There are a total of 100 points for this examination. It consists of four sections, encompassing material drawn from the laboratory and the lecture portions of the course. When answering the short answer and essay questions, be sure to plan your response carefully. Pay particular attention to the number of points assigned to each question. ANSWER ONLY IN THE SPACE PROVIDED. This examination is designed to take 2 hours.

Section 1. Histopathology. (This section is worth a total of 20 points).

1. A 35-year-old man with no prior medical problems has had a high fever and a cough productive of thick yellowish sputum for the past 2 days. Physical examination reveals a few crackles at the lung bases. Chest X-ray reveals bilateral pulmonary infiltrates. The histological appearance of a lung biopsy is shown in Figures 1 A, B, and C (next page).

   a. Based on the histopathology, what is the likely diagnosis? (2 points)
   - bronchopneumonia
   - Acute

   b. Explain the basis for your diagnosis.
   - Alveolar spaces are filled with a dense neutrophilic inflammatory exudate
   - Alveolar septa are slightly enlarged (thickened)
   - Local destruction of alveolar walls

   (2 points)

   c. Which of the following substances generated by the predominant cell type seen in this biopsy, would be most effective at clearing this infection? (2 points)
   - A. Platelet activating factor (PAF)
   - B. Kallikrein
   - C. Prostaglandins vasodilate
   - D. Hydrogen peroxide
   - E. Leukotrienes bronchoconstrict

   d. Why does this man have a fever? (2 points)
   - In response to the bronchopneumonia stimulus (most likely a bacterial infection), his body (lungs) has mounted an acute inflammatory response. IL-1, TNFα, the main cytokines responsible for mediating this inflammation, have also caused his fever, by setting a cascade of events that ultimately result in fever: they induce PGE2 production in the brain which stimulates the hypothalamus (IL-6 induced by IL-1 also does this which stimulates the sympathetics which cause vasoconstriction and therefore heat retention and fever.)
2. Figure 2 (A, B) illustrates a biopsy (from a 60 year old man) that has been sent to you for pathological examination.
2. a. On the basis of this biopsy, what is your diagnosis?

- Hypnosis of the liver

b. Justify your diagnosis.

- Disorganized hepatic parenchyma
- Portal tract-portal tract fibrotic bridging
- Some central vein-portal tract fibrotic bridging
- Some central vein necrosis (centrilobular)

- Nodules, with some clusters of regenerating hepatocytes in the fibrotic tracts

3. Why might this patient have a bleeding disorder?

- His synthesis and secretion of the coagulation factors (in both the intrinsic and extrinsic cascades) would be greatly impaired, making him susceptible to a bleeding disorder.

3. The histological section of myocardium in Figure 3 (next page) is from an autopsy on a 65-year-old man who died suddenly. Upon questioning, his wife said that he had, in the past 6 months or so, had several episodes of chest pain for which he refused to seek any medical evaluation. She wasn't sure how long before his death he had experienced his most recent episode of chest pain.

a. What is your diagnosis? What was the timing of this event? Describe the histological findings that allowed you to make this diagnosis.

- Myocardial infarction, about 5-7 days ago.
- Growth of granulation tissue - many macrophages, fibroblasts present; new capillaries beginning to grow; some hemorrhage because the new capillaries are leaky
- This is characteristic of myocardium starting to heal itself about 5-7 days after a myocardial infarction

b. What might the cause of death have been in this patient, and how does this correlate with the histological findings?

- Rupture of the myocardial wall with subsequent cardiac tamponade (pericardial sac becomes engorged with blood, greatly increasing the pressure on the heart - impairing its ability to pump)
- This correlates with the histology because as the granulation tissue is forming (pre-fibrotic scarring), the myocardium (scar) is weakened locally (scar not yet formed) making it highly susceptible to rupture.
Section 2. Multiple choice questions. There is only one correct answer for each question. Each question is worth 2 points (Total 20 points)

1. In the springtime, a 21-year-old healthy man is bothered by episodes of nasal congestion, sneezing and watery eyes. On physical examination, he has moderate swelling of his nasal mucosa. Which chemical mediator primarily produces his symptoms?
   A. TGF-α
   B. Complement C3b
   C. Leukotriene D4
   D. Histamine
   E. Interferon gamma

2. A 45-year-old man with end-stage renal failure undergoes successful renal transplantation. One month later he develops oliguria and an increasing BUN and creatinine (consistent with declining renal function). Biopsy of the transplanted kidney shows that graft cells expressing HLA Class I antigens are being destroyed. What cells are mediating this response?
   A. T Helper cells (Th1 cells)
   B. CD8 lymphocytes
   C. B cells
   D. Dendritic cells
   E. CD4 lymphocytes

