This examination consists of three sections – histopathology, multiple choice, and short answer. When answering the questions, please pay careful attention to the number of points allotted and ANSWER ONLY IN THE SPACE PROVIDED.

SECTION 1 HISTOPATHOLOGY (total of 33 points)

1. A 45 year old man presents to your clinic with mild lymphadenopathy, a history of skeletal fractures, and bone pain. A histological section of his spleen is shown in Figure 1A, B below. (5 points)

What is your diagnosis? (1 point) Gaucher's disease

Describe what you see histologically. (2 points)

Many congested macrophages with abundant cytoplasm that included granular material. (This is particularly visible in the upper left hand corner of slide 1B)

What are the biochemical mechanisms by which these pathologic changes develop? (2 points)

This is an enzyme deficiency - the missing enzyme is glucocerebrosidase. It leaves glucocerebroside in the macrophages, which cannot be broken down.

Figure 1A  Figure 1B
2. A 35 year old woman who grew up in Australia comes to your dermatology clinic with a lesion on the skin. You biopsy the lesion and send it to the pathology laboratory. The pathologist diagnoses skin cancer. A section from this biopsy is shown in Figures 2A and 2B. (9 points)

What are the different types of skin cancer? (2 points)

Basal Cell Carcinoma & Malignant Melanoma

What type of skin cancer does this woman have? (1 point)

Melanoma

On what basis did the pathologist make this diagnosis? (2 points)

In figure 2B, many pleomorphic melanocytes with large, irregular nuclei and many mitoses are seen. The most important diagnostic feature are the pigment deposits in figure 2A.

What type of DNA damage would you expect to find in the cancer cells? (1 point)

Pyrimidine dimers from UV light

Explain how this type of DNA damage is repaired. (2 points)

Nucleotide Excision Repair clears pyrimidine dimers from the DNA.

What disease is associated with an inherited defect in this repair system? (1 point)

Xeroderma Pigmentosum
3. A routine pap smear from a 40 year old woman reveals malignant cells. She is referred for biopsy. The biopsy of her cervix shown in Figure 3 confirms that she has Stage I squamous cell carcinoma of the cervix. (9 points)

What causes this disease? (1 point)

Human Papilloma Virus, especially 16 and 18

What are the major risk factors associated with this disease? (2 points)

Early sexual activity
Many sexual partners
Smoking
(oral contraceptives—not well supported)

Briefly describe the mechanisms by which this malignancy develops. (3 points)

HPV elaborates 2 early proteins, E6 and E7, that alter the function of two very important tumor suppressor genes, p53 and Rb. E6 binds and degrades p53 removing important DNA repair (checkpoints) and apoptotic mechanisms. E7 binds Rb, making it release the E2F transcription activator and initiating cell proliferation.

What would you tell this woman about her prognosis? (Give your reasoning) (3 points)

While a portion of the lesion looks well-differentiated (it's producing keratin) - the cells surrounding it look pleomorphic and some abnormal mitoses appear. Since we don't see either a surface or basement membrane in this figure, we can assume that this tumor has invaded and may have metastatic potential. I would say that the prognosis is not particularly good. However, cervical cancer is not one of the three big killer diseases and treatment perhaps things will turn out okay.)

They do.

Prognosis for Stage I is good

Figure 3
4. A 65 year old man presents to his physician with a history of cough and weight loss that occurred over a period of about 6 months. His lung biopsy is shown in Figures 4A and 4B. (4 points)

What is your diagnosis? (1 point)

Small Cell Carcinoma of the lung

On what basis did you make your diagnosis? (2 points)

Numerous, disorganized, small, darkly staining cells have large nuclei and little cytoplasm. They do not form any sort of gland-like structures so they are not an adenocarcinoma and they do not form nests of cells so they are not a squamous cell carcinoma.

What is the primary cause of this type of lesion? (1 point)

Smoking cigarettes is correlated with this and most kinds of lung cancer.

