Bio 186 General Pathology
Midterm examination

March 18, 2002 1:00-3:00 PM

There are a total of 100 points for this examination. Please answer each question clearly and concisely ONLY IN THE SPACE PROVIDED. Note the points allotted to each question when planning your answer. This examination is designed to take 2 hours.

SECTION 1. Histopathology. This section is worth a total of 9 points.

1. One of your longterm HIV-infected patients comes into your office with difficulty breathing. A histologic section of a biopsy you ordered is shown in Figure 1 A and B.

   a. Describe the morphological changes shown in this section (including identification of the tissue.) (4 points)

      *this is lung tissue - Pneumocystis pneumonia (PCP)*
      We see that the alveoli are filled with "cotton candy" like material produced by the infecting organism.
      This fills up alveolar spaces and makes it difficult to breathe.
      Also, we see septal thickening from prolonged inflammation and fibrosis.

   b. What microorganism produces these types of changes? (1 point)

      *Pneumocystis - it is a protozoan infection. (Actually, it is a fungus.)*

2. Figure 2 A and B illustrates a histologic section of a heart from a patient with an infarct.

   a. Is this a recent or an old infarct? (2 points)

      *very recent*

   b. On what basis did you make this diagnosis? (2 points)

      In M1, loss of nuclei and hypereosinophilia happen within first 24 hrs. If this was later, we would see neutrophils/macrophages/fibroblasts - all of which are absent here.
SECTION 2. Multiple choice questions (24 points) There is only one answer for each question.

1. Histologic examination of an inflammatory lesion reveals a blood vessel engorged with red blood cells and neutrophils lining the vessel walls. What type of inflammatory response would this most likely be?
   A. Acute inflammation
   B. Chronic inflammation
   C. Granulomatous inflammation
   D. Type I hypersensitivity
   E. Type II hypersensitivity

2. The regulation of protein degradation is thought to be one of the key biochemical events in atrophy. Where in the cell are damaged proteins degraded?
   A. primary lysosomes
   B. secondary lysosomes
   C. proteosomes
   D. golgi
   E. residual bodies

3. A 20 year old woman comes to your family practice clinic with a butterfly rash on her face, weight loss, and fever. What anti-nuclear antibodies would most helpful in establishing a diagnosis?
   A. generic ANA
   B. anti-double-stranded DNA
   C. Anti DNA topoisomerase I
   D. Anticentromere
   E. Anti-nuclear RNP

4. Your 6 year old child has severe immunologically-mediated asthma that has been difficult to control. Which one of the following cytokines is the MOST POTENT inducer of bronchial smooth muscle contraction?
   A. histamine
   B. IL-4
   C. Platelet activating factor
   D. Leukotrienes C4, D4, E4
   E. TNF-α
5. An 18 year old college student is admitted to the hospital with headache, stiff neck, photophobia, and a fever of 103°, all suggestive of meningitis. Intensive antibiotic treatment is administered immediately. The cerebral spinal fluid is cloudy with a high number of neutrophils. Bacterial culture is positive for Neisseria meningitidis. What cytokine would you expect to be elevated in this student's blood?

A. IL-1
B. IL-2  →  promotes TH1  cells  to  activate  Macrophages  via  IL-12
C. IL-3
D. Transforming growth factor (TGF)-α
E. Platelet-derived growth factor (PDGF)

6. A kidney biopsy is performed on a 29 year old man to confirm a diagnosis of Goodpasture's syndrome. The kidney is affected in Goodpasture's syndrome because:

A. Podocytes are uniquely sensitive to cytotoxic T lymphocytes
B. DNA is deposited in the basement membranes of the kidneys
C. The endothelium of the kidney is fenestrated with diaphragms
D. Antibodies are produced against cell surface antigens on endothelial cells in the kidney
E. Antibodies are produced against cell surface antigens on podocytes

7. Fatty streaks are found in the intima in certain blood vessels. Which of the following statements about fatty streaks are NOT true?

A. They occur commonly in childhood
B. They may be precursor lesions to atherosclerotic plaques
C. They are composed of large numbers of neutrophils, fibrous cap, and intracellular lipid
D. They are found in the thoracic aorta in children
E. They tend to occur in both females and males

8. Hypertrophic cardiomyopathy involves thickening of the wall of the heart. What would you expect to find on microscopic examination of tissue from someone who died with this condition?

