Bio 186 General Pathology
Midterm examination

March 19, 2001  1:00-4:00 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 1 1/2 - 2 hours.

Section 1. Histopathology. This section is worth a total of 24 points.

1. Describe the morphological changes illustrated in Figure 1 A,B, including identification of the organ. What agent that you have studied in this course produces this type of change? How does this agent produce such alterations? (5 points)

This is the kidney. The glomeruli look intact, but the tubules look necrotic (have no nuclei) and are very eosinophilic and swollen (you can barely see the lumen in some of them). There are also some acute inflammatory cells (neutrophils) present in the interstitium. This could be due to mercury poisoning which damages the Na/K ATPase pump in the PCT, causing acute tubular necrosis.

2. Figure 2 A,B illustrates an H&E stained section of a liver from a 40-year-old man. Describe the morphologic features of the liver in this section? Are these changes reversible or irreversible? What are the mechanisms by which these changes are produced? (6 points)

There is evidence of fatty change, the hepatocytes look swollen and have eosinophilic inclusion (Maltese crosses), and there is a some fibrosis around the central vein. Some of hepatocytes seem to be missing-their nuclei which is a sign of necrosis and there are acute inflammatory cells (neutrophils), but it also looks like there is a macrophage. This slide looks like alcoholic hepatitis which is a reversible condition if the patient stops drinking (but the fibrosis that has occurred is irreversible). The fatty change is caused by many factors: (1) since the patient is consuming too much alcohol and is malnourished, there is increased peripheral metabolism of fats, and decreased protein synthesis causes less apoproteins to be made so fats cannot be packaged into lipoproteins and transported, the decreased protein synthesis also causes less EST to be made== causing more free radicals to induce damage to lipids, but proteins. (2) The alcohol metabolized to acetaldheyde and then to acetic acid producing NADH which shif the fat metabolism -towards synthesis of fats== causing fatty change. With an alcohol consumption, excess pyruvate metabolism of alcohol is induced causing more free radicals damage which is worsened when intake of alcohol-like acetaldheyde-cause protein crosslinking.
3. The H & E stained section in Figure 3 A,B is from a 40 year old woman. Describe the morphology of this lesion. Briefly explain what you think could have caused this lesion and the basis on which you have made this determination. (4 points)

This looks like it could be a papillomatous lesion, due to TBC due to tuberculous TBC A close-up of a granuloma, causing salpingitis. TB B looks like it is a close-up of a granuloma due to the presence of a mycobacterial giant cell, foreign body giant cells, necrosis and caseation of the normal architecture of the organ. These are usually immunological. The macrophages are called to due to the tuberculous granuloma. The mycobacterial ulceration of a granuloma cannot be contained because due to TBC or immunosuppression, it can spread to other organs such as the salpingitis that it caused. The mycobacterial giant cells have a waxy coat and cannot be killed by neutrophils. They inhibit the formation of the granulomas so macrophages can adhere to the tissue. These macrophages are found in the tissues producing TH cells producing TFN-beta, so the macrophages become epithelial cells (pink cells with intracytoplasmic nuclei, histiocytes, etc.) and epithelial cells can fuse to form multinucleated giant cells. The macrophages cause tissue damage due to the cell death of epithelial cells, and therefore we see the loss of normal tissue architecture. The macrophages also react to help in phagocytosis and collagen to contain the macrophage and wall off the granuloma.

4. The section illustrated in Figure 4 A,B is from a patient who had a myocardial infarction. Based on the most salient morphological features in this section, how long ago do you think this patient had the MI? Explain your answer and indicate what you would expect to see on gross examination of this heart. Would the TTC assay be useful? Why or why not? (7 points)

This section shows the presence of acute inflammatory cells (lots of neutrophils), between the myocardial cells. The myocytes are necrotic because they have no nuclei, are missing cross-striations and are eosinophilic. They also appear wavier than normal. This patient probably had the MI a few days ago (2-3 days) because it takes a few days before neutrophils arrive after inflammatory cells arrive. Also necrosis is not visible in section immediately after the MI (MI w/ MI) and it takes about 1-2 days after to see loss of nuclei. On gross exam, at 2-3 days after the MI, this area would have a yellow tan center due to the breakdown of the RRQ hemoglobin. A hyperemic ring would probably not be apparent. This appears red around the infarcted area at days 3-7 due to the increase in granulation tissue (angiogenesis) surrounding the area.

