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

**SECTION 1. HISTOPATHOLOGY (14 points)**

1. A 50 year-old high school teacher comes to the emergency room with cough and blood in his sputum. You order a variety of tests, including an X-ray and additional sputum samples. The X-ray reveals a small focus of consolidation in the apex of the lungs. The histopathology of the biopsy specimen is shown in Figures 1A, B, and C. (4 points)

   What is your diagnosis?  
   **Tuberculosis**

   How would you confirm the diagnosis?  
   culture for mycobacteria
   stain for acid-fast bacilli

   Briefly describe the histopathology of this lesion.
   This is a typical granulomatous lesion showing Langhans giant cells as well as epithelioid cells characteristic of a granuloma. There is also a dense infiltrate of lymphocytes. If a large view were available, the lesion would probably appear nodular. In Figure 1C a band of fibroblast appears at the outer lymphocytes periphery.

2. A 40 year old worker at a local factory where they manufacture mercury-containing instruments comes to your occupational health clinic with a history of exposure to high levels of mercury (mercuric chloride) after a spill. He is quite sick with muscle tremors, loss of appetite, and weakness. You order biopsies of several organs, one of which is shown in Figures 2A and 2B. (4 points)

   What organ is this?  
   **Kidney**

   Describe what you see histologically.
   While glomeruli are fairly well preserved there are many necrotic (anucleated + eosinophilic) tubules. It must be very recent necrosis because few inflammatory cells are present.
3. Figures 3A and 3B show a biopsy of the liver from a 60 year old worker in a dry cleaning plant. (6 points)
How would you diagnose the changes seen in this liver section? **Fatty Change**

What agent MOST LIKELY caused these changes in this woman? **CCl4**

(Though there is eosinophilia around portal tracts - not the place we'd expect the most damage)

Describe the mechanisms by which these histological changes are produced.

Fatty liver develops due to oxidative damage to hepatocytes via the cytochrome P450 enzyme in the smooth ER. **CCl4** → **CCL3**

This produces two major product from the P450 and releases a highly reactive free radical. Both are capable of lipid peroxidation which can disrupt the SER and subsequently (via malondialdehyde) spread to and damage lipid membranes such as the nearby rough ER. This will cause ribosomes to detach and protein synthesis will halt. The apoproteins necessary to export fat from the liver will not be made and fat will accumulate inside the hepatocytes.

SECTION 2. MULTIPLE CHOICE (2.5 points each, total of 27.5 points)

1. A 75 year old woman has a major stroke. After intensive therapy, she is released to a rehabilitation center where she dies 3 weeks later. Her family requested an autopsy to determine the cause of death. What would you expect to see in her brain?

   A. Coagulative necrosis
   B. Liquefactive necrosis
   C. Hyperplasia
   D. Acute inflammation
   E. Granulomatous inflammation

2. Reactive oxygen species are generated in a variety of ways, including ionizing radiation and normal metabolic processes. Which of the following enzymes is important in protecting cells from oxidant injury?

   A. Caspase
   B. Superoxide dismutase
   C. DNase
   D. NADPH oxidase
   E. Cytochrome P450
3. Von Willebrand Factor is synthesized by endothelial cells and functions as a carrier for Factor VIII. It is critical in hemostasis. A defect in this factor could affect which of the following processes?

A. Vascular constriction
B. Fibrinolysis
C. The release of mediators from platelets
D. Platelet adhesion
E. Platelet aggregation

4. A 25 year old cross-country runner tore his anterior cruciate ligament while running. The only option open to him was to have arthroscopic surgery, which involved small slits in the skin. Healing was uncomplicated. What would you expect to see histologically in the skin wound **24 hours** after surgery?

A. Granulation tissue **3-7 days**
B. A dense meshwork of Type I collagen **2 weeks**
C. An influx of neutrophils
D. Abundant angiogenesis **3-7 days**
E. Extensive fibroblast proliferation

5. A 45 year old man is brought to the emergency room after ingesting a bottle of acetaminophen (200 500 mg capsules). Despite administration of antioxidants, he expired 24 hours after admission. Biopsy of his liver would MOST LIKELY reveal which of the following changes?

A. Coagulative necrosis around the central vein
B. Coagulative necrosis around the portal vein
C. Thrombosis involving the hepatic artery
D. Caseous necrosis around the central vein
E. Caseous necrosis around the portal vein

6. You are an infectious disease specialist who has been called in to consult on a young patient with recurrent streptococcus infection. His mother also suffered from recurrent infections since early childhood. A thorough genetic workup revealed deficiency in **NADPH oxidase** in both mother and child. Based on this deficiency, what component of inflammation is compromised?