A. An increased number of cardiac muscle cells
B. Multiple nuclei in the cardiac muscle cells
C. No changes in cardiac muscle cells
D. An increase in the size of cardiac muscle cells
E. Altered differentiation of cardiac muscle cells

SECTION 3. Short answers. (52 points)

1. Approximately 5 hours after returning from a pleasant hike, you begin to itch and notice some red bumps on your arm. You become concerned that you walked through poison ivy without noticing it. How likely is it that the reaction you are having is due to poison ivy? Briefly explain your answer. (4 points)

This is probably not poison ivy. Poison ivy causes contact dermatitis — a delayed type hypersensitivity (type IV) reaction. In this type, cytotoxic T cells need to be activated or macrophages needed to be activated through TH1 cells. This process takes about 24 hrs to happen. In this case, an arthus reaction, a type III hypersensitivity is a possibility but it takes 4-8 hrs.
2. Cell death by apoptosis or necrosis can be distinguished in multiple ways. What DNA pattern would be shown on agarose gel electrophoresis if cell death was triggered by hormone withdrawal? What type of cell death causes this pattern? (3 points)

Hormone withdrawal causes apoptosis, not necrosis. Execution caspases activated by hormone withdrawal activate endonucleases which cleave DNA into very specific (180-200 bp) segments. Therefore, you would see a DNA ladder with a diffuse smear in apoptosis. In necrosis, you would see a DNA ladder because DNA falls apart in no particular pattern.

3. The histologic section shown below is from a keloid that formed following a skin wound. Describe the cellular changes that occurred during healing of this wound at the following time points and list ONE MAJOR growth factor or cytokine responsible for these events. (9 points)

First 24 hours: TGF-β, PGE, PDGF, and PDGF are released at this point. As soon as the injury occurs, blood fills the wound and clot when it comes into contact with air (scab). Coagulation cascade and platelets are activated to make clots. Neutrophils also enter the area.

3-7 days: Neutrophils are replaced by macrophages. Vascular permeability is increased. Endothelial cells and angiogenesis begins (mediated by VEGF, FGF).

2-4 weeks: Collagen returns tensile strength (TGF-β, PDGF). Collagen and extracellular matrix proteins are produced and collagen synthesis keeps happening without stopping. Excessive fibroblasts should mediate wound contraction.
4. An unidentified, homeless man who appeared to be in his early twenties was found dead in Providence. At autopsy, multiple soft, yellow lesions and cavities were found in his lungs. Staining of lung tissue reveals numerous acid fast bacilli. (8 points)

a. What is the most likely organism responsible for these lung lesions?

\[ \text{tuberculosis} \quad (\text{Mycobacterium tuberculosis}) \]

b. Describe the major morphologic features of lesions produced by this organism.

The lesion in the lung of this individual is a granuloma. These are typically TB-type IV hypersensitivity. In the center of the lesion, we see caseous necrosis (yellowish-white cheesy-looking masses of dead cells) - surrounded by live macrophages (epithelioid keratinocytes) and some multinucleated giant cells, and T-lymphocytes in the caseous rim.

c. What are the mechanisms by which these organisms produce lesions?

The bacteria taken up by APCs or macrophages present are surrounded by fibrosis antigen to a T-cell. IL-12 released by macrophages causes Th cell differentiation to Th1 cells. Th1 cells produce IFN-gamma (activates vascular permeability) & TNF-alpha (activates macrophages to differentiate in epithelioid keratinocytes). Vascular permeability allows macrophages to migrate into where the bacteria are & differentiate. Here they take up organisms.

However, killed macrophages release substances that prevent further replication. This is the case with nonviable bacteria. Surrounding is a wall of macrophages & T cells secreting substances needed to carry on inflammatory reactions.

5. Endothelial cells often determine whether a thrombus forms by affecting the local pro- or anti-thrombotic balance. Give two examples each of pro-thrombotic and anti-thrombotic properties of endothelial cells. (4 points)

a. Pro-thrombotic:

- Release tissue factor (TF) which activates extrinsic pathway and fibrin production to form 2nd clot.
- Release EPCR - tissue plasminogen activator inhibitor which inactivates

b. Anti-thrombotic:

- Produces thrombomodulin which activates protein C. Protein C in conjunction with protein S inactivates factor V & VIII in coagulation cascade.
- NO & PGI2 - are vasodilators & inhibit platelet aggregation.

6. Mitochondria are particularly vulnerable to ischemia. Briefly explain what is meant by the mitochondrial permeability transition. (3 points)

Mitochondrial membranes are normally very selective with the substances they let in and out of their membranes. This is because they have to maintain the H+ concentration (the proton motive force) in order to pump the ATP synthesis protein. In ischemia, mitochondrial permeability transition happens where outer loose their ability to keep up in the interspace - mitochondrial membrane space. The membrane break up free and release cytochrome C, calcium, which could cause...
7. A 15-year old woman presented with nausea and severe chest pain that radiated down her left arm. She was found to have changes on EKG consistent with an acute myocardial infarction, and was treated with thrombolytic therapy. Upon questioning, it was revealed that her father died at age 50 of a heart attack, and her mother has hypercholesterolemia. She has no siblings, but has several aunts and uncles on both sides with histories of "heart attacks" before age 50. What is your tentative diagnosis? What is the MOST LIKELY cause of this woman's condition? How would you confirm your tentative diagnosis? What would you expect to find? (4 points)

**Diagnosis:** Myocardial Infarct

**Possible Causes:**
- Acute plaque change in the vessel's cap that ruptured and initiated thrombosis.
- The thrombus might have completely occluded the vessel and caused ischemia to certain parts of the heart. With mom w/ hypercholesterolemia, she might be at least heterozygotic for low LDL Receptors, which means she has more atherosclerotic plaques than other 15-yr olds.

