is another vasoactive mediator, present in platelets and some mast cells (not in humans). serotonin acts primarily on venules during the early phase of acute inflammation, when it is released from mast cells, basophils and platelets. The release of histamine and serotonin from platelets (the platelet release reaction) is stimulated when platelets aggregate after contact with collagen, thrombin, ADP, and antigen-antibody complexes.

Plasma Proteases

Three interrelated systems (ie complement, kinin and clotting) are important in the inflammatory response and are found within plasma. All are capable of being activated by activated Hageman's factor (factor XIIa of the coagulation cascade).

Complement system set of plasma proteins that act together to attack extracellular forms of microbial pathogens. It can be activated directly by certain pathogens or by antibodies binding to a pathogen. When pathogens (microorganism) are coated with complement proteins their removal by leukocytes is facilitated (opsonized) &/or they are directly killed by the membrane attack complex (MAC). Besides facilitated removal & killing of targeted microorganisms, activated complement is also involved in:

a. Vascular permeability (esp C3a & C5a) – via histamine release from mast cells.
b. Chemotaxis - C5a chemoattractant for neutrophils, monocytes, eosinopils & basophils.

Kinin System

The kinin system generates vasoactive peptides from plasma proteins called kininogens by the action of specific proteases called kallikreins which ultimately leads to activation of bradykinin. bradykinin has the following actions:

1. vasodilation and stimulation of histamine release by mast cells increased vascular permeability
2. contraction of non-vascular smooth muscle
3. produce pain
4. activate the arachidonic acid cascade

Clotting system

The clotting system and inflammation are intimately connected. The intrinsic clotting system is a sequence of plasma proteins that can be activated by Hageman factor . (factor XII – produced in liver and circulating in inactive form). The final phase of the cascade is the conversion of fibrinogen to fibrin by the action of thrombin. Thrombin also binds to a receptor on platelets, endothelium, smooth muscle cells and others to make them:

1. Mobilize P-selectin to the cell membrane and express adhesion molecules for integrins
2. Produce of chemokines .
3. Induce cyclooxygenase-2 – production of prostaglandins .
4. Produce platelet activating factor (PAF) & nitric oxide (NO)
5. Change endothelial shape

Arachidonic Acid Metabolites

Two enzymes are able to produce these products: COX-1 and COX-2.

COX-1 is normally present and necessary for everyday activities; also synthesized at sites of inflammation. COX-2 is transcriptionally regulated - present in various circumstances (eg inflammation). The main 3 products resulting from this pathway are:

i) **Thromboxane A2** is found in platelets and other cells is a potent platelet aggregator and vasoconstrictor

ii) **Prostacyclin (PG I2)** is found predominantly in endothelial cells; a potent inhibitor of platelet aggregation and vasodilator.

iii) **Prostaglandins (PG's E2, D2, F2α)** cause vasodilation, increased vascular permeability & pain.

Lipoxygenase Pathway:

i) **Leukotrienes**

o **Leukotriene B4 -** is one of the most potent chemotactic agents for neutrophils and macrophages.

o **Leukotrienes C4, D4, E4**

Potent vasoconstrictors and potent mediators of increased vascular permeability on venules only. These are up to 1000X as potent as histamine in producing increased vascular permeability. They also cause bronchospasm.

ii) **Lipoxins**

o **Lipoxins A4 and B4**

Inhibit neutrophil chemotaxis and adhesion to endothelium; these are, therefore, anti-inflammatory substances that seem to counteract the leukotrienes.

Other mediators are:

Platelet Activating Factor (PAF)

