March 21, 2005
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There are a total of 100 points for this examination. It consists of three sections: histopathology, multiple choice, and short answers. Pay particular attention to the number of points assigned to each question and ANSWER ONLY IN THE SPACE PROVIDED.

SECTION 1. HISTOPATHOLOGY (14 points)

1. A 70 year old man died two years after a diagnosis of colon cancer. A heart biopsy obtained on autopsy revealed that he had had a previous heart attack. (4 points)
   Based what you see in the micrograph shown in Figures 1A,B how long ago do you think he had the heart attack? at least 8 weeks ago ✓

   Justify your answer.
   The micrographs show a healed, fibrotic area with minimal inflammatory cell infiltrates, which indicates that this is not a recent MI. The heart will form a scar, the paler area, in 8 weeks and thus this must have happened at least that long ago.

2. A biopsy from a 40 year old man with a history of fatigue and loss of appetite is shown in Figures 2AB,C. His SGOT and SGPT were within normal range. (5 points)
   From what organ was this biopsy taken? liver ✓

   What is your diagnosis? chronic viral hepatitis ✓

   Explain your rationale for making this diagnosis, based on the histolopathologic features of this tissue.
   Chronic viral hepatitis causes infiltration of the portal triad with inflammatory cells, referred to as portal triad expansion. The lymphocytes are spilling over the limiting plate into the liver parenchyma, which looks like the hepatocytes are swollen. There is no remarkable fatty change (Steatosis), which would indicate alcoholic hepatitis instead of chronic viral hepatitis.

3. An 80 year old woman in a nursing home had an abrupt rise in her temperature, shaking chills, and a cough with mucuspurulent sputum. Her physicians were concerned because of her age and treated her aggressively. However, she did not respond to antibiotics and died. Her lung biopsy is shown in Figures 3A,B,C. (5 points)
   What is your diagnosis? bronchopneumonia ✓

   Describe the histolopathology of this lung and how it relates to her clinical symptoms.
   The patients alveoli are filled with inflammatory cell infiltrate ✓ (although alveolar septa are still apparent) which would produce a mucopurulent sputum if coughed up. This type of inflammatory reaction with neutrophil infiltration could also lead to a systemic response with fever, shaking, and chills if enough cytokines (IL-1, TNF α) were produced in response to infection.
SECTION 2. MULTIPLE CHOICE (2.5 points each, total of 30 points)

1. Peroxisomes are sub-cellular organelles that generate hydrogen peroxide. These organelles also produce which of the following anti-oxidants? \( \text{H}_2\text{O}_2 \)
   - A. Catalase
   - B. Superoxide dismutase
   - C. Glutathione peroxidase
   - D. Vitamin C → d\text{ie}t
   - E. Vitamin A → d\text{ie}t

2. After a painful running injury, a young athlete is anxious to return to training for a marathon. The doctor told him to rest for 2 months but he decides to treat himself, consuming 8 tablets of extra-strength Tylenol (500 mg each) per day over a period of 2 months. What type of liver damage is he at risk of developing?
   - A. Coagulative necrosis around the portal tract
   - B. Liquefactive necrosis around the portal tract
   - C. Liquefactive necrosis in the centrilobular region
   - D. Liquefactive necrosis in the centrilobular region
   - E. Caseous necrosis around the portal tract

3. A young girl has spontaneous bleeding from her mucous membranes and excessive bleeding from wounds. Her mother also has a history of bleeding problems. The child’s platelet count is normal but the bleeding time is prolonged. What disease do you think she has?
   - A. Hemophilia A
   - B. Von Willebrand’s disease
   - C. Protein C deficiency
   - D. Protein S deficiency
   - E. Factor XII deficiency

4. A mother brings her 5 year old child to your office with a fever of 103° and multiple abscesses on his arm. You think that he is infected with Staphylococcus aureus, which has stimulated an acute inflammatory response, and order a culture. The abscess is painful to the touch. After your diagnosis is confirmed, you prescribe antibiotics and explain to the mother why her child has fever and pain.
   Which of the following mediators causes pain?
   - A. Histamine
   - B. Serotonin
   - C. Bradykinin
   - D. Interleukin-6
   - E. Interleukin-7

Which of the following mediators is MOST LIKELY involved in the induction of this child’s fever?
   - A. C3a
   - B. Interleukin-1
   - C. Platelet activating factor
   - D. Nitric oxide
   - E. RANTES


What inflammatory cells in the abscess are MOST SPECIFIC to acute inflammation?

A. Cytotoxic T lymphocytes
B. Mast cells
C. Plasma cells
D. Eosinophils
E. Neutrophils

5. Clinical trials have demonstrated statins to be effective in lowering cholesterol levels and reducing mortality from heart disease. Researchers are still studying the mechanisms by which statins reduce heart disease. What mechanism of action of the statins is MOST WELL UNDERSTOOD at the moment?

