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. Good luck!

HISTOPATHOLOGY (17 points)

1. A 30-year-old businessman was found unconscious by the police on the sidewalk near his car in downtown Providence. He regained consciousness briefly, at which time he told the police that he had just left a holiday party – his tenth party in the last two weeks. He was rushed to the emergency room but died soon after arrival from a subdural hematoma incurred when he fell. An incidental finding at autopsy is shown in a section of his liver below. (5 points)

![Image of liver tissue]

What is your diagnosis? Alcoholic Hepatitis (with Fatty Change)

Briefly describe the mechanisms by which this type of cell injury occurred in this case.

- Consumption of alcohol causes epinephrine release from the adrenal medulla, which increases fat catabolism and the release of FFA to the liver.
- When alcohol (Ethanol) is metabolized first to acetaldehyde by ADH, then to acetic acid by ACO, there is production of NADH. The increase in the NADH/NAD⁺ Ratio favors fatty acid biosynthesis.
- The acetaldehyde mentioned above can inhibit proper cytoskeletal function, leading to decreased export of lipoproteins from the liver. 
- Necrosis can also be caused by excessive Free Radical Formation due to ethanol Metabolism. This can deplete GSH and cause necrosis, because GSH is very important in Free Radical Defense.
2. An adventurous group of young children broke into an abandoned factory and stole a 10lb bag of liquid mercury. They took it to their apartment building where the bag broke, spilling its contents. A biopsy taken from one of the children is shown in the slide below. (7 points)

What is this organ? **Kidney**

What are the cellular targets of this agent? **Proximal convoluted tubules**

Is the dominant form of cell injury shown above necrosis or apoptosis? **Necrosis**

Justify why you think this is necrosis or apoptosis on the basis of the morphological appearance of the tissue section.

- The cells of the PCT appear to be enlarged and have enhanced eosinophilia. The primary observation that leads me to believe necrosis is the lack of nuclei in the PCT cells. During necrosis, the cell nuclei condense, fragment, and dissolve, leaving behind eosinophilic, anucleate cells.
- This loss of nuclei is not seen in apoptosis; rather, apoptotic nuclei are fragmented, and the cell will be divided into apoptotic bodies destined for phagocytosis. This is not seen.
- Moreover, there appear to be some fragmenting/dissolving nuclei in some of the tubules.
3. A 78-year-old man complains of chills, nausea, and pain in his back. He has a fever of 102°F and urinalysis reveals the presence of WBCs. A renal biopsy indicates that the patient has acute pyelonephritis as shown below. (5 points)

What is the dominant inflammatory cell type in this section? **NEUTROPHILS**

**Briefly** explain why this cell type dominates in acute pyelonephritis.

Acute inflammatory reactions are characterized by the presence of neutrophils. This is because of several chemotactic factors released at the site of infection or cell injury. Neutrophils are the first to arrive on the scene, and the acute inflammatory response is usually very successful. It is only when this acute response fails that the inflammation may proceed to chronic, as neutrophils die within 24 hours and are replaced by macrophages, etc.
MULTIPLE CHOICE/SHORT ANSWER QUESTIONS (2.5 points, total of 44 points)

1. An autopsy is performed on a 60-year-old man who died suddenly of a myocardial infarction. The man had smoked for over 40 years. Sections from his bronchi revealed areas of squamous differentiation. Based on this information, what tissue changes BEST fit the microscopic evidence in the epithelium?
   a. Hyper trophy
   b. Hyperplasia
   c. Metaplasia
   d. Atrophy
   e. Apoptosis

2. On the first day of a clinical rotation in pathology, you are given a slide that the pathologist diagnosed as cloudy swelling or hydropic degeneration. You recall from your pathology course that hydropic degeneration involves swelling of the mitochondria and endoplasmic reticulum. What is the mechanism by which this type of cell injury occurs?
   a. Lipid peroxidation
   b. DNA fragmentation
   c. Fatty acid oxidation
   d. Release of lysosomal enzymes into the cytoplasm
   e. Impairment of the Na⁺-K⁺ pump

