This examination consists of four sections, encompassing material drawn from the laboratory and the lecture portions of the course. 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 (20 points)**

1. A section of spleen from a patient with Gaucher's disease is shown in Figure 1 (A, B, C). Describe the morphologic features in this section and the underlying biochemical mechanisms that produce these histopathologic changes.

   *Gaucher's disease is a storage disorder due to a defective glucocerebrosidase enzyme resulting in accumulation of glucocerebrosides. These are engulfed by macrophages which get a wrinkled-tissue paper appearance and are called Gaucher cells. Various types of Gaucher disease may include fatal CNS problems (due to build up of this toxic metabolite). Gaucher cells are particularly prevalent in the spleen as depicted in this figure. These cells are eosinophilic with foamy cytoplasm. These enlarged cells may disrupt normal splenic architecture. Figures A & B also depict lymphoid follicles filled with dark-staining lymphocytes. Also present are numerous RBCs. Many of the macrophages have prominent nucleoli.*

2. The morphology of this biopsy in Figure 2 (A and B) is MOST CONSISTENT with what genetic disease? Draw a three-generation pedigree that illustrates the main features of inheritance of this disease.

   *This appears to be a section of spleen depicting sickle cell anemia. Figure B shows a periarteriolar lymphoid sheath (PALS). Figure C shows some basophilic cells including lymphocytes. The most prominent feature are sickle-shaped RBCs due to crystallization of a mutated hemoglobin at low [O₂]. Sickle cell is an autosomal recessive disease: O = homozygous - healthy.*
3. Figure 3 (A, B, C) illustrates a skin biopsy from a 40 year old man that has been sent to you for pathological examination. What is your diagnosis? What is the prognosis for this patient? On what basis did you make this prognosis?

Two key types of skin CA that we’ve learned about are basal cell carcinoma & malignant melanoma. This section appears to be the latter. Figure B shows an abnormal-looking clump of melanocytes. On the other hand, basal cell carcinoma is usually characterized by large cell groups surrounded by a pallisading border - which doesn’t appear evident here. Too bad, because basal cell carc, is malignant but non-metastatic. This melanoma can be highly metastatic and has already invaded deep into the dermis. Cells are pleomorphic and disorganized, with clump looking chromatin. Figure C shows a raised bump - which is very characteristic and must be removed - hopefully it has not metastasized yet. (Poor prognosis if caught too late)

4. Is the lesion shown in Figure 4 (A,B) benign or malignant? Explain your answer. In what age group or groups are such lesions most common?

This lesion shows very abundant fibrous tissue with compressed, slit-like glands. It is a benign fibroadenoma of the breast. This may be palpable as a firm nodule. Women are encouraged to check for such nodules from their teenage years and on. Young and older women are both at risk. Hormonal changes like after puberty and menopause may be related to fibroadenoma development.

5. What type of cancer is illustrated in Figure 5 (A, B, C)? What are the characteristic morphological features of this tumor? How common is this tumor?

This cancer is renal clear cell carcinoma. It is characterized by abundant clear-looking (glycogene filled) cytoplasm. The nuclei on these slides appear dark with somewhat clumpy chromatin. A key difference between this cancer and nephroblastoma is that this cancer is not limited to younger kids (as is largely the case with nephroblastoma). This tumor is less common than colon, breast, prostate and lung tumors.

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

1. Teratogens are agents such as alcohol or thalidomide that affect the conceptus during development. A pregnant woman is GENERALLY most susceptible to teratogens during what period of development?

A. implantation
B. organogenesis
C. the second trimester of pregnancy
D. the third trimester of pregnancy
E. impossible to predict the period of susceptibility
2. One of your longterm patients was diagnosed with a well-differentiated carcinoma of the prostate which was detected during a routine physical examination. Researchers at your medical school are conducting a study of the prognostic value of immunohistochemical staining for adhesion molecules in prostate cancer. Based on the differentiation state of the tumor, what MIGHT you would expect to find in this tumor?

A. high levels of E-cadherin
B. low levels of E-cadherin assoc. with metastatic potential
C. high levels of collagenase type I
D. low levels of collagenase type I
E. none of the above

3. A 16 year-old girl is diagnosed with Hodgkin's disease and must undergo radiation treatment. Her parents are quite concerned about the longterm consequences of this exposure to radiation. What would you tell the parents about this risk?

A. There is a very marginal risk of subsequent cancers.
B. It is very likely that she will develop subsequent cancers.
C. She might develop breast cancer in the next few years.
D. She might develop breast cancer in 15-25 years. Leukemia is especially common though.
E. You can't give them any information about the risk.

4. The death rates for stomach cancer have steadily decreased since the 1930s. Which of the following is the MOST LIKELY explanation for this decrease?