Lysosomal Constituents

Oxygen-Derived Free Radicals

Cytokines and Chemokines

(B). The events are as follows

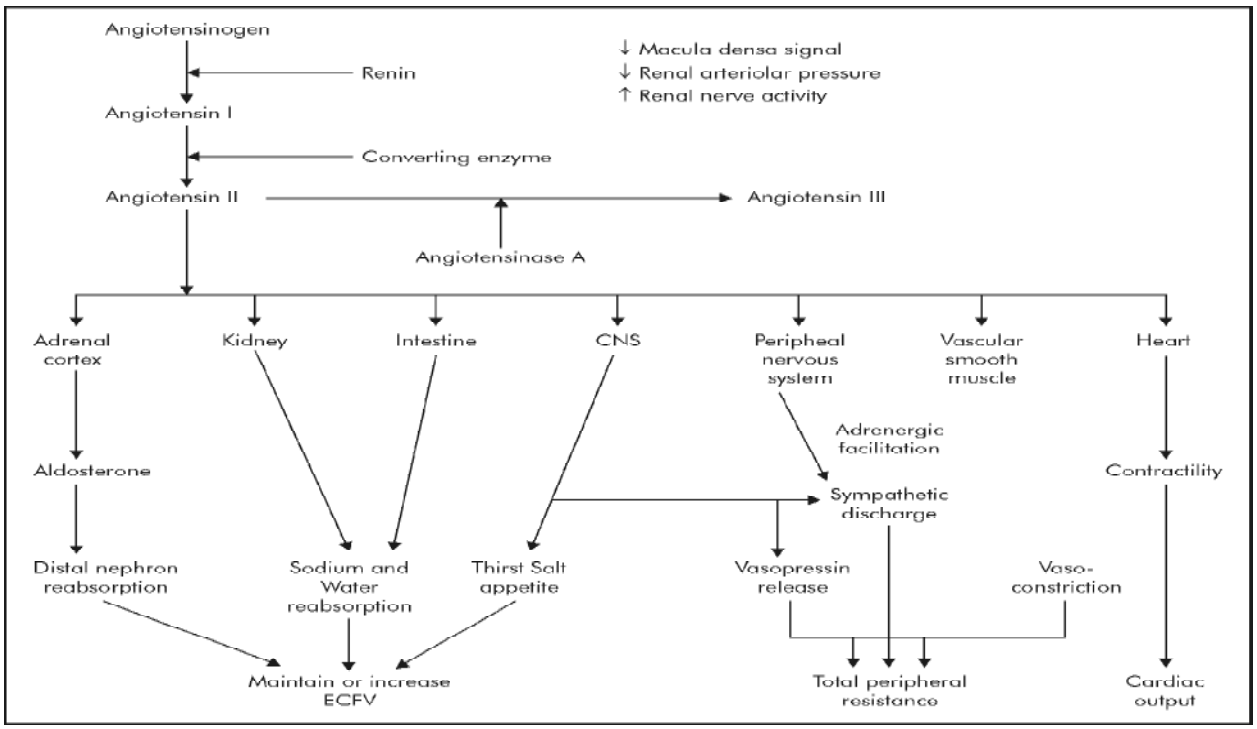
- **Vasodilation:** Brief arteriolar vasoconstriction followed by vasodilation . Accounts for warmth and redness. Opens microvascular beds. Increased intravascular pressure causes an early transudate (protein-poor filtrate of plasma) into interstitium (vascular permeability still not increased yet).
- **Vascular leakage:** Vascular permeability (leakiness) commences. Transudate gives way to exudate (protein-rich). Increases interstitial osmotic pressure contributing to edema (water and ions)

- **Five mechanisms known to cause vascular leakiness:**

- Histamines, bradykinins, leukotrienes cause an early, brief (15 – 30 min.) *immediate transient response* in the form of endothelial cell contraction that *widens intercellular gaps* of venules (not arterioles, capillaries)
- Cytokine mediators (TNF, IL-1) induce *endothelial cell junction retraction* through cytoskeleton reorganization (4 – 6 hrs post injury, lasting 24 hrs or more)
- Severe injuries may cause immediate *direct endothelial cell damage* (necrosis, detachment) making them leaky until they are repaired (*immediate sustained response*), or may cause delayed damage as in thermal or UV injury.
- (cont'd) or some bacterial toxins (*delayed prolonged leakage*)
- Marginating and endothelial cell-adherent leukocytes may pile-up and damage the endothelium through activation and release of toxic oxygen radicals and proteolytic enzymes (*leukocyte-dependent endothelial cell injury*) making the vessel leaky
- Certain mediators (VEGF) may cause *increased transcytosis* via intracellular vesicles which travel from the luminal to basement membrane surface of the endothelial cell

- All or any combination of these events may occur in response to a given stimulus.