3. A 25-year-old woman has a malignant lymphoma involving lymph nodes in the mediastinal and retroperitoneal areas. She is treated with a chemotherapeutic agent that results in the loss of individual neoplastic cells through fragmentation of individual cell nuclei and cytoplasm. After several weeks, a repeat CT scan reveals a 50% decrease in the size of the involved lymph nodes. What is the primary mechanism by which her lymphoma has responded to treatment?
   A. Autolysis
   B. Acute inflammation
   C. Coagulative necrosis
   D. Lipid peroxidation
   E. Apoptosis

4. A 53-year-old man has experienced severe chest pain for the past couple of hours. He is found to have an elevated serum troponin I level. A coronary angiogram is performed emergently and reveals occlusion of the left anterior descending artery. In this setting, irreversible injury to myocardial fibers will have occurred when:
   A. Glycogen stores are depleted.
   B. There is an increase in cytoplasmic sodium. 
   C. Nuclei have undergone karyorrhexis.
   D. Intracellular pH decreases.
   E. Blebs form on cell membranes.
5. A 65-year-old man has a dark red-black appearance to several toes on his left foot (the great, second, and third toes). On examination, the toes are cold to touch and have no sensation. The dorsalis pedis and posterior tibial pulses are not palpable on the left. These findings are most typical for a patient with:
A. Venous thrombophlebitis
B. Monckeberg's arteriosclerosis
C. Foreign body reaction
D. Diabetes mellitus
E. Type III hypersensitivity reaction

6. A 44-year-old woman develops marked right lower quadrant abdominal pain over the past day. On examination there is rebound tenderness. Surgery is performed, and the appendix is swollen, erythematous, and partly covered by a yellowish exudate. It is removed, and microscopic section shows infiltration with neutrophils. The pain experienced by this patient was largely the result of:
A. IgG and Complement C3b
B. Interleukin-1 and TNF-α
C. Histamine and serotonin
D. Prostaglandin and bradykinin
E. Leukotrienes B4, C4, and D4

7. A 12-year-old boy is working on a wooden bench when a sliver becomes embedded in his finger. He doesn't remove it, and over the next few days the area around the sliver becomes red, swollen, and very tender. Neutrophils migrate into the injured tissue via diapedesis, as a consequence of release of:
A. Histamine
B. Prostaglandin
C. Hageman factor
D. Bradykinin
E. Complement C5a

X. The surgical wound following suturing of the incision site for a cholecystectomy will have ingrowth of new capillaries. What is the major factor that macrophages produce to stimulate this capillary proliferation?

A. Platelet-derived growth factor
B. Phospholipase C
C. Fibroblast growth factor
D. Epidermal growth factor

9. A 52-year-old woman with a bladder infection developed acute pyelonephritis. She became septic, and blood cultures grew E. coli. She developed hypotension and purpuric lesions. Her prothrombin time (PT) and partial thromboplastin time (PTT) were prolonged, and a platelet count was 20,000/microliter. Fibrin split products were elevated. These findings are most characteristic of:
A. Hemophilia A
B. von Willebrand disease
C. Disseminated intravascular coagulation
D. Antiphospholipid syndrome
E. Acute fulminant hepatitis
10. An 89-year-old male nursing home resident died and underwent an autopsy. The gross appearance of the brain (Figure A) is most consistent with:

A. Glioma  
B. Infarction  
C. Edema  
D. Meningitis  
E. Atrophy

Section 3. Short answers. (40 points)

1. A 56-year-old woman has smoked 2 packs of cigarettes per day for the past 35 years. She has had a chronic cough for years, but recently has noted increased sputum production. Bronchoscopy with biopsy is performed. The biopsy reveals bronchial epithelium with squamous metaplasia. What is the significance of this finding for the patient? (2 points)

Normal bronchial epithelium is columnar epithelium; however, here epithelium is squamous. This metaplastic change is a result of the chronic inhalation of toxic substances (her cigarette smoking) in an effort to protect themselves. However, with this change comes decreased production of mucus and loss of elasticity, potential for emphysema.

2. An 18-year-old woman is given intravenous penicillin to treat bacterial endocarditis. Within minutes of the start of the penicillin infusion, she develops severe difficulty breathing and wheezing, and develops an erythematous rash over most of her body. What type of reaction is responsible for these symptoms? (2 points)

Hypersensitivity type I (anaphylaxis)

0.5

usually dendritic cells

re-sensitization: APC present antigen to Tcells, which differentiate to Th1 or Th2 (3 points)
cells (IL-4 induced). Tcells secrete more IL-4 to cause isotype switching in Bcells, IgE production. Mastcells have an FcReceptor for IgE, become coated, and degranulated: IgE recognized by IgE, causes cross-linking on mast cells, degranulation (histamine, vasodilation, leukotrienes, prostaglandin, leukotrienes are also produced; transcription necessary for IL production begins) these mediators can damage the epithelium (deactivate it), which then leads to secretion of PAF and eosinophils which attract eosinophils (late phase reaction). IL-3,5,8,13 secrete by Th1, Th2 cells also attract eosinophils which secrete major basic protein (eosinophil cationic protein) which help to kill the Ag; further contribute to the inflammatory response.

