This examination consists of four sections. When answering the short answer and essay-type 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.

Section 1. Slide Identification (21 points)

1. Figure 1 A, B, illustrates a biopsy from a 60-year-old woman that has been sent to you for pathological examination. What is your diagnosis? On what basis did you make this diagnosis? What is the prognosis for this patient? Why? (5 points)

   The tissue architecture is destroyed. The tumor consists of pleomorphic cells with large nuclei and little cytoplasm. There are mitotic figures seen in (B) (the nuclei) have clumped hyperchromatic chromatin, especially around the periphery and appear vacuolated/clear in the center of the nuclei making it look like "ground glass". The diagnoses might be small cell carcinoma (I can't tell which organ this is from - maybe lung). Small cell carcinoma have bad prognosis. This tumor would have a bad prognosis because it seems to have aggressively invaded the tissue and is poorly differentiated.

2. Describe the morphology of the lesion shown in Figure 2 A,B. What disease produces these changes? What is the cause of this disease? (5 points)

   The hepatocytes have round eosinophilic globules within their cytoplasm and are larger than normal. There also appears to be some fibrosis in the portal triad. α-1 antitrypsin deficiency can produce these changes. This is an autosomal recessive genetic disorder in which patients are missing an important enzyme (α-1 antitrypsin) and are more susceptible to getting emphysema of the lung and cirrhosis of the liver.

3. What is your diagnosis of the lesion illustrated in Figure 3 A, B? On what basis would you make this diagnosis? What are the risk factors for this disease? (6 points)

   This looks like it is from an ovary with a papillary carcinoma because of the finger-like projections that have a fibrovascular core. The bottom right of 3B might contain a psammoma body. Out of the ovarian tumors that we studied the diagnosis could be a papillary serous cystadenocarcinoma. This tumor does seem to be have an epithelial border around enclosing a fluid filled space - making it cystic. Risk factors for this disease, which originates from the serosal covering of the ovary are having a family history of cancers (especially breast cancer), having a BRCA mutation, and having oral contraceptive use.
4. The morphology of this biopsy in Figure 4A, B is MOST CONSISTENT with what genetic disease? Draw a three-generation pedigree that illustrates the main features of inheritance of this disease. What are the clinical consequences of this disease? (5 points)

This appears to be a spleen of a patient with sickle cell anemia. This can cause congestion of the spleen & splenomegaly as well as blocked blood flow to several parts of the body and can result in sevenemic events, painful episodes. It is inherited in autosomal recessive fashion, but homozygous recessive mutations are lethal and only heterozygotes survive. (Heterozygotes also are not affected by malaria)

Section 2. Multiple choice questions. Each question is worth 3 points (Total 30 points)

1. A 60 year old man is referred to your occupational clinic with respiratory symptoms. You have been trained to take a careful work history. You learn that your patient worked in the shipyards for about 35 years. He also indicates that he has smoked for 40 years. What would be the MOST LIKELY cause of this man's symptoms?

A. asthma
B. silicosis
C. mesothelioma
D. bronchogenic carcinoma
E. pneumonitis

2. One of the major radioactive isotopes typically released during accidents at nuclear power stations is iodine-131 which emits beta-radiation. What tissue will be MOST affected if this isotope is inhaled or ingested?

A. lung
B. colon
C. thyroid
D. bone marrow
E. breast

3. A 22 year old woman presents with multiple squamous cell carcinomas on sun-exposed areas of the skin. Biopsy of additional skin lesions reveals premalignant changes. Mutations in genes in which of the following cellular processes could cause carcinomas in this woman?

A. repair of DNA single strand breaks
B. nucleotide excision repair
C. base excision repair
D. recombination
E. differentiation
4. Diethylstilbesterol (DES) is an endocrine disruptor that causes cellular changes in the male and female genital tract. What conditions are associated with DES exposure?

A. vaginal adenosis  
B. ovarian carcinoma 
C. endometrial hyperplasia 
D. testicular cancer  
E. hypertrophy of the prostate  

5. A 60 year old man presents with blood in his stools. He undergoes a colonoscopy which reveals an anaplastic adenocarcinoma. On the basis of this information, what would you tell this man about his prognosis?

A. the prognosis is good because the tumor is well-differentiated  
B. the prognosis is poor because the tumor is poorly differentiated  
C. the prognosis is good because the tumor is benign  
D. the prognosis is poor because he has a stage IV cancer  
E. the prognosis is good because he has a stage I cancer

6. The mean doubling time of rapidly growing tumors can be as short as 10-20 days. This has been assessed by radioactively labeling tumor tissue with 3H-thymidine. This assay will tell you the proportion of cells that are:

A. dead  
B. terminally differentiated  
C. in G0  
D. in mitosis  
E. synthesizing DNA

7. It has been quite well established experimentally that tumors will not grow larger than 2 mm unless angiogenesis is triggered. One important growth factor that stimulates the proliferation of endothelial cells is:

A. hepatocyte growth factor (HGF)  
B. basic fibroblast growth factor (bFGF)  
C. fas  
D. angiotatin  
E. transforming growth factor-beta (TGF-b)
8. Aflatoxin is produced by a type of mold that contaminates improperly stored nuts. This toxin is a *liver* carcinogen. What gene is the molecular target for aflatoxin?