A. Formation of the membrane attack complex
B. Immune complex formation
C. Engulfment of bacteria
D. Chemotaxis
E. Killing of bacteria
7. A 20 year old woman presents with drooping eyelids and an enlarged thymus. You remember hearing about a syndrome like this in General Pathology and immediately suspect that this young woman has Myasthenia Gravis. You decide to look for the presence of autoantibodies. What type of autoantibodies might you find?

A. Antibodies against nuclear antigens  
B. Antibodies against the thyroid stimulating hormone receptor  
C. Antibodies against the acetylcholine receptor  
D. Antibodies against type IV collagen  
E. Antibodies against red blood cell antigens

8. The death rate from atherosclerosis in the U.S. is one of the highest in the world. In part, this is due to the ubiquity of risk factors among residents of the U.S. Which of the following is NOT a risk factor for atherosclerosis?

A. Hyperlipidemia  
B. Carbon tetrachloride  
C. Hypertension  
D. Smoking  
E. Diabetes

9. Hypersensitivity reactions vary in the cells and mediators involved. Which of the following diseases does NOT involve complement?

A. Hay fever  
B. Systemic lupus erythematosus  
C. Erythroblastosis fetalis  
D. The Arthus reaction  
E. Transfusion reactions

10. A young man with a deficiency in Factor XII comes in for surgery. At first you are concerned that he will experience bleeding problems. But then you recall the specifics of the coagulation pathway. Why does this deficiency NOT lead to bleeding disorders?

A. Factor X activates the extrinsic pathway  
B. Factor XII is most important in the complement system  
C. Tissue Factor-Factor VIIa activates Factor X  
D. Tissue Factor-Factor VIIa activates Factor IX  
E. This is not understood

11. A 6 year old woman undergoes a routine cholesterol test. Her cholesterol levels are elevated 5-6 times above normal. Which of the following MOST LIKELY accounts for these abnormal findings?
SECTION 4. SHORT ANSWERS (58.5 points)

1. A child born in Times Beach, MO, a town that was ultimately shut down because of extensive contamination with dioxin, played in her yard and ate dioxin-contaminated dirt. A biopsy of her thymus showed phagocytic cells engulfing small pieces of cells and cells with fragmented chromatin. DNA analysis of the tissue revealed cleavage of the DNA with a regular pattern. (4 points)

What type of cell death would best describe this process? **Apoptosis**

What is a critical enzyme that regulates this process?
- **Caspases** → caspase 8 → caspases 3, 6, 7

2. For most patients who suffer from asthma, asthma is a chronic disease because the triggers tend to be widespread in the environment. Based on what you have learned about the mechanisms of asthma, what do you think would be a particularly effective therapy to deal with the Chronicity of this disease? Briefly explain why you think this approach would be most effective. (5 points)

Asthma is a type I hypersensitivity reaction involving IgE and degranulation of mast cells. While the late phase of the reaction causes the most tissue damage and is the most important to treat symptomatically, if there was a way to halt the reaction from beginning in the first place it would address the development of the reaction to as many triggers as one could bind and remove IgE molecules esp those specific to a person's allergens while inducing plasma cells to class 2 to 3. More importantly, if there were a way to halt the response to new allergens, then the reaction might be less of a chronic problem.

3. What are the two most prevalent sites of severe atherosclerosis? (2 points)

- Abdominal aorta
- Coronary arteries (proximal)
4. Endothelial cells produce a variety of anticoagulant factors, one of which is heparin sulfate. How does heparin sulfate influence blood coagulation? (3 points)

Heparin sulfate binds ATIII which is an anti-coagulant factor.

5. Many of the mediators of the inflammatory response circulate in the blood as inactive precursors. When activated, they tend to act quickly and have a short half-life. (3 points)

What molecule is the link between the kinin cascade and the fibrinolytic system?

Kallikrein

What are two functions of this molecule?
- cleaves HMWK to become Bradykinin
- cleaves Plasminogen to Plasmin

6. You attended a large banquet at the local school on honors night last May at which stuffed chicken was served. About 24 hours later many of the students and their parents became sick with abdominal pain, diarrhea, nausea, and fever. The health department was called in because food poisoning was suspected. The diagnosis was salmonella infection. (5 points)

How does the lipopolysaccharide (LPS) surface on this organism help it escape the immune response?

The LPS surface helps the bacteria evade complement activation. It can do this by making long chain LPS that doesn't become hypercoagulable, allowing MAC to get over the cell or by having sialic acid residues attached. Simply a very thick coat will keep complement from killing as well. Briefly describe how LPS induces fever.