Figure 4A

Figure 4B
5. A 60-year old woman presents with a nodule in her neck. Her clinical history reveals childhood radiation therapy for enlarged tonsils. A section from the biopsy is shown in Figures 5A and 5B. (6 points)

What is your diagnosis? (1 point)

Papillary Carcinoma of the thyroid

Describe the histopathologic features of this section that helped you reach your diagnosis. (2 points)

Normal thyroid follicles filled with colloid are visible (matted). The bulk of each slide is filled with papillae (epithelial cells surrounding a fibrovascular core).

What is known about the molecular mechanisms that produce this tumor? (3 points)

Subsequent to ionizing radiation thyroid cell DNA may have double stranded break that results in the fusion of the ret and T4 genes. This chimeric gene results in a growth factor receptor protein that is permanently dimerized and therefore continually on. (This kind of a break is much more common with strongly ionizing radiation like α or β than with the Y radiation used in radiotherapy, but perhaps this is involved in why there was such a long time from radiation to tumor presentation.) The mutated ret receptor provides both continual proliferation signals as well as anti-apoptotic signals as well - both of which sustain the tumor.
SECTION 2. MULTIPLE CHOICE (2.5 points each; total 30 points)

1. A 50 year old man is referred by his primary care physicians for a baseline colonoscopy. A small adenoma is detected, removed, and biopsied. What is the genetic alteration MOST LIKELY found in this tumor?

A. A translocation between chromosome 8 and chromosome 14
B. A mutation in the APC gene
C. A mutation in K-ras
D. Amplification of p53
E. Amplification of the EGF receptor

2. In 1957, thalidomide was marketed in Germany as a sedative and widely prescribed to control morning sickness in pregnant women. Which of the following is the MOST CHARACTERISTIC malformation in babies exposed to this drug in utero?

A. Renal malformations
B. Deafness
C. Congenital heart disease
D. Intestinal atresis
E. Phocomelia

3. Epidemiologic research on occupational diseases has been important in determining the causal relationship between a variety of synthetic chemicals and cancer. Which of the following cancers is associated with occupational exposure to vinyl chloride?

A. Burkitt’s lymphoma
B. Transitional carcinoma of the bladder
C. Adenocarcinoma of the lung
D. Angiosarcoma of the liver
E. Melanoma

4. Survival data from epidemiological studies is an important measure of how well cancer is managed. However, this data is subject to certain artifacts. What is a MAJOR source of bias in interpreting survival data?

A. Lead time bias
B. Increased reporting of cancer
C. Changes in diagnostic criteria of specific diseases
D. Changes in the relative proportion of certain histological types of cancer
E. Changes over time in the levels of exposure to chemicals
5. Silicosis is the most prevalent occupational disease in the world. Disease can be progressive, even after exposure ceases. Which of the following mediators released from activated macrophages has been shown to be important in the pathogenesis of silicosis?

A. Oxygen-derived free radicals
B. Epidermal growth factor
C. Her-2/neu
D. Lysozyme
E. Cdk-inhibitors

6. Osteosarcoma occurs at a higher rate than normal in patients with the hereditary form of retinoblastoma. However, these patients do not tend to have a higher risk of developing other types of cancers. Which of the following is the MOST LIKELY explanation for this finding?

A. Other cell types with mutations in both alleles of the Rb gene may be more susceptible to apoptosis.
B. Bone cells and retinoblasts are inherently more susceptible to carcinogenic agents.
C. Bone cells and retinoblasts are inherently more susceptible to radiation damage.
D. Mutations in both alleles of the Rb gene only occur in bone cells and retinoblasts.
E. There are no reasonable hypotheses to explain this observation at this time.

7. Fractionated radiotherapy has been shown to be more effective in the treatment of cancer than a few large doses. Prostate cancers are treated with a larger dose per fraction than head and neck cancers. What is the MOST LIKELY explanation for using a large dose in prostate cancer?