The TTC would not be useful at this point because we already have evidence of necrosis and inflammation. TTC is used early on (like 2-3 hrs. after infarct) because at this early stage (12 hrs) there is no gross evidence of MI and most of the evidence before 4 hrs. can only seen with the (mitochondria swelling densities in mitochondria, etc.)

TTC stains the tissue red and leaves the infarcted area white because it stains for cardiac enzymes (CK-IDH). So a few hrs after the damage the myocytes in the infarcted area have less enough cardiac enzymes (due to necrosis) damage of cell membranes that TTC will not stain them. However in this section, which is from a later stage, TTC is less useful than at an earlier stage because there are other signs of damage to the area (histological and grossly!)
Section 2. Short answers. This section is worth a total of 40 points.

1. A three year old girl is brought to your office by her parents with jaundice, vomiting, and drowsiness. In taking her history, you find out that the parents have just bought a dry cleaning store. What do you think might have caused the child’s illness? Briefly describe the mechanisms by which her clinical symptoms could be produced? What possible reason(s) might account for the fact that this child, but not her sister, is affected? (7 points)

   This child’s illness could be due to cyanide poisoning present in many dry cleaning agents. Cyanide is metabolized by the liver’s cytochrome P450 in the SER, which is especially present in the hepatocytes around the central vein. The SER is broken down and released into the blood, which is a free radical that causes damage to the SER and membranes. The cells in the SER cause it to dilate and cause lipid peroxidation, which propagates to the RER. This disrupts the normal cells of the RER and damages the RER membrane so severe is decreased protein synthesis, disordered synthesis, and fat injury in the hepatocytes. The lipid peroxides can also damage the cell membrane and nucleic acids, leading to necrosis. If the damage is severe enough, CO2 will increase in the cell due to damage of mitochondria and damage of SER, and store CO2 and damage to the cell membrane. The necrosis of hepatocytes can cause her to have liver failure causing the patient’s jaundice. Jaundice is caused by many things, including inflammation cells, and therefore she will have an inflammatory disease. It could cause her to be more sleepy. The systemic effects of cyanide can also affect her central nervous system (making her more sleepy) and induce vomiting. One reason that she might not be affected is that she might have been known to play with dry cleaning agents or been exposed to cyanide in another way. (The sister might have been known to play with dry cleaning agents or been exposed to cyanide in another way.)

2. Apoptosis and necrosis represent irreversible alterations of cells. These two distinct processes of cell death can be distinguished by light and electron microscopy and biochemically. What are the main ultrastructural features of apoptosis? (4 points)

   In apoptosis, only a cell is affected at a time and it does not cause inflammation (unlike necrosis). An apoptotic cell will shrivel, appear more eosinophilic, and produce apoptotic bodies (blebbing). The chromatin is clumped, condensed, and appears pyknotic. Chromatin crescents (in end) also become more eosinophilic if one can see DNA. An apoptotic cell can be identified by its characteristic DNA ladder. In apoptosis, the caspase cascade is activated causing proteases and endonucleases to be activated, and thereby the cytoskeleton and DNA are damaged. Transglutaminases cause cross-linking of proteins, further damaging the cytoskeleton. So, if blebbing, the nuclear membrane is broken down (due to break of oligosaccharides) but no caspase effectors.
3. Reduced glutathione (GSH) is a major cellular defense mechanism. How does selenium deficiency lead to depletion of GSH? (3 points)

Selenium is needed as a cofactor for GSH reductase which makes GSSG into GSH. So if there is no selenium, you can’t recycle GSSG back to GSH, and deplete your stores of GSH.

4. Phagocytic cells have evolved 

- Two mechanisms by which bacteria evade killing by phagocytic cells? You do not need to describe the mechanisms. (4 points)
  1. Bacteria can develop a waxy coat (like T5) and prevent the fusion of the phagosome and lysosome.
  2. Bacteria also can make catalase which breaks down 
  H2O2 and therefore are less likely to be killed by free radicals.

5. Clinical consequences of atherosclerosis are often triggered by “acute plaque change” (for example, rupture or development of a fissure in the fibrous cap.) Why might this process induce thrombosis? (5 points)

Thrombosis is induced by endothelial injury, stasis or turbulence, or hypercoagulability. These are two things that can result from acute plaques change. Acute plaque change due to a rupture can expose the collagen in the subendothelial layer causing platelets to stick and the endothelium is injured when it is ruptured causing pro-platelet and pro-coagulation factors (tissue factor) to be made/exposed.

The acute plaque change can also change the flow of blood in the blood vessel making it easier for platelets to adhere forming a thrombus. The development of a fissure could cause hemorrhage into the blood vessel which could then clot.