LPS induces macrophages to produce TNFα/IL-1. TNFα/IL-1 act on hypothalamus to induce local production of prostaglandins (PGs) which act on the vasomotor center to direct blood flow centrally and away from periphery. Peripheral vasoconstriction causes decreased heat dissipation and therefore increased temperature.

7. One of your long term cardiac patients needs to have coronary bypass surgery. For many years, he had taken aspirin as a preventive measure for heart disease. In your pre-op
discussions, you direct him to stop taking aspirin at least 7-10 days before surgery. Why is this important? (3 points)

Aspirin halts the effectiveness of platelets for the platelet’s lifetime by interrupting the cyclooxygenase aim of the arachidonic acid cascade in platelets. It will be important for him to have functional platelets by the time of the surgery—so that he can heal from the surgical wounds.

8. For each of the following mediators, indicate a) the main cell type in which it is synthesized or from which it is released and b) one important function. (These mediators might be produced by more than one cell type; 10 points)

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Cell type(s)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>platelets</td>
<td>↑vascular permeability</td>
</tr>
<tr>
<td>Thromboxane A2</td>
<td>platelets</td>
<td>vasoconstriction</td>
</tr>
<tr>
<td>Eotaxin</td>
<td>mast cells</td>
<td>chemotactic for eosinophils</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>endothelial cells</td>
<td>vasodilation</td>
</tr>
<tr>
<td>Major basic protein</td>
<td>eosinophils</td>
<td>killing parasites</td>
</tr>
</tbody>
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9. For many years, the dominant view was that excess cholesterol caused atherosclerosis. More recently, scientists have suggested that the etiology of atherosclerosis is more complex and that homocysteine might be involved. What are the implications of each theory for prevention of atherosclerosis? In 1-2 sentences, explain the rationale for each. (5 points)

Homocysteine theory: If true, atherosclerosis results from protein intoxication (and all those folks on Atkins will be the real winners!) without the necessary co-factors for protein metabolism (B6, B12, folate). Atherosclerosis could be prevented by decreasing animal protein and taking B6, B12, and folate supplements.

Cholesterol theory: If true, high LDL levels and low HDL levels are responsible and could be prevented with a diet that lowers LDL and raises HDL as well as medication to slow LDL uptake as well as cholesterol synthesis. (Statins)

10. You have decided to take a 6-mile hike on Martha’s Vineyard. After 4 miles you encounter a patch of poison ivy on the trail that is 4 feet high. You have no choice but to walk through it, even though you have had unpleasant encounters with poison ivy in the past. (5 points)

How long will it take you to know whether you will have a hypersensitivity response to the poison ivy?

1 to 2 days.
Give a brief *mechanistic* explanation to account for this time frame. (No more than 2-3 sentences.)

The hapten from poison ivy will bind to skin proteins and trigger pre-sensitized memory T cells to induce a cytotoxic response. This will take longer than 24 hours because CTLs must be recruited to the site.

11. A 50 year old man comes to your office complaining of weakness. You note that he has muscle wasting and ascites and ultimately diagnose him with alcoholic cirrhosis. (5 points)

Are these changes reversible or irreversible? **irreversible**

(A) Briefly explain your answer, drawing on your knowledge of the cell types involved in this process (not the details of alcohol metabolism!)

While hepatocytes do have regenerative capacities in this case they will not grow back with the proper architecture because of the centrilobular damage done earlier. (Centrilobular hepatocytes have stronger p-450 activity and thus are damaged the most.) Fibrosis also occurs, perhaps due to HSC cells found in spaces of Disse, turning into fibroblasts.

12. A 50 year old woman comes to the emergency room, complaining of chest pain and nausea. What blood enzymes (discussed in class) would you test for in order to determine if she had a myocardial infarction? What enzyme(s) would be elevated at 12 hours? (3 points)

Creatine Kinase MB & Troponin I will be elevated at 4-8 hours and peak at 18 hours. So they would be present.

13. Selectins play critical roles in the inflammatory response. What effect(s) might a mutation in the P-selectin gene have on the inflammatory response to bacterial infection? (2.5 points)

Selectins are important for the margination and rolling of leukocytes along the endothelium. A mutation would result in failure to get inflammatory cells out of vessels and into the tissues where they need to work.

Why are macrophages important in the development of atherosclerotic plaques? (3 points)

Macrophages take up oxidized LDL via scavenger receptors and are responsible (with smooth muscle cells) for the trapping of cholesterol in plaques. (Though there is extracellular cholesterol as well) They are responsible for the necrotic lipid core.

Additionally, MΦ are very important in determining whether or not the plaque will be problematic later on.