3. The cardiac muscle undergoes hypertrophy in response to chronic stressors, such as untreated hypertension. The mechanisms of myocyte hypertrophy involve induction of many genes that produce cellular growth factors. How would you define hypertrophy?
   a. An increase in the size of the cells
   b. An increase in the number of cells
   c. A shift from one undifferentiated cell type to another undifferentiated cell type
   d. A shift from one differentiated cell type to another differentiated cell type
   e. Cancerous change

4. The stock of a biotechnology company soars after one of their products, an antagonist of the cell adhesion molecule ICAM-1, is shown to be effective as an anti-inflammatory agent in clinical trials. Your office receives numerous calls that day from patients wanting to know when the drug will be on the market. An antagonist of ICAM-1 inhibits inflammation through which of the following mechanisms?
   a. Inhibition of platelet aggregation
   b. Inhibition of macrophage activation
   c. Inhibition of prostaglandin synthesis
   d. Inhibition of lymphocyte activation
   e. Inhibition of leukocyte adhesion to endothelial cells
5. A 40-year-old woman reports a recent history of skin rashes that are exacerbated by the sun (particularly on the cheeks and nose), and swelling of the joints. What disease presents in this way?
   a. Hashimoto’s thyroiditis
   b. Systemic lupus erythematosus
   c. Rheumatoid arthritis
   d. Myasthenia gravis
   e. Contact dermatitis

A blood test for which of the following would help you make the diagnosis?
   a. Rheumatoid factor
   b. Antibodies to TNF
   c. Antibodies to double-stranded DNA
   d. Antibodies directed against acetylcholine
   e. Antibodies to thyroglobulin

6. A great deal of research in the past decade has focused on developing specific inhibitors of the cyclooxygenase pathway of arachidonic metabolism. Celebrex, for example, is a specific inhibitor of COX-2. What drug inhibits COX-3?
   a. Ibuprofen
   b. Acetaminophen
   c. Indomethacin
   d. Aspirin
   e. Naprosyn

7. A 20-year-old college student goes to health services complaining of sudden onset of a fever, chills, a severe headache, and a stiff neck. The staff immediately suspect meningitis, which is caused by the Gram-negative bacterium Neisseria meningitides (meningococcus.) A spinal tap confirms the diagnosis and the student is placed on intravenous antibiotics immediately. This bacterium is particularly dangerous because it has evolved mechanisms to evade immune attack. Which of the following is an important mechanism by which meningococci evade the immune system?
   a. Inhibition of humoral immunity
   b. Surface LPS limits access of the membrane attack complex to the microbe
   c. Addition of sialic acid to lipoooligosaccharide inhibits complement fixation
   d. Humans lack specific T lymphocytes that recognize this microbe
   e. The polysaccharide capsule inhibits activation of complement by the alternative pathway
8. A 60-year-old man comes to your clinic with a two-month history of coughing up blood. You suspect tuberculosis and take a sputum sample to identify the microorganism and to determine antibiotic sensitivity. You place your patient on standard antibiotic treatment for tuberculosis while awaiting the laboratory results. However, the man dies seven days after the first clinic visit. Autopsy reveals lesions in the lung as shown below.

How would you diagnose this lesion?
- a. Acute inflammation
- b. Chronic inflammation
- c. Granulomatous inflammation
- d. Metaplasia
- e. Immediate hypersensitivity

Explain why you made this diagnosis. There is a large necrotic area surrounded by lymphocytes, which is very characteristic of granulomatous inflammation. Cell seen in this field.

