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 1/2 - 2 hours. Good luck!

Section 1. Histopathology (16 points).

1. **Figure 1 (A and B)** illustrates a hematoxylin- and eosin-stained section from a patient who had a myocardial infarction. Describe the morphology of this lesion. How long ago did the patient have the **myocardial infarction**? On what basis can you make this judgment? (5 points)

   This slide shows eosinophilic necrosis that still seems somewhat intact although some nuclei may be missing. The extracellular spaces are filled with inflammatory cells—most of which are neutrophils, suggesting a fairly acute reaction. In the upper right of Figure A—some neutrophils seem to be missing but this may just be the color copy. The patient must have had the infarction in the last couple of days. It is not much recent than that, because neutrophils do not arrive immediately. It cannot be older than a couple of days because the KPNs only persist for 24 hrs. Also, the dying myocytes would begin to disappear.

   2. A 60 year old man comes to your clinic coughing up blood. You suspect tuberculosis and take a sputum sample to identify the bacillus and to determine antibiotic sensitivity. You put your patient on standard antibiotic treatment for tuberculosis while awaiting the laboratory results. However, the man dies two days after the clinic visit. Autopsy reveals lesions in the lung as shown in **Figure 2 A, B and C**. Describe the morphology of this lesion, including the key cell types involved. Is this lesion consistent with a diagnosis of tuberculosis? Why or why not? (5 points)

   These slides show intense inflammatory infiltrate in the alveoli with extensive damage and necrosis to the alveolar lining. There are some fibroblasts (spindle-like cells) which are probably mediating fibrosis. Alveolar spaces are filled with alveolar (histiocytes), possibly some plasma cells and a few RBCs. This lesion is not really consistent with TB because there is no obvious granuloma (with epithelioid macrophages surrounded by lymphocytes). Typically TB exhibits granulomas of caseous necrosis.
3. What are the key morphologic features of the lesion shown in Figure 3A and B? (Include an identification of the organ.) What agent could cause this type of cell injury? Briefly explain the mechanisms by which this type of injury is induced. (6 points)

This slide depicts fatty liver. The hepatocytes are vacuolated and filled with lipid (which is dissolved in slide preparation). Fatty liver can be caused by agents including CCl₄, alcohol, and ethanol. This agent probably causes CCl₄ toxicity because alcohol hepatitis is usually also characterized by fibrosis which appears to be evident here.

CCl₄ is metabolized in the P450 system (2E1) in the liver. The trichloromethyl radical that is produced causes extensive lipid peroxidation in the SRE, PPR, etc. Damage to the PPR distorts protein synthesis. Loss of apoprotein synthesis prevents the liver from making lipoproteins for lipid export. Therefore, liver fat builds up in the liver. Centrilobular necrosis is likely because this area of the liver has the highest P450 activity.

Section 2. Short answers (41 points)

1. A defect in Factor XII could affect which major systems that produce plasma-derived mediators of inflammation? (4 points)

Hageman factor can influence a number of systems as depicted on the right. The scheme indicates influences on production of bradykinin (A more permanently, not), activation of C3 (affecting most all activation pathways), and the generation of fibrin split products (not more probably). All of these factors can play a role in modifying the inflammatory response. Notably, inflammatory mediators can come from other sources as well (CUBics, endothelium) so the inflammatory response could probably still occur.

2. What are the major components of an atherosclerotic plaque? (3 points)

1) Fibro-fatty cap composed of smooth muscle cells, collagen, and some lipid

2) Nuclei, core (comprise) of macrophages (chideros, oxidized LDL, foamy macrophages, and necrotic debris)

These components develop because 2 macrophages that are infected of internal fat accumulation and foam cells have (activation secondary to endothelial injury).
3. After running a 10K road race, your big toe became painful and inflamed. You decide to take aspirin before calling your physician. How does aspirin work to control inflammation? (6 points)

Aspirin is an inhibitor of the cyclooxygenase enzyme, which is involved in the production of prostaglandins from membrane arachidonic acid. Prostaglandins (e.g., prostacyclin) typically increase vascular permeability and vasodilation. If you prevent prostaglandin synthesis, you may reduce swelling, edema, and pain. One potentially dangerous aspect of aspirin that you may want to consider, is that because the COX pathway is inhibited, lipoygenase activity can sometimes increase, leading to more leukotriene synthesis. If you are predisposed to asthma or suffering from the early effects of it (after a race on a nice spring day), aspirin could make the asthma worse.