A. A change in exposure to carcinogenic agent or agents
B. Increased detection of stomach cancer
C. Improved treatment for stomach cancer
D. Change in age structure of the population
E. Early detection of stomach cancer

5. You have a patient with histologically-confirmed Burkitt's lymphoma. Because you studied so hard in medical school, you remember that Burkitt's lymphoma is associated with Epstein-Barr virus infection. However, further testing reveals that the tumor is negative for EBV. You then recall that most cases of Burkitt's outside of Africa are EBV negative and that other factors are involved in the development of this tumor. What could you analyze the DNA from this tumor for?

A. amplification of c-myc
B. amplification of c-ras
C. translocation of c-myc
D. translocation of c-ras
E. point mutation in c-ras
6. The biopsy you ordered on your 30 year old patient comes back with a diagnosis of seminoma. How would you explain this diagnosis to your patient?

A. This is a premalignant tumor with an excellent prognosis
B. This is a benign tumor with an excellent prognosis
C. This is a benign tumor that can become problematic because it compresses blood vessels.
D. This is a malignant tumor with a good prognosis.
E. This is a malignant tumor with a poor prognosis.

7. The clonal origin of human cancers has been studied most extensively in women who are heterozygous for the enzyme glucose-6-phosphate dehydrogenase. It is possible to study clonality of tumors in these women because:

A. X chromosomal inactivation is not usually a random event
B. X chromosomal inactivation is usually a random event
C. The X chromosome is not involved
D. X chromosomal inactivation is variable in different cell types
E. This is an easily accessible population of women

8. Human papillomaviruses are important causes of cancer worldwide. Based on our current understanding of the biology of this family of viruses, the primary mechanism of transformation involves:

A. Insertional mutagenesis
B. Transduction
C. Loss of regulation of cellular oncogenes
D. Altered regulation of viral transforming proteins
E. Induction of mutations in cellular suppressor genes

9. Most tissues in the body both express TGF-β proteins and have receptors for these proteins. There is now strong evidence that this family of proteins play important roles in cell growth, differentiation, extracellular matrix production, and apoptosis. In some cell types, TGF-β arrests the cells in the G1 phase of the cell cycle. In which cell type do you think this effect is MOST LIKELY to occur?

A. normal epithelial cells
B. malignant epithelial cells
C. normal fibroblastic cells
D. malignant fibroblastic cells
E. malignant endothelial cells
10. Carcinoembryonic antigen (CEA) is normally expressed in embryonic tissue of the gastrointestinal tract, the liver, and the pancreas. In addition, it is expressed at high levels in a variety of benign disorders as well as some forms of cancer, including colorectal cancer. Despite this lack of specificity, CEA is a very useful marker for:

A. early detection of colorectal cancer
B. monitoring the use of preventive measures such as dietary changes
C. predicting the stage of disease
D. monitoring the tumor burden after treatment
E. distinguishing between benign and malignant colon tumors

Section 3. Short answers. (25 points)

1. Two new proteins XRCC4 and Ku important in repair of DNA breaks have been recently identified. Mutations in these proteins can lead to chromosome instability. Diagram the consequences for cells with mutations in XRCC4 or Ku, depending on whether wild-type p53 is present or absent. (5 points)

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XRCC4/Ku mutation
normal p53

G1 arrest (via p21 cdki) ─ successful repair → new cell
DNA repair (via RAD51)

XRCC4/Ku mutation
no p53

Cell cycle continues, mutated DNA is replicated, and more and more cells end up with the mutation. Mutations go unchecked without p53, "the guardian of the genome." Mutations DNA repair (especially if you lack p53) will probably lead to cancer.
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2. Patients with xeroderma pigmentosa develop skin cancers at a much higher frequency than non-skin cancers. How can this differential susceptibility BEST be explained? (4 points)

These patients have a defect in UV-endonuclease and have difficulty repairing the pyrimidine dimers that may form due to UV-B exposure. The high frequency of skin cancer is because skin is a surface tissue and therefore most commonly exposed to light. These patients also get blood vessel, lymphocyte, and retinal problems because all of these cells may be exposed to UV-damage at certain points.
3. Despite serious reservations expressed by many clinicians and researchers, genetic testing of women for mutations in BRCA1 and BRCA2 genes is becoming increasingly common. If testing indicates the presence of a mutation, woman can opt for close followup with mammography and clinical breast examination or prophylactic mastectomy. Based on what you know about the function of BRCA1 and BRCA2, COULD there be a risk with mammography? BRIEFLY explain your response. (4 points)

There is a potential risk with mammography because the BRCA genes may have a tumor suppressor function and are thought to possibly mediate DNA repair via RAD51. A woman with a mutation in BRCA-1 or BRCA-2 may not be able to efficiently repair the damage that could result from mammography. It is possible that the screening could actually put her at greater risk for the disease.