5. A) Renin may play a critical role in the pathogenesis of most hypertension,



B). Sympathetic influence

- Epinephrine 6 ↑HR (*tachycardia*) and ↑ contractility
- Norepinephrine 6 general vasoconstrictor

- Parasympathetic influence
  - Acetylcholine→↓HR (*bradycardia*)
  - Endurance (aerobic) trg. increases vagal dominance

Sympathetic Fibers

- Innervate SA node & ventricles
- Increase heart rate
- Increase contractility
- Increase pressure

Parasympathetic Nerve

- Innervates SA node & AV node
- Releases acetylcholine
- Slows heart rate
- Lowers pressure

Cerebral cortex impulses pass through cardiovascular control center in medulla oblongata.

- Emotional state affects cardiovascular response
- Cause heart rate to increase in anticipation of exercise

Peripheral receptors monitor state of active muscle; modify vagal or sympathetic

- Chemoreceptors
  - Monitor pCO_2, H^+, pO_2
- Mechanoreceptors
  - Heart and skeletal muscle mechanical receptors
- Baroreceptors : in carotid sinus and aortic arch.
  - ↑ pressure → ? HR & contractility
  - ↓ pressure → ? HR & contractility

6. Pathophysiology of schizophrenia

   Should cover following points

1. Symptoms
    a. Positive
    b. Negative
2. Pathophysilogy:
    a. Dopamine theory
    b. Glutamate theory
3. Diagnosis
4. Treatment
    a. Non-pharmacological
    b. Pharmacological
    c. Behavioral counseling

7. A peptic ulcer is a sore on the lining of the stomach or duodenum, the beginning of the small intestine. Less commonly, a peptic ulcer may develop just above the stomach in the esophagus, the tube that connects the mouth to the stomach. A bacterium called *Helicobacter pylori (H. pylori)* is a major cause of peptic ulcers.

H. pylori is a type of bacteria—a germ that may cause infection. *H. pylori* infection is common, particularly in developing countries, and often begins in childhood. Symptoms usually don't occur until adulthood, although most people never have any symptoms. Nonsteroidal anti-infl ammatory drugs (NSAIDs), such as aspirin and ibuprofen, are another common cause. Rarely, cancerous or noncancerous tumors in the stomach, duodenum, or pancreas cause ulcers. Peptic ulcers are not caused by stress or eating spicy food, but both can make ulcer symptoms worse. Smoking and drinking alcohol also can worsen ulcers and prevent healing.

Symptoms:

Abdominal discomfort is the most common symptom of both duodenal and gastric ulcers. Felt anywhere between the navel and the breastbone, this discomfort usually

- is a dull or burning pain
- occurs when the stomach is empty— between meals or during the night

- may be briefly relieved by eating food, in the case of duodenal ulcers, or by taking antacids, in both types of peptic ulcers
- lasts for minutes to hours
- comes and goes for several days or weeks

Other symptoms of a peptic ulcer may include

- weight loss
- poor appetite
- bloating
- burping
- nausea
- vomiting

Some people experience only mild symptoms

Treatment:

Antibiotics are used to kill *H. pylori.* Antibiotic regimens may differ throughout the world because some strains of *H. pylori* have become resistant to certain antibiotics—meaning that an antibiotic that once destroyed the bacterium is no longer effective. Doctors closely follow research on antibiotic treatments for *H. pylori* infection to know which treatment strategy will destroy which strain.

Medicines that reduce stomach acid include proton pump inhibitors (PPIs) and histamine receptor blockers (H2 blockers). Both acid-reducing medicines help relieve peptic ulcer pain after a few weeks and promote ulcer healing. PPIs and H2 blockers work in different ways:

- PPIs suppress acid production by halting the mechanism that pumps acid into the stomach.
- H2 blockers work by blocking histamine, which stimulates acid secretion.
- clarithromycin-based triple therapy—triple therapy, for short—is the standard treatment for an ulcer caused by *H. pylori*. The doctor prescribes the antibiotic clarithromycin, a PPI, and the antibiotics amoxicillin or metronidazole for 10 to 14 days. Because

research shows higher cure rates with 14 days of treatment, some doctors now prescribe triple therapy for this longer period.

- Bismuth quadruple therapy is another treatment strategy used in the United States. The patient takes a PPI, bismuth subsalicylate, and the antibiotics tetracycline and metronidazole for 10 to 14 days.