Larger normal circumstances (to permit) but here it is killing the Ag (histamine; mast cells) 
most cells (also basophils) are responsible for the immediate effects, eosinophils (the newly synthesized products of mast cells) are responsible for the late phases of the response. What are these effects?
3. A 35 year old man from Costa Rica is tested with a PPD (tuberculin skin test). If he had been exposed to TB in the past, what type of immunologic reaction would occur? What would the local skin reaction look like, and what would be the timing of this reaction? Briefly describe key cells and mediators responsible for this reaction. 

- Type IV hypersensitivity reaction: DTH.
- The local skin reaction would look like a small raised bump, and would occur within 48-72 hours of the PPD (not immediately).

- Key cells: CD4+ Th1
- Key mediators: IFNγ, IL-12, TNFα

- Pre-sensitization (prior TB exposure):
  - APC (MHC II) + TB antigen presented to CD4+ T cells
  - Th1 differentiation

- PPD: memory Th1 cells proliferate
  - Stimulate macrophages (via IL-12 more importantly IFNγ)
  - IFNγ + TNFα
  - Enhance permeability of small blood vessels
  - Cause damage + inflame host tissue

- Small bump on skin

4. Free radical injury is one of the most frequent types of cell injury. Describe four cellular defense mechanisms for protection against free-radical mediated oxidant damage.

- Superoxide dismutase converts the superoxide anion \( \text{O}_2^- \) to \( \text{H}_2\text{O}_2 \) (hydrogen peroxide)
- Catalase: in liver, peroxisomes, it converts \( \text{H}_2\text{O}_2 \) into 2 molecules of water
- GST/glutathione peroxidase: \( \text{GST} + \text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{GSSG} \) (which gets reduced back to GST)
- Spontaneous decay of the free radicals

5. A 36-year-old man died from complications of destruction of the aortic valve by large, irregular vegetations from which Staphylococcus aureus was cultured. At autopsy, the spleen on sectioning grossly revealed a large wedge-shaped lesion, shown below. This most likely represents the result of:

- Coagulative necrosis
- Abscess formation
- Metaplasia
- Caseous necrosis
- Liquefactive necrosis

Which part of the diagram represents the damaged region (top or bottom)? How do you know? Bottom white triangle occurs in the spleen
6. A 5-year-old boy sustains a small 0.5 cm long laceration to his right index finger while playing with a letter opener. On contact with injured vascular basement membrane, what activates both the coagulation cascade and the kinin system as an initial response to this injury? (2 points)

factor XII (Hageman factor)

What is the major product of the kinin system, and what are the consequences of its production? (2 points)

bradykinin → causes pain (also vasodilation + increased permeability)

7. A 57-year-old man has a history of exercise-induced angina. A coronary arteriogram is performed, and reveals only a moderate narrowing of the Left Anterior Descending coronary artery due to atherosclerosis. If you were able to actually look inside his coronary artery, what plaque characteristics would put him at risk for an "acute event"? (2 points)

circumferential necrotic core of lipid that was especially soft

lots of macrophages

a thin fibrous cap

8. A 48-year-old woman has progressive muscular weakness, particularly worse toward the end of the day. She does not have arthralgias or myalgias, and she is on no medications. An antinuclear antibody test is negative. A chest CT scan reveals an anterior mediastinal mass. What is the likely diagnosis? (2 points)

What is the likely immunological mechanism for her symptoms? (Include type of reaction and brief description of mechanism). What treatment might be effective? (3 points)

Type III hypersensitivity → receptor interactions

Autoantibodies against ACh receptors at neuromuscular junction inhibit receptors

Myasthenia Gravis

Removal of the humerus might be helpful.

9. Although atherosclerosis is a process that affects the intima of vessel walls, severe atherosclerosis can affect the media in certain vessels. Describe how this can occur and which vessel(s) can be involved. What are the potential clinical consequences due to this process? (3 points)

This is most likely to occur in the abdominal aorta, which can lead to aneurysm formation (where thinning out of the media → lots of smooth muscle emigration from the media to the intima in severe atherosclerosis, leading to local weakness + outpouching).