A. Prostate cancers are comprised of rapidly dividing cells that respond well to radiotherapy.
B. Prostate cancers are comprised of slowly dividing cells that respond poorly to radiotherapy.
C. Prostate cancers are comprised of slow dividing cells that respond well to radiotherapy.
D. Prostate cancers are comprised of slowly dividing cells that respond poorly to radiotherapy.
E. Prostate cancers cannot repair DNA damage

8. Molecular genetic studies have shown that 90% of pancreatic cancers carry a mutation in the K-ras oncogene. What are the functional consequences of this mutation?

A. It produces a chimeric protein with enhanced tyrosine kinase activity.
B. It produces higher levels of the ras protein.
C. It decreases the activity of the NF-1 tumor suppressor gene.
D. It inhibits the GTPase activity of K-ras.
E. It suppresses p53 expression.
9. Clinical, molecular, and epidemiological evidence has demonstrated that cancer is a multistep process. One of the **EARLIEST** steps in the process of invasion of some epithelial-derived cancers is altered expression in which of the following molecules?

A. An increase in VEGF
B. Decrease in cathepsin D
C. Increase in integrins
D. Decrease in E-cadherins
E. Increase in motility factors, such as hepatocyte growth factor

10. Pesticides that are now banned in the U.S. continue to be exported by manufacturers and used extensively in countries with less stringent regulation of hazardous chemicals. In the Philippines, pesticides are used to kill nematode worms on banana plantations. Which of the following health effects of pesticides was documented in Filipino workers?

A. Mental retardation
B. Bladder cancer
C. Parkinson’s syndrome
D. Sterility
E. Leukemia

11. A young family’s car broke down during a fierce snowstorm in Michigan. Because of the cold temperatures, they kept the car running to keep warm. When the police arrived, the children were unconscious and the parents were nauseous and dizzy. The police immediately determined they were suffering from carbon monoxide poisoning and rushed them to the hospital. CO binding to hemoglobin produces neurological damage through which of the following mechanisms?

A. Impaired cytochrome C oxidase
B. Reduction of NADPH-cytochrome P-450 reductase
C. N-glucuronidation
D. Binding to sulphydryl groups
E. Activation of cytochrome P-450

12. A 55 year old man who worked at the Quincy shipyards for 30 years presents with a history of cough, weight loss, and pain in his upper chest. You do a biopsy, collect a sputum sample, and take a chest x-ray. What is the MOST LIKELY diagnosis based on his occupational history?

A. Re-activation of tuberculosis
B. Mesothelioma
C. Myocardial infarction
D. Silicosis
E. An acute asthma attack
SECTION 3: SHORT ANSWERS

1. Irradiation of food has generated a great deal of controversy. Is irradiation of food a health risk? In evaluating the health consequences of irradiation of beef for school lunches, what issues related to radiation do you think should be considered? (4 points)

   Radiation of food with X-rays or γ-rays doesn’t leave any radiation behind. Because of this, it is perfectly safe. However, the quality of the food is diminished and for that reason may not be the best for children to eat. Important nutrients may be altered. because of radiation or food

2. For each of the tumors listed below, indicate whether it is benign or malignant and the cell type from which it derives. (5 points)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Benign/malignant</th>
<th>Cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratoma</td>
<td>Benign</td>
<td>Totipotent</td>
</tr>
<tr>
<td>leiomyoma</td>
<td>Benign</td>
<td>Smooth muscle</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Malignant</td>
<td>Squamous cell (in any case)</td>
</tr>
<tr>
<td>Seminoma</td>
<td>Malignant</td>
<td>Germ cell</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Malignant</td>
<td>Skeletal muscle</td>
</tr>
</tbody>
</table>

3. A 65 year old woman presents with uterine bleeding. Her history reveals that she has taken estrogen replacement therapy for many years. Biopsy reveals atypical hyperplasia. What morphological changes would you expect to see in this biopsy? (2 points)

   I would expect to see more (but normal) cells—the basic architecture of the tissue should be normal as well.