Incidentally, reduced prostaglandins may also reduce the production of other inflammatory mediators because lowered vascular permeability and vasodilation may reduce the amount of WBC chemotaxis. (WBCs also promote inflammation.)

4. Hepatitis B virus is not cytotoxic to infected hepatocytes. Instead, infection of hepatocytes triggers a virus-specific cytotoxic T lymphocyte (CTL) response. What are the mechanisms by which CTLs kill infected hepatocytes? (6 points)

CTLs have several important mechanisms of killing. Initially, they will recognize virus-infected hepatocytes because of presentation of viral antigen on hepatocyte MHC I. This will induce CTLs to make TNF & IFN-γ which decrease viral synthesis & increase apoptosis. Also, IL-12 will be secreted, which causes hepatocyte expression of Fas. Fas binds to a trimeric receptor, which when bound to the Fas ligand, from the CTL, causes activation of caspase 8, which then leads to activation of the execution caspases 3, 6, & 7 and eventual cell death by apoptosis. Also, CTLs secrete perforin—which allows for the entrance of CTL-produced granzyme into the cell activating the caspases as well. Caspases cause apoptosis by cleavage of endonucleases, transglutaminase, and direct cleavage of cytoskeleton & nuclear lamina.
5. A 29 year old woman with poorly-controlled myasthenia gravis is pregnant with her first child and is quite anxious about this pregnancy. What would you tell the mother about the clinical consequences that her condition might have for the baby, the prognosis for her baby, and why the baby might be affected? (Your concern in this question is not with the effects of any drugs she might be taking on the fetus). (5 points)

Myasthenia gravis is an autoimmune condition in which IgG (or IgA) is directed against muscle nAChRs thus inhibiting the function of skeletal muscle. Maternal IgG is passed to the fetus through the placenta - normally playing a protective role. Colostrum with IgA from breast milk in the first few months of life before the baby is entirely immunocompetent. The baby will have maternal anti-nAChR IgG for a while and may therefore exhibit muscle weakness early on, but eventually after a few months - the child's immune system will take over and maternal IgG will no longer circulate. If the child makes it to this stage, he/she should be fine.

6. Disruption of the plasma membrane permeability barrier due to free radicals leads to irreversible cellular injury. Briefly describe how oxidants damage the plasma membrane. (6 points)

Oxidants can lead to membrane damage in a number of ways. First, oxidants can cause direct lipid peroxidation, damaging the integrity of the membrane. Oxidants can also damage the mitochondria, leading to the intracellular release of Ca^2+ which can activate phospholipases, resulting in membrane damage. Oxidation of SH bonds can damage proteins such as the Na^+/K^+ ATPase. Extreme osmotic swelling resulting from this might cause the membrane to rupture. Radical damage to the RER can adversely affect protein synthesis - including that of proteins destined for the membrane. Finally, extensive mitochondrial damage reduces ATP production - halting available repair mechanisms.
7. Thrombosis occurs when prothrombotic stimuli overwhelm protective mechanisms. What are the main mechanisms that protect against thrombosis? (Just list the mechanisms. You do not need to describe them - 3 points)

1) endothelial integrity (covers subendothelial collagen & BM which promote thrombus formation)
2) heparin sulfates on endothelium (allows for antithrombin III activity)
3) thrombomodulin expression on endothelium
4) NO & ADP release production by endothelium (antiplatelet effect)

8. Individuals with familial hypercholesterolemia have elevated levels of cholesterol. What is the pattern of inheritance of familial hypercholesterolemia? What is the current explanation for high levels of cholesterol observed in these patients? Do cholesterol levels differ in homozygotes and heterozygotes? Explain why or why not. (8 points)

Familial hypercholesterolemia is an autosomal dominant disorder. High levels of cholesterol can have a number of causes, mostly involving the ability of cells to internalize LDL. Mutations can lower the affinity of the LDL-R for LDL. Also, a mutation may prevent surface expression of the receptor or perhaps internalization of the receptor/LDL complex after binding. Without proper entry of LDL into cells - the feedback mechanism by which LDL inhibits HMG-coenzyme A reductase (cholesterol synthesis) and upregulates ACAT activity (cholesterol storage) - is not in effect. So inability of cells to internalize LDL may actually cause additional synthesis of cholesterol (talk about adding insult to injury!).