The aneurysm could potentially rupture, which would be bad, or cause mural thrombi to form (which could embolize - also bad).
10. During a prolonged hospitalization, a 42-year-old woman develops thrombophlebitis in the left calf.
   a. What are the possible outcomes for this venous thrombosis? (2 points)
      - Resolution - lysis
      - Organization/ recanalization
      - Embolization (esp. pulmonary embolus)
      - Propagation

   -0.5

   b. What factors might determine whether she develops a complication from this thrombus? (2 points)
      - How long she's immobile
      - Where the thrombus is located (4 risk of PE if it's a deep venous thrombus! - yes!)
      - Size of thrombus
      - Local balance of pro/anti-thrombotic forces
      - Collaterals?

11. A 60 year-old man owns a dry cleaning store, and has been in business for over 40 years. Describe the two major histological findings that might be found on a liver biopsy. (2 points)
   - Fatty change
   - Pseudo central lobular necrosis

   Briefly explain the mechanisms responsible for these histological findings. (3 points)
   - CCl₄ toxicity - used in dry cleaning agents
   - It's metabolized to a toxic intermediate, CCl₃:
     - Disrupts ribosomal function
     - Production of apoptosis + therefore impaired lipoprotein synthesis + secretion
     - Accumulation of fat
     - Disrupts mitochondrial plasma membrane permeability
     - Ca²⁺ release
     - Precipitates in mitochondria
     - ATP disruption transports chain, necrosis
Section 4. Essay Question (20 points). Answer ONLY in the space provided.

A 30 year-old man presents with a history of severe substernal “crushing” chest pain that lasted an hour, and was associated with shortness of breath. He did not seek medical attention when it happened. However, he had another brief episode of chest pain twelve hours later, and his wife finally convinced him to come into the Emergency Room for evaluation.

a. How will you be able to determine whether the pain was cardiac in origin? If these symptoms were due to myocardial infarction, what might you expect to see on gross and microscopic examination of the heart? How would these findings correlate to your diagnostic test results? If you have been taught that CK-MB enzymes test his serum for, you know there must have been damage to the heart histologically: many myocytes
hypereosinophilla
lead to CK-MB
(both start to rise at 4 hrs... peak at 18 hrs.)

What risk factors would you ask about and why?
- Current cholesterol status (LDL, HDL risk of atherosclerosis)
- Smoker? (smoking increases risk of atherosclerosis)
- Diet (related to cholesterol, but also vit B6,12 → homocysteine theory)
- Stress in life lately (possible aggravator)
- Diabetic?
- Hypertension?

You would ask about the risk factors that would predispose him to atherosclerosis / MI: (see above)
Would a family history be helpful? Why/why not?

Yes. There is a strong genetic component to heart disease/MIatherosclerosis. [see previous answer]

What laboratory studies would you want to obtain to assess future risk of myocardial infarction? Why? (Be as specific as you can be—what results would make you worry about a higher risk of future myocardial infarction?)

Cholesterol level:
- Total: ↑>240
- LDL: ↑>160 →worry
- HDL: ↓<40
- Genetic test for LDL receptor gene (defective in familial hyperlipidemia)
  →if defective, worry.
- Test for homocysteine levels? If ↑, maybe worry? (potentially related to heart problems)

This patient was told by his neighbor that Vitamin E would be very helpful in decreasing the likelihood of having another heart attack. Is there any truth to this statement? How could you incorporate this statement into what you know about the causation of atherosclerosis?

Vitamin E is an antioxidant, while it may be useful in preventing against free radical damage (it wouldn't necessarily help in preventing heart attacks) which almost always are due to occlusion of a coronary artery (often due to atherosclerosis-related plaques/thrombus or emboli) and subsequent ischemia/myocardial necrosis. Oxidation of LDL (e.g., for uptake by macrophages) and its enrichment with cholesterol and other lipids are significant factors in atherosclerosis. Vitamin E has been shown to slow the progression of atherosclerosis by inhibiting oxidation of LDL and reducing the formation of fatty streaks in the arteries. However, there is no strong evidence to support the claim that Vitamin E will prevent heart attacks or decrease the risk of myocardial infarction.

BONUS QUESTION:
A 35-year-old man who leads a very sedentary lifestyle, eats lots of pizza and "junk food," and has a history of hypertension, diabetes, and hypercholesterolemia, has been advised by his doctor to take Vitamin E supplements. How might this advice affect his health?

A. Pancreatic fatty necrosis
B. Fatty metamorphosis of the liver potentially
C. Metaplasia of muscle to adipose tissue no
D. Hypertrophy of smooth muscle →fatty infiltration of muscle
E. Fatty degeneration of myocardium

Vitamin E might mitigate some of their negative effects.