Which of the following mediators plays a critical role in the formation of this lesion?
- a. Platelet activating factor (PAF)
- b. Histamine
- c. Tumor necrosis factor-α (TNF-α)
- d. Eotaxin
- e. Serotonin
9. A 50-year-old man has been taking phenobarbitol (a barbituate) to control his epilepsy for many years. Three years ago, he got divorced and began drinking heavily. In the last two years, the frequency of his seizures increased. Based on what you have learned in General Pathology, what is the most probable explanation for this increase in seizure activity?
   a. Ethanol commonly causes seizures in 50 year olds
   b. This is the normal course of epilepsy
   c. Ethanol has induced lysosomal enzymes to destroy neural tissue, leading to seizures
   d. Ethanol has induced cytochrome P-450 enzymes so the levels of phenobarbitol are sub-therapeutic
   e. Ethanol has induced apoptosis of glial cells

10. A 26-year-old man developed recurrent infections with Neisseria gonorrhoeae. His 35-year-old brother also suffered from gonococcal infections. A genetic work-up revealed a deficiency in the C3b component of complement in both men. What functions of the inflammatory response would be affected in these individuals?
   a. Chemotaxis
   b. Anaphylaxis
   c. Vascular permeability
   d. Phagocytosis
   e. Smooth muscle contraction

11. A 4-year-old develops a fever of 101°F and complains of a sore throat. The mother tells you that several children at the child’s day care center had streptococcal infections over the past few weeks. A throat culture comes back positive and you prescribe antibiotics. Which of the following cytokines is an important mediator of fever?
   a. IFN-γ
   b. IL-2
   c. TGF-β
   d. TGF-α
   e. IL-1

With what disease might you be concerned 3-4 weeks after the initial infection?
   a. Alveolitis
   b. Thyroiditis
   c. Hyperthyroidism
   d. Glomerulonephritis
   e. The Arthus reaction
12. A 35-year-old woman complains of nausea, fatigue, and loss of appetite of about one month duration. Her liver enzymes were only slightly elevated. A needle biopsy of her liver is taken and you diagnose chronic active hepatitis.

What is the major inflammatory cell type in this liver section?
- a. Monocytes
- b. Cytotoxic T lymphocytes
- c. Polymorphonuclear leukocytes
- d. Mast cells
- e. Plasma cells

What organism is responsible for this disease?
- a. Hepatitis B virus
- b. Human papillomavirus
- c. Pneumocystis carinii
- d. Mycobacteria tuberculosis
- e. Salmonella enteritidis

Briefly explain the mechanisms by which liver damage occurs. The hepatocytes infected with HIV will present Ag complexed on MHC-I to CD8+ T cells, which will kill the hepatocytes by Fas ligand or perforin/granzyme.
SHORT ANSWERS. 39 points (Answer ONLY in the space provided)

1. Within about 30-40 minutes after a myocardial infarction, myocytes undergo irreversible cell injury. What are the two major organelles whose dysfunction is characteristic of irreversible injury? (3 points)
   a. Mitochondria
   b. Plasma Membrane

2. A 29-year-old woman presents with muscular weakness and fatigability of the voluntary muscles. You diagnose her with myasthenia gravis. (5 points)

   What causes the clinical symptoms in myasthenia gravis?
   Antibody Binding to the Ach Receptors at the neuromuscular junction. This will inhibit the binding of Ach, which, in turn, will inhibit the desired Motor function, resulting in weakness & fatigability of voluntary muscles

   How might you treat this disease?
   With Acetylcholine esterase inhibitors, many show improvement w/ Thymectomy

3. Free radicals are continuously produced in both physiological and pathological processes. The body has evolved numerous mechanisms as a defense against free radical injury. For each of the free-radical scavenging enzyme systems below, indicate where in the cell it is found and how it works to neutralize free radicals. (6 points)

   Superoxide dismutase:
   Location
   Cytoplasm
   Catalase
   Location
   Peroxisomes

   Mechanism
   Converts the Superoxide anion Radical into $H_2O_2$
   $O_2^-$ $\rightarrow$ $H_2O_2$

   Mechanism
   Converts Hydrogen Peroxide to Water and $O_2$
   $2H_2O_2$ $\rightarrow$ $2H_2O + O_2$

4. You decided to enter your first marathon, even though you were plagued by injuries during training. About 5 miles into the marathon, you twisted your ankle. You tried to run on it for a few miles but ultimately had to drop out of the race. The next day your ankle was quite swollen. You iced the ankle and took ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenase. One physiologically important metabolite of arachidonic acid metabolism is thromboxane A$_2$ (TXA$_2$). List the cellular origin and functions of each mediator. (2 points)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TXA$_2$</td>
<td>Platelets</td>
</tr>
</tbody>
</table>
5. A 26-year-old painter was admitted to the hospital with symptoms of rapidly progressive glomerulonephritis. Immunofluorescent staining of a kidney biopsy shows a linear pattern. (6 points)
What disease is this staining pattern consistent with?

