Part I  Multiple Choice, 2 points each.

1. Xenobiotics such as benzene that produce severe toxicity in the bone marrow with indiscriminate destruction of precursor cells will result in
   A) megaloblastic macrocytic anemia.  B) microcytic hypochromic anemia.  C) the appearance of reticulocytes in the circulating blood.  D) thrombocytopenia  E) pancytopenia

2. The folic acid antagonist methotrexate is used as a treatment for cancer and acts by impairing DNA synthesis.  This drug produces a characteristic anemia called ____________ that is due to an attempt to replace lost red blood cells with immature nucleated forms.
   A) reticulocytosis  B) pancytopenia  C) megaloblastic macrocytic anemia  D) microcytic hypochromic anemia  E) thrombocytopenia

3. Chronic excessive use of aspirin will result in:
   A) inhibition of platelet aggregation.  B) vasodilation.  C) vitamin B₁₂ deficiency  D) hemolytic anemia  E) myocardial infarcts.

4. ____________ can be induced by drugs that stimulate macrophages to produce a pathologic overproduction of NO, which acts as a vasodilator.
   A) toxic shock  B) granulocytopenia  C) diapedesis  D) hemolysis  E) hypersensitivity

5. ____________ is a normal inflammatory response of neutrophils and macrophages to infection or tissue damage and glucocorticoids or glucocorticoid-like drugs can inhibit this response.
   A) phagocytosis  B) diapedesis  C) complement fixation  D) platelet aggregation  E) none of the above.

6. A toxicant that specifically targets the megakaryocytes in the bone marrow will cause
   A) leukocytopenia  B) anemia  C) hemorrhaging  D) aplastic anemia  E) granulocytopenia

7. Polycythemia can be induced by
   A) exposure to low O₂ partial pressures  B) living at high altitudes (@10,000 feet)  C) overproduction of erythropoietin  D) ingestion of Cobalt  E) All of these.

8. ____________ hypoxia occurs under normal oxygenation or elevated partial pressure of O₂ and is characterized by the inability of tissue cells to utilize the O₂.
   A) histotoxic  B) stagnant  C) anemic  D) arterial  E) polycythemic

9. When toxic agents shift the oxygen dissociation curve of hemoglobin to the left, the hemoglobin has a ____________ affinity for oxygen and will release O₂ at ____________.
   A) greater, higher O₂ tensions than normal  B) lower, higher O₂ tensions than normal  C) greater, lower O₂ tensions than normal  D) lower, lower O₂ tensions than normal  D) greater, normal O₂ tensions

10. Methemoglobin results from
    A) oxidation of the Fe²⁺ in hemoglobin to Fe³⁺  B) exposure to aromatic amino and nitro compounds  C) exposure to carbon monoxide  D) the action of methemoglobin reductase  E) both A and B are true.

11. Suppression of the immune system often involves a prior exposure to an antigen.
    A) True  B) False
12. A hapten activates the immune system by:
   A) binding directly to the antibody receptors of B-lymphocytes   B) binding to receptors of mast cells   C) irreversibly binding to large molecules such as proteins   D) binding to DNA   E) stimulating macrophages

13. The effects of TCDD (dioxin) on the immune system are more severe in young individuals because
   A) it damages the bone marrow   B) it is activated in the bone marrow to a reactive quinone   C) it causes severe thymic atrophy   D) as an alkylating agent it is toxic to rapidly proliferating cells   E) it interferes with B-cell maturation.

For numbers 14-17 match the immune system reaction on the left with the description on the right.

14. Type I reaction   A) IgG antibody reactions forming immune complexes in small vessels and capillaries leading to thrombosis and inflammation.

15. Type II reactions   B) Delayed sensitivity reaction resulting in damage to targeted cells by activated cytotoxic T-cells.

16. Type III reactions   C) involves activation of mast cells via IgE and is the basis of the anaphylaxis reaction.

17. Type IV reactions   D) involves interaction of free antibodies with cell surface antigens resulting in lysis of the cells by action of cytotoxic cells or complement.

18. The severity of a hypersensitivity reaction is dependent on the dose of the toxicant
   A) True   B) False

19. Toxic agents that induce autoimmune reactions produce reactions similar to hypersensitivity reactions
   A) Type I & II.   B) Type II & III.   C) Type III & IV.   D) Type I & III.   E) Type II & IV.

20. One of the postulated mechanisms for the induction of autoimmune reactions is
   A) activation of CD 4 lymphocytes   B) interference with T-helper cells (CD4)   C) interference with the immunoregulation activity of CD8 T-suppressor cells   D) improper reactivity to hapten-protein complexes   E) mediated by the release of histamine from mast cells that possess reactive IgE on their surfaces

21. Which of the following metals does not induce hypersensitivity type reactions?
   A) cobalt   B) nickel   C) lead   D) platinum   E) chromium

22. Toxins that induce autoimmune reactions do so by
   A) acting as haptens and binding to self-proteins that the immune system targets.   B) hyperactivating CD4 T-helper cells.   C) altering self-proteins that become immune system targets.   D) altering the reactivity of Ig producing B-lymphocytes.   E) Both C & D are true.

23. Acute cytotoxic liver damage can be detected clinically by the presence of _______ in blood plasma.
   A) bilirubin   B) methemoglobin   C) aspartate aminotransferase   D) alanine aminotransferase   E) both C & D.