6. What role does the endothelium play in the fibrinolytic process? How could this be important in determining whether a thrombus develops at a local site? (5 points)

The endothelium makes fibrinolytic agents such as TPA which cause Plasminogen to go to Plasmin which then can break down fibrin. If the endothelium next to an injured area is functionally poor it can control the formation of a thrombus or at least help break it down when it starts to encroach into the uninjured endothelium. However, endothelium can also make Plasminogen activator inhibitors which would favor thrombus formation, therefore it is the balance of these 2 factors (TPA + its inhibitors) that determine whether a thrombus develops.
7. In the Nurses Health Study, a 35-40% decrease in the incidence of MI after a 4-8 year follow-up period was seen in subjects who had the highest quintile of Vitamin E intake. How might you explain the benefit of Vitamin E in this study based on what is known about OXIDATION OF LDL? (5 points)

Vitamin E is an antioxidant and therefore could prevent or reduce the formation of atherosclerotic plaques. Oxidized LDL is produced when the LDL in the circulation gets into the intima (due to vascular permeability) and then the macrophages in the intima release ROS which oxidize the LDL. The oxidized LDL gets taken up by macrophages via the scavenger receptor pathway (also taken up by smooth muscle cells) and form foam cells which are characteristic in atherosclerotic plaques. Oxidized LDL also cause macrophages to migrate (chemotactically) and then immobilize them in the intima causing further plaque formation and necrosis. The oxidized LDL also is cytotoxic to endothelial cells and smooth muscle cells. The endothelial damage can cause thrombosis in a coronary artery leading to MI. The more macrophages, the bigger the necrotic core, thinner the fibrous cap, the more likely the plaque will become unstable and cause thrombus, embolus, etc. causing MI if damage or occlusion occurs. A 45-year-old man comes to your clinic with symptoms of glomerulonephritis and pneumonia. You suspect he might have Goodpasture’s syndrome. One of the triggers that is hypothesized to lead to this disease is exposure to viruses. How would you explain to your patient what you think is happening? (This question assumes that your patient is an intelligent human being. In other words, don’t talk down to your patient.) (7 points)

Exposure to a viral antigen could cause his immune system to make antibodies against those viral antigens. (Ag is presented via an APC to a CD4 T cell which differentiates into a Th2 cell causing B cells to make Ab). Those Abs which were trying to help the patient fight the virus also to unfortunately bind to collagen IV in the basement membrane of the patient’s kidney glomeruli and in the alveoli. This could cause Goodpasture’s syndrome. The Ab deposited into BM of his kidney glomeruli and his lung are probably IgG or IgM complex with the Ag in his BM (part of collagen IV) which is similar to the viral Ag. This Ab:Ag complex triggers the activation of complement (classical pathway) causing the formation of the MAC which can cause lysis of cells & tissue damage (Ab helps opsonize the immune complexes & CSA causes chemotaxis of neutrophils, adhesion of neutrophils to endothelial & histamine release from mast cells causing vasodilation & vascular permeability which & neutrophil migration & diapedesis). CSA also can cause arachidonic acid metabolism (PGE2, PGI2, PGE2, PII2, TXA2), which increase vasodilation and mediate inflammation. The neutrophils which arrived at this site then try to phagocytose the immune complexes and in doing so produce lysosomes and ROS which cause tissue damage.

Treat? Testing?
Section 3. Multiple Choice Questions: Each question is worth 3 points, for a total of 24 points.

1. Plasma-derived proteins are important mediators of inflammation. What is one important effect of bradykinin?
   A. trigger the clotting cascade
   B. fibrinolysis
   C. pain
   D. platelet aggregation
   E. activate complement
   [C]

2. Hepatitis B (HBV) is an intracellular virus that infects liver cells, sometimes triggering a persistent, non-lytic infection. What are the dominant histological features of HBV infection in the liver?
   A. centrilobular necrosis
   B. neutrophil infiltration of the portal triad
   C. lymphocytic infiltration of the portal triad
   D. lymphocytic infiltration around the central vein
   E. germinal centers in the portal triad
   [B][C]

A. Hashimoto’s thyroiditis is an autoimmune disease with a higher incidence in women than in men. Based on what you have learned about the mechanisms of this disease, monoclonal antibodies directed against which of the following molecules might have the BEST potential to relieve symptoms?
   A. Pro-Caspase 8
   B. IL-1
   C. Fibronectin
   D. Platelet activating factor
   E. C3a
   [B]

4. In immediate hypersensitivity reactions, a complex mixture of mediators are released from mast cells after antigen exposure. One important mediator, TNF-α, is present in mast cell granules. The primary function of TNF-α IN THIS CONTEXT is to:
   A. degrade the basement membrane of blood vessels
   B. increase mucous secretion
   C. promote vasodilatation
   D. trigger smooth muscle contraction
   E. upregulate adhesion molecules
   [C]
5. You have had annoying ragweed allergies for years and would very much like to find something to manage them. Based on what you know about the mechanisms of allergy, what of the available options make the MOST sense?