- A. c-myc √
- B. Rb ×
- C. p53 √
- D. c-ras √
- E. c-abl ×

9. Avian leukosis virus (ALV) is a slow transforming retrovirus which produces tumors in chickens over a period of approximately 8-12 months. The mechanism by which ALV transforms cells is referred to as:

- A. transduction √
- B. insertional mutagenesis ×
- C. point mutation ×
- D. chromosomal translocation ×
- E. gene amplification ×

10. Point mutations in K-ras are found in approximately 90% of pancreatic cancers. The MOST LIKELY consequence of this mutation on cell proliferation is:

- A. activation of GAP
- B. loss of GDP binding activity
- C. inhibition of cytoplasmic kinases
- D. transient activation of c-myc
- E. loss of GTPase activity ×

Section 3. Short answers. (27 points)

1. Latex allergies are a serious health concern, occurring in 5-12% of health care workers. What are two conditions produced by exposure to latex? (2 points)

- 1. Contact dermatitis in areas of skin exposed to latex.
- 2. Anaphylactic shock if there is a severe hypersensitivity type I reaction.

2. One of the two major repair pathways for DNA double strand breaks is called error-free. How can repair of DNA double strand breaks by this “error-free” mechanism contribute to carcinogenesis? (3 points)

This “error-free mechanism” is due to homologous recombination. So if the chromosome that gets damaged is the wild-type (non-mutated one) and the template from which the new sequence is made comes from the undamaged one, then there is a loss of heterozygosity for the
3. Exposure to radon produces a high incidence of bone cancer. Why is this specific type of cancer associated with radium? (3 points)

Radium gets incorporated into bone (like Ca^{2+}) and decays to produce radon releasing α particles in the process. α radiation is highly ionizing, but has low penetration ability, so therefore the cancer you get is mainly of the bone (doesn't affect bone marrow or other organs as much).

4. On May 8, 2001, the New York Times reported that a new drug, known as STI-271, shows great promise in treating patients with chronic myelogenous leukemia. Based on what you have learned in this class, what do you think is the molecular target for this drug? How do you think this drug might work? (4 points)

This new drug specifically targets rapidly dividing bone marrow cells and therefore has decreased side effects (no hair loss, less fatigue, GI tract, etc.). In CML, the mutation is often due to a c-ABL translocation from chromosome 9 → 22. This results in a new hybrid chromosome 22 that has c-ABL right next to each and ABL has increased tyrosine kinase activity resulting in a point of hematopoietic cells. Therefore this drug might specifically target the RNA splicing function, the mutated cells no longer get a signal to keep going through the cell cycle and therefore stop proliferating at such a fast rate.

5. The clonality of tumors was first established by studying tumors in women who were heterozygous for the enzyme glucose-6-phosphate dehydrogenase. Could this study have been performed in men? Why or why not? (4 points)

No, this study could not have been in men because they do not have X inactivation. Men only have 1 X chromosome and therefore only inherit 1 isotype of the G6PD gene. The study was done in women because they have 2 X chromosomes, one of which is randomly inactivated (forming X body). Therefore in females, some cells have 1 isotype of the G6PD gene and the other cells have the other form. This allows scientists to determine that most tumors are monoclonal—because (using G6PD as a marker) they could tell that the cells in the tumor came from the same cell (they all would have same G6PD isoform, versus if the tumor was polyclonal then it would have a mix of G6PD isoforms.)
6. A 70 year old man died suddenly at home and an autopsy was performed. He has previously given consent to be part of a study in which his prostate would be biopsied after his death. The pathology report states that the individual has dysplastic lesions. What changes would you expect to see? (4 points)

Dysplastic lesions are due to cellular alterations and have a different morphology. Cells tend to be pleomorphic (have irregular size and shape), hyperchromatic nuclei, prominent nucleoli, increased nuclear:cytoplasmic ratio (enlarged nuclei and loss cytoplasm), mitotic figures increased in frequency/abnormal. The normal tissue architecture is not evident in dysplastic lesions and mitotic figures no longer present in the layer/location where they are supposed to be. Dysplastic lesions can precede malignancy, but can also regress.