**Diagnosing:**
- CK-MB levels would peak 4-8 hrs later (disappear ~18 days).
- LDH levels would peak 3 days later.
- Troponin T would peak 2-4 hrs later, but stay elevated for 7 days.

8. Control of the host immune response to transplanted organs, such as kidneys, requires administration of potent immunosuppressive drugs. What antigen on donor tissue are recognized by cells of the immune system? What are the major cell types involved? (3 points)

- MHC I and II are very specific - they differ from person to person.
- Host cell recognizes foreign MHCs and tries to kill them.

9. Why is the reticuloendothelial system important in protection from immune complex disease? (3 points)

Some immune complex diseases are caused by deposition of antigen-antibody complexes in tissues where they do not belong - b/w kidney, heart, joints etc. The mononuclear phagocytic system is in charge of degrading these complexes and prevent them from activating complement & causing tissue damage.
A 17-year-old high school student indulged in a week of binge drinking to celebrate his graduation. He drove a motorcycle without wearing a helmet, crashed, and suffered severe head injury. He carried an organ donation card. After 24 hours in a deep coma, he was pronounced dead and a transplant team harvested his liver for transplantation. The pathologist is called to the operating room to review a needle biopsy of the donor liver. A histologic section of the biopsy is shown below. (11 points)

a. What is your diagnosis?
   
   fatty liver (steatosis)  

b. Would you recommend that this liver be transplanted? Why or why not?
   
   Yes - fatty change in liver is reversible, fatty change has no inflammatory response associated with it. Also it weighs no tissue is damaged.

c. If the donor had been a 55 year old man with a chronic drinking habit for 30 years, what additional changes would you expect to see in his needle biopsy?
   
   You could see alcoholic hepatitis where there would be fatty change and rare necrosis within the lobule. Intrahepatic bile duct fibrosis may also be present.

   Cirrhosis is also a possibility - here there is extensive damage and nodular fibrosis between portal areas.

   d. Would you recommend that the older man's liver be transplanted? Why or why not?
   
   Possible areas
   
   No. The cirrhosis and alcoholic hepatitis both have some inflammatory response associated & subsequent tissue damage. He has probably hyperactivated his P4502E1 w/ excessive drinking over the years. the recipient of liver could die from acetaminophen or other drug toxicity if they receive a liver with P4502E1. All the alcohol production from breakdown of EtOH is also toxic to liver because it breaks down structural proteins.
SECTION 4. Essay question (15 points) Answer ONLY in the space provided.

For many years the theory that high cholesterol was THE major risk factor for atherosclerosis dominated in biomedicine. Recently, the view that high homocysteine levels may be important has gained some acceptance. Outline the main elements of the homocystine and the cholesterol theories of atherosclerosis, including proposed mechanisms and prevention strategies. How would proponents of each theory explain that the death rates from atherosclerosis have decreased?

**Cholesterol** theory says that high levels of cholesterol in the diet or increased de novo synthesis of cholesterol due to lack of regulation of HMGCoA reductase cause high levels of circulating LDLs. LDLs are apolipoproteins that transport cholesterol around the body. Sometimes, these LDL's get oxidized. In this case scavenger receptors on macrophages take up the oxidized LDLs and become foam cells. This process happens in the intimal layer of large to medium sized muscular arteries.

They prove the theory by suggesting that people who are homozygous for familial hypercholesterolemia have larger number of atherosclerotic plaques than those who are heterozygotes. Lower cholesterol diets and drugs that lower circulating cholesterol levels would be recommended treatments in this case. They would point to eskerinos, who eat large amounts of omega-3 acids in their diet, which increases HDL & lowers LDLs as the model. They would explain lowered death rates by saying that we have switched to lower cholesterol diets and exercise more often.

**Homocysteine** theory would say that homocysteine is an amino acid that is formed from methionine. Homocysteine helps the oxidation process of LDLs and therefore their uptake by macrophages. The foam cells formed would go on to form the core of the atheromatous plaque. Deficiency in vitamin B6 would prevent conversion of homocysteine to cysteine & deficiency in B12 & folate acid would prevent its conversion to methionine. They attribute atherosclerosis to high levels of homocysteine. They argued that high protein intake, deficiencies in vit B6, B12 & folate acid would help prevent atherosclerosis. They would say eating unprocessed foods, low protein diet & supplements of B6, B12 & folate acid are important in preventing atherosclerosis. They suggest that this is true because women (usually white pregnant) get these supplements and have fewer plaques. They explain lowered death rates by suggesting that we are getting the vitamins we need to process homocysteine. In the case of the eskimos, fish contains B6 & B12 & therefore they lower risk for atherosclerosis despite high fat diet.

And discussion overall

1. Familial hypercholesterolemia is an inherited disease where HMGCoA reductase is not downregulated by circulating cholesterol. This means LDL-CoA reductase is not downregulated by circulating cholesterol & produced more cholesterol.