What other organ(s) might be affected?

LUNG

Explain the mechanisms by which this disease occurs and its organ specificity.

This disease is caused by Ab's directed against the non-collagenous domain of the α 3 chain of type IV collagen, found in Basement Membranes. The Abs tend to leak through the endothelium at sites characterized by turbulent blood flow. Two areas of rather tortuous blood flow are the Glomerulos and Lung Capillaries. They then Bind B.M. and the described linear Be seen above.

6. A young child comes into your clinic with one eye swollen shut. You immediately suspect a hypersensitivity reaction. The parents tell you that a bee stung her at a backyard picnic a few hours ago and her eye swelled immediately. They also tell you that she was stung by a bee just a month ago when they were camping but that she had no reaction at that time. (6 points)
What type of hypersensitivity reaction do you think this is?

How would you explain the mechanisms to the parents, including the cells and mediators involved? Be sure to include an explanation for the time frame. (ASSUME THAT THEY CAN UNDERSTAND TECHNICAL TERMINOLOGY.)

Upon first exposure to the bee allergen (a few days ago), this antigen was captured and presented to undifferentiated T cell. This presentation, combined with IL-4 in the environment, can lead to the differentiation of these cells to a Th2 subset. The cytokines secreted by the Th2 subset cause the formation of Effector Memory B-cells that secrete IgE specific for the Antigen. The released IgE can bind to high- affinity FcεR on Mast cells, which "Arms" them. THIS PHASE TAKES ~ 3 weeks.

Upon re-exposure to the Ag, it will bind the Most cell IgE, cross-link the attached FcεR receptors, causing degranulation. The Mast cells contain histamine, which increases vascular permeability, leading to the Swelling(Cytokine: IL-1, IL-3, IL-4, IL-6, IL-8, TNFα, IL-10, IL-12, IFNα, IL-13, IL-15, IL-17, IL-18, GM-CSF, Recruitment)

7. A 2-year-old child has repeated bacterial infections. According to her parents, none of her older siblings had any unusual health problems. After an extensive work-up, she is diagnosed with myeloperoxidase deficiency. What is the role of myeloperoxidase in the defense against bacteria? (3 points)

Myeloperoxidase, in the presence of a halide ion, such as Cl-, can convert Hydrogen Peroxide to ClO⁻. (Essentially, this is the equivalent of bleach).

The ClO⁻ Radical is the Most effective means by which neutrophils can kill Microorganisms.
8. One of your long-term patients has chronic asthma which has been difficult to control, except with steroids. If you did a biopsy of the bronchial mucosa in your patient, you might see an inflammatory infiltrate rich in eosinophils. (5 points)

What subset of T lymphocytes are most important in asthma? **Th2**

Describe how eosinophils are recruited to the site of antigen exposure and how they damage tissue. **The Th2 subset secretes a variety of cytokines, of which IL-4, IL-5, and GM-CSF stimulate the recruitment and survival of eosinophils to the site of antigen exposure. The tissue damage caused by eosinophils is due to the release of cellular contents, namely ROSs. The Reactive Oxygen Species are toxic to the tissues → damage.**

9. A 68-year-old man died suddenly after having a massive myocardial infarction. This was his second heart attack, the first occurring when he was 50 years old. The section below shows a healed infarct from the first heart attack. (3 points)

What are the major cellular and extra-cellular matrix components in this healed infarct?

The main cellular component will be fibroblasts, though they should not be very abundant by this time.

The main extracellular components are collagen type I (primarily), hyaluronic acid, proteoglycans, and fibronectin.