A. Statins inhibit binding of LDL to its receptors on cells
B. Statins activate acyl-CoA: cholesterol transferase (ACAT)
C. Statins inhibit the activity of 3-hydroxy-3-methylglutaryl coenzyme A-reductase (3-HMG)
D. Statins activate C-reactive protein
E. Statins inhibit platelet aggregation

6. You have volunteered to work with Doctors Without Borders in a war zone where many of the wounded are starving. You note that wound healing is impaired in many war victims. Which of the following mechanisms is the MOST LIKELY cause of compromised healing?

A. Defects in platelet-derived growth factor, leading to decreased synthesis of collagen
B. Vitamin C deficiency that inhibits hydroxylation of collagen
C. Low levels of TGF-β that inhibit the formation of granulation tissue
D. Defects in synthesis of basic fibroblast growth factor that inhibits the translation of collagen
E. Defects in platelet aggregation that lead to an unstable platelet plug

7. A 35-year old man develops liver failure as a result of fulminant hepatitis. After a histocompatible donor was located, he received a liver transplant. He was placed on longterm immunosuppressive therapy to prevent rejection. Which cell type is MOST CENTRAL in REGULATING the complex mechanisms leading to graft rejection?

A. CD4+ T lymphocytes
B. CD8+ T lymphocytes
C. Dendritic cells
D. Plasma cells
E. Mast cells

8. A 65 year old woman has a heart attack and dies suddenly. Two weeks ago she had a normal physical examination. What would you expect to see on autopsy that could BEST EXPLAIN her sudden death?

A. Fatty streaks in her coronary arteries
B. Cystic medial degeneration
C. Medial calcific sclerosis
D. Evidence of Chlamydia pneumoniae infection
E. Tear of the fibrous cap on an atherosclerotic plaque in one of the coronary arteries
9. A 35 year old woman develops a butterfly rash on her face. After a series of laboratory tests, the doctor diagnoses [systemic lupus erythematosus](https://www.nhlbi.nih.gov/health-topics/systemic-lupus-erythematosus). Which antibodies are MOST SPECIFIC to lupus?
   A. Anti-nuclear antibodies
   B. Anti-Smith antibodies and anti-DNA antibodies
   C. Anti-nucleoprotein antibodies
   D. Anti-histone antibodies
   E. Anti-nucleolar antibodies

10. A 60-year old man died suddenly after returning from a 24 hour plane ride to Australia. He had been sick with the flu several weeks before leaving Australia but had no history of heart disease or cardiac disease risk factors. In the absence of additional information, which of the following conditions would be MOST IMPORTANT to consider in your differential diagnosis?
   A. Disseminated intravascular coagulation
   B. Familial hypercholesterolemia
   C. complications of influenza
   D. pulmonary embolism
   E. arteriosclerosis

SECTION 3. SHORT ANSWERS (56)

1. A 55 year old man suffers multiple leg fractures in a serious car accident. After the leg has been immobilized in a cast for 6 weeks, the cast is removed. The fractures have healed well but the calf muscle has atrophied. Is atrophy a reversible or irreversible process? Explain in 2-3 sentences what is happening in the cells at the molecular level. (5 points)

   [Atrophy is a reversible decrease in the intracellular content and function of cells. Cells can decrease their contents by autophagy where ER membrane surrounds organelles and other cellular constituents and fuses with a lysosome, leading to degradation of its contents. Cell contents may also be degraded after being tagged with ubiquitin and processed by the proteasome.]

2. Over the past several years, several pharmaceutical companies have actively marketed COX-2 inhibitors, such as Vioxx or Celebrex, for patients with arthritis. Recently, however, the industry and clinical medicine -- has been thrown into turmoil by results of clinical trials, showing that COX-2 inhibitors increase the risk of heart attacks. (Part of the turmoil is due to the fact that at least one of the companies suppressed their findings.)

   Explain the mechanisms by which COX inhibitors regulate inflammation? (4)

   [Aspirin irreversibly acetylates COX enzymes that are responsible for the production of prostaglandins and thromboxanes from arachidonic acid. This decreases the synthesis of some of the lipid mediators of inflammation that are responsible for such varied effects as vasodilation, increased vascular permeability, and vasconstriction, both promoting and inhibiting platelet aggregation. *Leukotriene Synthesis is unaffected.*]
What was the original scientific rationale for the development of specific inhibitors of COX enzymes? (2 points)

Cox-1 is an enzyme that is constitutively expressed in many locations, including the gut while Cox-2 is inducible by inflammatory stimuli. The goal is to inhibit just the production of inflammatory mediators while leaving prostaglandin synthesis unperturbed in the GI tract, where it is protective against ulcer formation.