7. You have been invited to participate on a study section at NIH which will review grant applications for funding. One of the grants that you are assigned to review proposes to investigate the higher death rates from colon cancer among African-American women. (Incidence and mortality rates are shown in Table 10.) Specifically, the principal investigator will compare the prevalence of specific polymorphisms in a newly described gene associated with colon cancer in White, African-American, Asian, and Latino women in Los Angeles in what is referred to as a molecular epidemiology study. What questions about this study design would you raise? Explain why you would raise these questions (7 points)

First I would raise questions above the study's classification/categorization by race. These categories are man-made and have no genetic bases and there are many variations within each of these broad socially constructed groups. For example there are many different types of Asian or Latina women.) So therefore this groups will not have unique polymorphisms in the gene for colon cancer. In addition identifying specific polymorphisms for each group will not necessarily explain the differences in incidence nor in mortality because these groups have different cultural, socioeconomic backgrounds, eat different foods and have different lifestyles which could account for the different incidences in each group. Another limitation to the study could be that it is just in L.A. so it might not represent the population as a whole and where might be an environmental agent specifically in L.A. that is not equally distributed or equally affecting white, African American, Asian or Latinos equally, therefore skewing the result. Another question I would raise is that genetic variations probably do not account for most cancers and therefore I would suspect that other reasons are causing the increase in death rates from cancer in African American, Asian, or Latino women such as long reported
Essay Questions (22 points)

1. Genetic tests for BRCA-1 are being aggressively marketed by several companies. If a member of your family asks you about whether she should be tested, what you would tell her about the issues she should consider before being tested. (This should be based on your reading.) (10 points)

There are many issues to consider before being tested, regarding why she wants the genetic test, what the tests means and what could result if have a +. First, I would want to know why she would want to have the test done and what risk factors she has for developing breast cancer (family history, previous history of breast cancer, nulliparity, oral contraceptives, early menarche, late menopause, etc.). She should be aware that less than 10% of breast cancers are inherited and of these, 17% have a BRCA mutation. However, there is a fairly high degree of penetrance of the BRCA mutation was measured (75-80% of people with mutation developed breast cancer), but this information came from studies where only severe family cases were used and detection methods were better than in the screening (i.e., could detect mutations in the introns—where screening methods cannot). Therefore, it is not really known in the general population what the penetrance of BRCA mutation really is.

Another issue is that the screening tests give many false negatives because they do not pick up mutations in the introns and the risk has to be interpreted along with the other risk factors. She should also be aware of the BRCA-1 mutation means. BRCA-1 is involved in maintaining the integrity of the genome, DNA repair of double strand breaks (like those caused by radiation) and in regulating cell cycle. BRCA-1 is a tumor suppressor so a mutation in the gene increases the chances developing breast cancer, but it is not the only thing that causes cancers as many other factors are involved (most of which are not known!) and you need many other mutations to develop cancer. If a test were to come back + for a mutation when it does not necessarily mean she will have cancer and she must consider what she would do then. A mastectomy would be pretty extreme and just knowing that you are + for BRCA-1 mutation would have major psychosocial affects on her. Another consideration is that if she is + for BRCA-1 and wants to get more frequent mammographic screenings, this will actually increase her likelihood of developing cancer. This is due to the fact that BRCA-1 is involved in repairing DNA when there is DNA damage due to radiation so many put these women at an increased risk if she gets more frequent mammographic screenings.
2. On April 19, 2001, an article in the Providence Journal stated that the EPA was considering plans to toughen standards for arsenic in drinking water (article attached.) You have just been appointed director of the Department of Health in New Mexico where arsenic is a hotly debated issue because the drinking water in Albuquerque contains the highest levels of arsenic anywhere in the United States. Using the line of reasoning outlined in our class discussion on phthalates, how would you begin to address the problem. What are the major issues to consider? Be sure to explain your reasoning. (12 points).

Arsenic is a known human carcinogen that can cause bladder, lung, skin and other cancers, therefore as the director of dept. of health, I would want to know the amounts of arsenic in the water supply, the average exposure in the population of New Mexico, the rates of cancer in the state compared to other states, now arsenic is metabolized if it is found in other places besides the water, what an acceptable daily dose is, the cost of eliminating arsenic in the water. Arsenic is different from phthalates especially because arsenic is associated with human cancer while with phthalates is not known or there is not a big risk of developing cancer. I would also want to know which is most susceptible to developing cancer from arsenic (the poor, elderly children, specific industry workers, people living near the source, people eating seafood etc.). A major issue to consider is what the acceptable level of arsenic in the water should be and what the acceptable daily intake (ADI) of arsenic is (i.e. the maximal dose at which there are no harmful effects). A dose response curve for arsenic should be studied to see if increasing the dose increases disease or if decreasing the dose decreases disease (cancer). Epidemiological studies comparing the dose in 2 similar populations that differ in exposure to arsenic should be performed. However, it is very difficult to determine exposures, people vary in the amount of water they consume and some water sources may have variable amounts of arsenic (depending on the flow, current dumping of industry byproducts, etc). In addition there is variation in how people metabolize carcinogens and there might be age or sex variations as well. The costs of eliminating arsenic also has to be considered and compared to the costs of medical care, treatment lost of wages, for those who get cancer from arsenic (not that human lives can be given a price).

I would also want to determine why Albuquerque has such a high concentration of arsenic in the water.