4. Diethylstilbestrol was prescribed to pregnant women from 1938-1971. In 1971, the FDA issued an advisory to physicians to cease use of this drug because it caused vaginal adenocarcinoma. What led researchers to link DES to this cancer? (2 points)

   Very young women (16-20 years old) began getting cancer that usually appears in much older (post-menopausal) women. This seemed to occur when the young women had been exposed to DES in utero (at about 7-9 wks gestation.)
5. Several years ago a new inhibitor of angiogenesis was discovered and was shown to inhibit tumors in mice. This discovery created great excitement after front page coverage in the *New York Times*. The company’s stock soared briefly. (5 points)

What is the target cell for angiogenesis inhibitors? **endothelial cells**

Why are angiogenesis inhibitors considered so promising for treatment of cancer as compared to conventional therapy?

Angiogenesis inhibitors are promising because they target a stable cell population. Endothelial cells are not likely to mutate and develop resistance to the inhibiting agent. Tumor cells can not grow much further than 1-2 mm from a blood vessel - so removing their nutrient supply is an effective way to kill them. Should some cells survive angiogenesis inhibitors could be applied again with the same effect.

6. Mutations in p53 are the most common mutations detected in human cancers. Aflatoxin produces a specific G:C → T:A transversion in codon 249 of p53 (called 249mut). What is the function of p53 in cells? Based on what you have learned about the function of p53, describe the mechanism by which p53 might contribute to the development of aflatoxin-induced hepatocellular carcinoma. (5 points)

p53 functions as an apoptosis + DNA repair regulator. It governs the expression of 3 products - p21, which halts the cell in G1, in order to allow time for DNA repair before entering S phase. GADD45, upregulated by p53, executes the repair. If the repair is successful the cell may continue, if not p53 will upregulate bax which will send the cell apoptotic signals. p53 is also responsible for a delay in G2 as well in order to assure that the cell is prepared for mitosis.

Lacking p53 will permit mutations in the hepatocyte’s DNA and will permit mutated cells to survive.

7. What role does Epstein Barr virus play in the development of Burkitt’s lymphoma in Africa? (3 points)

*EBV produces several proteins that alter the structure and the function of the transformed lymphocytes.*

EBNA1, upregulates LMP1 (an anti-apoptotic protein) and will cause overexpression of myc (under Ig promoters) and upregulate LMP1 as well as provide other pro proliferative signals to the cell (cyclin D others).
8. A 30 year old woman whose mother, maternal aunt, and maternal grandmother died of breast cancer finds a lump in her breast. A biopsy reveals malignant cancer and genetic testing indicates that she carries a mutation in BRCA1. (5 points)

Is BRCA1 associated with sporadic breast cancer? NO

What type of protein does the BRCA1 gene code for? DNA Repair (RAD50, NBS1, MRE11)

Briefly describe the function of BRCA1 in cells. BRCA1 activates three repair proteins involved in homologous recombination repair of double stranded DNA breaks. At what point in the cell cycle?

9. You are a medical student on a clinical rotation in a neighborhood where lead contaminated paint is still prevalent, despite a 1978 ban on lead additives in paint. Your preceptor asks you to conduct a workshop with parents on lead poisoning. Based on what you have learned about the hazards of lead poisoning and how it produces its harmful effects, what would you tell parents about 1) how lead is absorbed; 2) the differential susceptibility of children as compared to adults; and 3) the half-life of lead in tissue. (6 points)

1) Lead is absorbed either through inhalation (of dusts) or ingestion. Ingestion is particularly a problem with young children who may put paint chips in their mouths, lick the walls, you name it... Children, while generally, absorption through the GI is not as "efficient," generally absorption through the GI is not as "efficient." Inhalation, this does not hold true with children who may absorb the lead very efficiently by ingestion.

Children are much more susceptible to lead poisoning than adults. While in adults, there seems to be a threshold dose for effects in children there is no low dose threshold. The dose of 10 μg/dl in adults shows marked effects in children. At this dose, they will show pronounced neurological problems such as irritability and difficulty concentrating.

3) The half-life of lead in soft tissue is roughly 20-30 days while the half-life of lead in bone is much, much longer—months to years—depending on the rate of bone remodelling.