Based on what you have learned in your lectures on inflammation, hemostasis and thrombosis, how might you explain this surprising finding of an increase in heart attacks? (2 points)

Cox inhibitors do not affect the synthesis of leukotrienes, but do inhibit prostacyclin and other prostaglandin synthesis. This altered production of lipid mediators may lead to an increased propensity to form thrombi which can lead to myocardial infarct if the thrombus becomes a thromboembolism that lodges in the coronary circulation.

3. A 28 year old college student is brought to the emergency room in a coma by his friends. They report that he had been depressed and drinking excessively for the past week after failing his organic chemistry midterm. What would you MOST LIKELY expect to see on a liver biopsy? Briefly describe the mechanisms by which this type of cell injury is produced.

What would you do for this patient? (5 points)

The liver biopsy would likely show fatty change and centrilobular necrosis.

Fatty change is a result of increased NADH/NAD+ ratio in hepatocytes after degradation of EtOH to acetaldehyde, then to acetic acid by ADH and ALDH, respectively, coupled with decreased lipoprotein synthesis and increased fatty acid deposition in the liver from the periphery. Centrilobular necrosis is a result of EtOH metabolism to acetaldehyde by cytochrome P450 enzymes (EPA isozyme) in hepatocytes. This secondary pathway for EtOH degradation produces reactive oxygen species as a byproduct.

Zone 3 around the central vein has the highest cytochrome P450 activity and produces the most ROSs, and that is where we see the necrosis.

N-acetocysteine, a precursor to GSH, may be given to this patient to try to prevent some additional damage to hepatocytes by ROSs as the patient continues to metabolize EtOH.

4. Many chemical agents used to treat cancer damage DNA. Depending on the dose administered, this leads to cell death either by apoptosis or necrosis. Which mechanisms of cell death would you suspect, if microscopic examination of the tissue indicates the presence of isolated, shrunken cells with fragmented nuclei, an intact plasma membrane, and phagocytic cells engulfing cellular fragments. What proteases are responsible for these morphologic changes? (4 points)

Cell death is occurring by apoptosis. Caspases are the proteolytic enzymes required for programmed cell death (executioner caspases).

5. Leukocyte attraction to the site of injury involves margination, rolling, and adhesion. NAME two adhesion molecules expressed on the surface of endothelial cells that mediate rolling. To what receptor on leukocytes do they bind? (3 points)

Adhesion molecules on endothelial cells:

- P-Selectins
- E-Selectins

Receptor on leukocytes: Sialyl-Lewis X
6. You have elected to do a clinical rotation in a rural South African health clinic. On arrival you are asked to assist in a survey of the prevalence of tuberculosis. According to the PPD test, 70% of residents are positive. However, only 25% have pulmonary lesions on X-ray. This indicates that not all people who were infected went on to develop clinical disease. In the people with radiologically evident lesions, what would a lung biopsy reveal? What role does TNF-α play in pulmonary tuberculosis? (5 points)

A lung biopsy would reveal granuloma formation in the lung parenchyma. Granulomas caused by M. tuberculosis characteristically have a caseous necrotic center surrounded by epithelioid macrophages, which have enhanced secretory capacity, and around the epithelioid macrophages is usually a collar of lymphocytes (both CD4 and Th1 type cells). One may also see Langhan's giant cells with twenty or so nuclei arranged in a horseshoe shape. Great!

TNF-α is an inflammatory cytokine produced by activated macrophages that helps recruit and activate more macrophages. This is important in tuberculosis because recruitment and activation of macrophages is required for granuloma formation to contain the mycobacteria.

7. Screening for Rh (Rhesus) antigen is now a routine part of a pregnancy workup. In a conversation with your partner's grandmother, you find out that her first child was healthy and the second one slightly jaundiced. However, the next four pregnancies ended in stillbirths. She recalls her physicians mentioning something about Rh incompatibility. By what mechanisms does Rh incompatibility produce fetal death? (4 points)  

Rh incompatibility is a Type II hypersensitivity reaction where IgG antibodies are made against the Rh antigen present on fetal RBCs, but not maternal RBCs. Exposure of the mother to fetal RBCs during the delivery of her first child leads to sensitization and the production of anti-Rh antibodies. During the second pregnancy, the IgG antibodies are able to cross the placenta and bind to the Rh antigen on fetal RBCs. This leads to hemolysis by opsonization and phagocytosis. The release of hemoglobin and its breakdown products leads to jaundice. Subsequent pregnancies had such a high level of fetal hemolysis that the babies were not able to survive.

8. Fatty streaks are generally considered to be precursors to the development of atherosclerosis. What is ONE piece of evidence that indicates that the relationship between fatty streaks and atherosclerotic plaques is more complex than a simple uni-causal one? (2 points)

Fatty streaks tend to be found in locations that are not particularly susceptible to atherosclerotic plaque development. For example, fatty streaks are common in the thoracic aorta, but atheromas usually develop in the abdominal aorta.