4. Retinoblastoma is a rare tumor of the eye in which the function of the RB protein is lost. Why does this tumor develop primarily in young children? (3 points)

This tumor requires one or two new mutations (inherited vs sporadic forms) in order to completely lose RB. Children still have immature, dividing retinoblasts which are capable of developing the necessary mutation. Osteosarcoma can also happen because bone also has rapidly dividing cells.

5. Migrant studies are important epidemiological tools for understanding the etiology of cancer. Briefly explain how migrant studies are conducted and what they have revealed about the cause of cancer. (5 points)

Migrant studies have shown that cancer risk may be more closely linked to environmental rather than genetic factors. Japanese immigrant studies show that the profile of common tumors in immigrants begins to resemble the distribution of tumors in the host country (with increasing time spent in the U.S.) One important factor may be diet. The "Japanese diet could increase the risk for stomach cancer, while the American "Westernized" diet causes increase the risk for stomach cancer. This shows that is...
6. Angiogenesis inhibitors have generated a great deal of excitement for the treatment of cancer. Why is this treatment considered superior to conventional chemotherapy? (4 points)

Angiogenesis inhibitors (like endostatin) are great because they stop the endothelial growth required in tumor vascularization, without causing DNA damage. Endothelial cells are also a very stable population and do not readily acquire resistance to angiogenesis inhibitors. Therefore even multiple separate endostatin treatments will consistently cause tumor regression each time. Cancer cells have high energy requirements and depend on triggering vascularization (via VEGF, FGF, TGF-β) for their continued growth and enlargement.

Section 4. Essay Questions (25 points) Please respond in complete sentences.

Read the attached New York Times article on asbestos contamination in a mining town in Montana. Write an essay in which you critically analyze the health consequences of phthalates, drawing on the discussion in class, your research and the assigned reading. Compare the issues raised by phthalates to those raised by asbestos in the New York Times article. Include in your essay, principles of toxicology, relevant basic science questions, and the clinical relevance of both exposures for your future patients.

The problems of phthalate and asbestos contamination are two closely related issues involving public health, toxicology, and industrial irresponsibility. An historical analysis of how asbestos was identified as a health risk and the degree to which its usage was properly regulated provides an interesting perspective on how to handle the phthalate issue.

Phthalates are weakly estrogenic compounds derived from the manufacturing of plastics, pesticides and a number of other substances. There have been several cases of animal populations which may have been exposed to phthalates. These populations have exhibited certain abnormalities in fertility and embryonic development. One theory Colburn believes that these abnormalities are the result of endocrine.

On the other hand, Colburn believes that these abnormalities are the result of endocrin...
These effects are real, they may not apply to humans. Humans may metabolize substances differently than animals do. Also, even if phthalates are toxic at high levels, most chemicals are toxic at sufficient dosage in the right species. Furthermore, he argues that phthalate exposure accounts for less than 1% of our exposure to diet-derived estrogenic compounds.

Thecolumb asserts that there is human evidence too. She cites increases in breast and prostate cancer, hyperactivity in kids, decreased intelligence and decreased fertility as evidence that phthalates may already be wreaking havoc on our population. Her critics (including me) believe that her human evidence is weak, because humans are subject to so many complex (historical) exposures. A convincing argument for phthalate toxicity would show harmful effects at the concentrations to which humans are exposed. A typical dose-response relationship between phthalate concentration and toxic effects would solidify the argument. Finally, a strong scientific model of phthalates’ biological effects would be beneficial.

That said, the asbestos fiasco shows the danger of responding too slowly to warning signs. Asbestos was in use for many years before it was linked to problems such as asbestosis, mesothelioma, and lung cancer. These diseases may all have a latency period of years and years, making it difficult to immediately identify the danger of asbestos. Once the danger is identified — industry will play dumb — we’re done. Since we would have lost a lot of money without asbestos mining. Therefore they offered lung x-rays and health insurance to protect their backs (demonstrating they were well-aware of the danger of asbestos) while still stating that the danger was not yet fully understood. Had the government taken a stronger stance early-on, when the first warning signs appeared, countless deaths might have been avoided.

So how are the phthalate and asbestos issues different? Asbestos exposure and effects are easier to identify. Lungs can be analyzed histologically for the presence of fibers — while phthalate exposure is rarely hard to prove — especially post-mortem. Also asbestos exposure at any time may be dangerous, while phthalates may only target specific events during development. The results of dangerous, while phthalates may only target specific events during development. The results of phthalates, phthalate exposure are readily identifiable diseases, while some of the proposed effects of phthalates, such as hyperactivity and decreased intelligence, are harder to consistently identify.

Therefore, I believe that there is insufficient evidence to merit phthalate elimination. The asbestos article highlights the dangers of action, but sufficient scientific evidence is not yet available.