A. inhibit mediator release from neutrophils  
B. take corticosteroids  
C. inhibit mediator release from mast cells  
D. take aspirin  
E. reduce antigen exposure

6. Myasthenia gravis is an autoimmune disease. What evidence for the involvement of autoantibodies do you find MOST convincing?

A. Immunofluorescent staining of IgG at the neural synapse  
B. infants born to mothers with MG have disease which disappears around 6 months of age  
C. immunofluorescent staining of complement at the neural synapse  
D. the presence of other autoimmune diseases in patients with MG  
E. the presence of autoantibodies in the serum

7. A 45 year old man comes in with swelling, redness, and pain in the left leg, extending from the calf to the mid-thigh. He has no prior history of similar problems. His history is significant for a long airplane trip from Australia to the US, with his arrival in the US yesterday. After acute treatment with the blood thinner “heparin,” this patient will be treated as an outpatient with the anti-coagulant warfarin (coumadin) for six months. What is the mechanism for action of warfarin?

A. warfarin irreversibly acylates platelet cyclooxygenase  
B. warfarin inhibits the activation of Factor XIIa  
C. warfarin interferes with the reduction of Vitamin K epoxide to Vitamin K  
D. warfarin binds to Protein C  
E. warfarin inhibits secretion of growth factors by endothelial cells

8. A young man presents to the emergency room with clinical findings consistent with hypertrophic cardiomyopathy. Which of the following genes is MOST COMMONLY altered in this condition?

A. the LDL receptor  
B. Factor VIII  
C. Cytochrome c oxidase  
D. β-cardiac myosin heavy chain  
E. myosin-binding protein C
Section 4. Essay Questions (12 points) ANSWER ONLY IN THE SPACE PROVIDED

Sarah is a four year old who is recovering from appendicitis. Her parents are concerned that she has a low-grade fever, cough, and swollen lymph nodes; her surgical incision has not yet healed completely, although it is six weeks since her surgery. Her peripheral white blood cell count is elevated and her serum immunoglobulin levels are within normal limits. She does not attend day care. She had chickenpox that resolved quickly; however, she has suffered from repeated ear and sinus infections that required intensive antibiotic therapy.

What questions does this history raise for you? What do you think is the cause of the recurrent infections in this child? What would you ask the child’s parents that might help you determine the cause? How would you go about making a diagnosis? (Be specific in your discussion of pathogenesis.) Would other possible problems could she have with her neutrophils? (Phagocytosis)

This history raises questions about her ability to fight off bacterial infections. I am curious as to why she is getting recurrent bacterial infections and why she cannot heal a wound. By six weeks she should have a pretty well formed scar. I think this patient might have chronic granulomatous disease, where her NAPPH oxidase is mutated so she cannot kill bacteria via an ionic dependent manner. This is a X-linked recessive disease that cause a mutation in NAPPH oxidase so that O2 cannot be converted to O2- if superoxide cannot be made then H2O2 is made which is converted to OH- via the fonten reaction or to OCl- (which in macrophages). Therefore her innate immune system is defective. 

I would ask the parents for a complete family history (DC disease is genetic does one about or look carefully at her surgical wound to see what stage in healing it was at or to see if it was infected, preventing the healing, since healing requires inflammatory cells, it is not surprising that this could be impacted as well)

In order to make the diagnosis I would take a wound biopsy of her swollen lymph node and look for the presence of granulomas. Since her neutrophils can’t kill the bacteria, APCs present Ag to T cells in the node which differentiate into Th1 cells (secreting IFN-γ) which activate macrophages to kill the bacteria. The active macrophages form epithelial cells which fuse and form giant cells. They are surrounded by the lymphocytes in the periphery. I could also order diagnostic tests to analyze her NAPPH oxidase and determine if she has a mutation in the proteins (e.g., using a Western blot) or her DNA can be analyzed to see if there any mutations on her X chromosome. The only thing in this case is that complicated times is that CGD usually affects boys (e.g., X-linked) so it is very rare in girls.