9. A 25 year old woman seeks medical attention for drooping eyelids and generalized muscle weakness. You administer an anticholinesterase agent that relieves her symptoms. (3.5 points)  

What is your diagnosis? Myasthenia Gravis

What accounts for her muscle weakness? An autoimmune disease (and also Type II hypersensitivity reaction) where antibodies are produced against the ACh receptor, leading to antibody-mediated cellular dysfunction where ACh cannot bind to postsynaptic membrane.
10. On March 15, 2005, the Providence Journal reported on a recent publication in the Archives of Internal Medicine. According to the news article, “a simple and inexpensive test for elevated white blood cell counts could be used to predict heart disease.” The article goes on to quote a cardiologist that the new study is “really a wake-up call for the profession. Heart disease was not created by cholesterol alone.” Based on your lectures in Pathology, explain why a white blood cell count would have predictive value for heart disease? (5 points)

An elevated WBC count may be indicative of a chronic inflammatory problem much as C-reactive protein levels are. Since atherosclerosis is a chronic inflammatory process of the intima of large elastic and medium-sized muscular blood vessels, then elevated markers of chronic inflammation can indicate an increased risk of having atherosclerotic plaques, which may lead to heart disease. However, atherosclerotic plaques may occlude coronary arteries, leading to heart disease or may rupture, erode, or ulcerate allowing for thrombus formation and potential myocardial infarction. Elevated WBC counts, may therefore, have some predictive value for such examples of heart disease.

11. Your sister has had asthma since she was a 3 month old baby. One of the many antigens to which she is sensitized is Der p1. (5 points)

What is Der p1? A cysteine protease made by the dust mite (5 points)

Der p1 digests the outer mucin layer through epithelium.

Briefly explain how Der p1 causes the symptoms of asthma. Upon re-exposure to Der p1, the protein binds to IgE antibodies, leading to the cross-linking of FcεRI receptors and activation of T cells. This activates the release of pro-inflammatory mediators such as histamine and leukotriene C4, leading to increased vascular permeability and increased mucous production, causing coughing and wheezing.

12. Deficiency in Vitamin K produces defects in coagulation. Briefly explain the role of Vitamin K in coagulation. (4 points)

Vitamin K is required for one of the final steps in the production of Factors II, VII, IX, and X, the carboxylation of a glutamate residue. This final step is required in order to form factors that are able to be activated.

13. Eskimos have a high fat diet but low coronary heart disease. How could you explain this based on the homocysteine theory? (2.5 points)

Eskimos eat a large amount of fish oil, which is high in Vitamin E. Vitamin B9, along with vitamin B6 and folate, are required to metabolize homocysteine. A lack of these vitamins leads to homocysteine accumulation, endothelial damage and atherosclerosis development, which is linked to CHD. Therefore, eskimos with a high intake of Vitamin B6 have low CHD.
Notes

1. \(\uparrow\) in the intracellular content
   - autophagy - ER \(\rightarrow\) autophagosomes
     - KFERG tags
     - ubiquitin-mediated

2. irreversible acetylation of COX enzymes
   - \(\downarrow\) PG and TX production
   - \(\downarrow\) synthesis of lipid mediators of inflammation

3. Leukotriene \& lipoxin synthesis is \(\uparrow\).
   - tips balance in favor of
     - \(\text{LTB}\)
     - \(\text{LTC}\)
     - \(\text{LTD}\)
     - \(\text{LTE}\)

4. fatty change \(\rightarrow\) ADH \& ALD produce NADH \(\downarrow\) biosynthesis
   - \(\uparrow\) lipoprotein
   - \(\uparrow\) FA from periphery

5. Centrilobular necrosis
   - location of highest P450 activity 2nd pathway produces ROSS
   - \(\uparrow\) treatment

6. Caseous necrosis
   - epithelial m\(\Phi\)
   - Langhan's giant cells
   - \(T\) cell collag

7. Type II HS
   - 1st preg. = sensitization \(\rightarrow\) IgG ab. against Rh Ag of the fetus
   - 2nd preg. = IgG cross placenta, bind to Rh Ag on fetal RBCs and
     lead to 2nd stage of phagocytosis \(\rightarrow\) release of Hb from RBCs leads
     to jaundice

8. \(\uparrow\) WBC \(\rightarrow\) predict \(\odot\) disease

   \(\uparrow\) similar to C-reactive protein

   looking for chronic inflammatory marker

   atherosclerosis is a chronic inf process of the intima of large elastic
   \& medium vessels b.v. \(\rightarrow\) high correlation of atherosome disease and
   acute plaque \(\rightarrow\) thrombosis, \(\odot\) disease