24. Acute toxin induced liver necrosis can be due to
   A) lipid peroxidation.   B) binding of toxin to cellular macromolecules.   C) mitochondrial damage.   D) disruption of cytoskeleton.   E) All of the above.
25. Canalicular cholestasis can be differentiated from cholangiopdestructive cholestasis (bile duct damage) by  
   A) a decrease in volume of bile produced  B) the inability to secrete the dye bromsulphalein (BSP) in cholangiopdestructive cholestasis  C) increases in serum alkaline phosphatase released from bile duct epithelium in cholangiopdestructive cholestasis  D) increases in serum levels of bile acids  E) both B & C are diagnostic for canalicular cholestasis

26. Cirrhosis is the end stage of chronic liver injury and is most likely due to increased production of collagen by _______.  
   A) hepatocytes  B) Kupffer cells  C) sinusoidal endothelial cells  D) Ito cells  E) macrophages

27. Much of the liver damage associated with the detoxification/bioactivation mediated by cytochrome P450 enzymes occurs in ___________ of the liver acinus.  
   A) zone 1  B) zone 2  C) zone 3

28. The liver is often the target organ for many chemicals with diverse structures because  
   A) first pass uptake of xenobiotics readily occurs due to the thinness of the sinusoidal endothelial cells.  B) the liver contains many transport mechanism that concentrate and store substances, including xenobiotics, intracellularly.  C) the liver contains mechanisms for storage of heavy metals that can mediate the formation of ROS.  D) the liver contains the highest concentration of biotransforming enzymes compared to other organs.  E) All of the above.

29. The mushroom toxin, phalloidin, contributes to cholestasis by binding to cytoskeletal actin microfilaments and thereby impairing  
   A) paracellular tight junctions.  B) transcytosis.  C) contraction of hepatocytes and slowing down of bile movement in the canaliculus.  D) transporters involved in bile formation.  E) both A & B.

For numbers 30-34 match the items in the left column with an item in the right column

30. Anoxigenic chemical  A) carbon monoxide
31. nerve cell body damage (neuronopathy)  B) chemicals that impair slow axonal transport of neurofilaments.
32. produces neuroexcitatory effects  C) chemicals that interact with postsynaptic neuron receptors
33. Chemical sympathectomy  D) chemicals that impair protein synthesis & result in degeneration of nissil bodies
34. distal axonopathy  E) catecholeamines & dopamine
35. Catecholeamines which are normal neurotransmitters of the sympathetic nervous system are capable of causing neuronopathy because they  
   A) are mitochondrial toxins  B) they intercalate into DNA and disrupt RNA transcription  C) they bind to ribosomes and SH-containing molecules  D) they are converted to toxins by the action of monoamine oxidase-B  E) monoamine oxidase converts them to quinones that then generate superoxide, $O_2^{-*}$, radical.

36. Agents that damage and/or disrupt axonal microtubule polymerization and depolymerization cause peripheral sensorimotor and autonomic neuropathy by  
   A) inhibiting fast axonal transport.  B) inhibiting slow axonal transport component a, Sca.  C) inhibiting slow axonal transport component b, SCb.  D) impairing neurotransmitter release.  E) Both B & C.
37. Both the central nervous system and the myocardium of the heart maintain a high metabolic activity. To maintain this activity
   A) they both require a constant uninterrupted supply of O₂  B) the heart will utilize a variety of energy sources including carbohydrates, lipids, and amino acids.  C) the CNS requires glucose exclusively as an energy source.  D) all of the above.

38. A chemical that induces a Parkinson-like condition in both humans and in experimental laboratory mice.
   A) methyl mercury  B) MPTP  C) doxorubicin  D) catecholamines  E) trimethyltin

39. Which of the following is a renal adaptive or protective mechanism following exposure to toxins?
   A) increased glomerular filtration rate  B) induction of metallothionein  C) production of heat-shock proteins  D) increased proximal tubule reabsorption  E) all of the above

40. After exposure of a laboratory rat to an unknown chemical, you examine the urine and blood and find that the urine has a normal pH range except that it is produced in small volume with a normal specific gravity range and the plasma shows an elevated BUN. Where might the nephron be experiencing damage?
   A) collecting ducts  B) distal convoluted tubule  C) proximal convoluted tubule  D) glomerulus and Bowman’s capsule  E) both (A) and (D) are damaged

41. Which of the following is not an enzyme involved in bioactivation or concentration of chemicals in the kidney.
   A) Cytochromes P450  B) gamma glutamyl transferase  C) glutathione S-transferase  D) cysteine conjugate β-lyase  E) All of the above are involved

42. The highest concentration of cytochrome P450 enzymes in the kidney occur in the
   A) S1 portion of the proximal convoluted tubule.  B) S2 portion of the proximal convoluted tubule.  C) S3 portion of the proximal convoluted tubule.  D) distal convoluted tubule.  E) collecting duct.

43. Which of the following is a mechanism that contributes to the intracellular transport of mercury, Hg, in proximal tubule epithelial cells?
   A) endocytosis of Hg bound to proteins  B) transport of Hg-glutathione complexes via the action of brush border associated γ-glutamyltranspeptidase and amino acid transporters  C) transport via a basolateral anion transporter of Hg-SH-protein conjugates.  D) transport of Hg-glutathione complexes via the action of brush border dipeptidases and amino acid transporters  E) All of the above.

44. Which of the following are potential targets for cardiotoxic chemicals
   A) calcium channels  B) catecholeamine receptors  C) cytochrome electron transfer system in aerobic metabolism  D) actin & myosin  E) all of the above

45. A metabolite of chronic alcohol consumption that induces cardiomyopathy.
   A) isoproterenol  B) ethanol  C) nitrogen oxide  D) quinone  E) acetaldehyde
Part II.

46. Many chemicals and normal cellular processes are responsible for producing "oxidative stress". Discuss the various means by which oxidative species are generated and the mechanisms that cells have to protect themselves from these chemicals. Explain how oxidative stress can impair the function of an organ. 10 Points.