Homozygotes have extraordinarily high cholesterol levels - (200-1000) mg/dL. These people usually have extreme CHD in their teens and twenties. Heterozygotes have intermediate levels and may survive into their 40s or 50s.
Section 3. Multiple Choice (28 points)

MOST of the multiple choice questions below ask for some justification or elaboration of your answer which requires no more than 1-2 sentences. Each question is worth 3 or 5 points, depending on whether an explanation of the response is indicated.

1. Ionizing radiation, toxicants, and hormonal withdrawal all can induce apoptosis in target cells. Apoptosis is also important in normal tissue homeostasis. The intracellular organelle that is most important in the regulation of apoptosis is the:
   A. nucleus
   B. plasma membrane
   C. mitochondria
   D. ribosomes
   E. lysosomes

   Why is this organelle so important? Mitochondrial release of cytochrome C is very important for apoptosis. Cytochrome C complexes with ApoA-2, which activates caspase 9 through an ATP-dependent (and therefore mitochondrial-dependent) pathway.

2. A 25 year old young woman who works in the dry cleaning industry is referred to your occupational health clinic for evaluation of possible carbon tetrachloride poisoning. What organ would you expect to be most affected by this chemical?
   A. brain
   B. liver
   C. skin
   D. lungs
   E. gastrointestinal tract

   How would you explain the localization of injury to this organ? The liver has very high p450 activity, oxidizes many toxins. CCL metabolism leads to fatty liver and centrilobular necrosis, as explained in question #3.

3. Acute inflammation and chronic inflammation have a characteristic morphological appearance. What agents are most likely to trigger acute inflammation?
   A. fungi
   B. bacteria
   C. viruses
   D. sutures
   E. asbestos fibers

   What cell type(s) are MOST PROMINENT during acute inflammation?
   Neutrophils
4. A 29 year old avid gardener develops severe blistering of the skin consistent with a hypersensitivity reaction to poison ivy. Histological examination of a skin biopsy would MOST LIKELY reveal which of the following cell types?

A. eosinophils
B. basophils
C. T lymphocytes
D. B lymphocytes
E. neutrophils

What function does this cell type play in mediating the hypersensitivity response?

Th cells are activated when they recognize the presentation of the chemical hapten by an APC (e.g., macrophage). This secretes IFN-γ to stimulate macrophages, which are involved in tissue destruction in DTH, and these macrophages activate Th1 cells with IL-1, TNF, and IL-12.

5. Injury to blood vessel leads to a transient vascular constriction, followed by vasodilatation. Vasodilatation is mediated by:

A. local neurogenic response
B. release of platelet-derived growth factor by platelets
C. release of nitric oxide by platelets
D. release of nitric oxide by endothelial cells
E. release of thromboxane A2 by platelets

6. A genetic defect in von Willebrand Factor (vWF) can interfere with:

A. The aggregation of platelets at the site of tissue injury
B. The function of endothelial cells in normal homeostasis
C. Adhesion of platelets at the site of tissue injury
D. Repair of tissue injury by fibroblasts
E. The release of cytokines by platelets

Explain why this problem leads to bleeding.

vWF is secreted by endothelium and serves as a ligand between subendothelial collagen and the platelet GpIIb receptor. Without which, platelet adhesion at the site of injury will be inhibited. This will also blunt prevent platelet aggregation without initial platelet adhesion and aggregation - the primary homeostatic (platelet) plug will not form properly and bleeding will increase. Lack of platelet activation may also lead to problems in fibrin synthesis because the platelets surface and mediators are important for fibrinolysis...
Section 4. Essay Question (15 points)

You are a physician member of a research team at a leading pharmaceutical company. Your team has been charged with developing a 5-year plan for research on drug treatment for asthma. Based on what you know about the mechanisms of asthma, what approaches would you expect to be most fruitful? Explain why you selected these particular approaches, what the benefits are relative to current approaches for asthma therapy, and what problems you would expect to encounter in your research. (Answer only on this page.)

Atopic asthma is a type I hypersensitivity response. It is therefore characterized by initial mast cell degranulation (due to IgE cross-linking), and eventual eosinophil recruitment due to IL-5 secretion by mast cells and Th2 cells. IL-5 is also important as it mediates plasma cell switching to IgE production. Bronchoconstriction and mucus production are largely mediated by leukotriene production (from mast cells etc.).

All MBP and eosinophil cationic protein can damage endothelium.

In developing novel therapies, I would target IgE production.

In developing novel therapies, I would target IgE production. As the IL-5-mediated eosinophil recruitment and the effects of leukotrienes. As the IL-5-mediated eosinophil recruitment and effects of leukotrienes, I'll focus on these. Anti-IgE first two approaches are...