BIO 186 GENERAL PATHOLOGY  
Final Examination  
May 15, 2003 (2-5 pm)  

This examination consists of five sections, encompassing material drawn from the laboratory and the lecture portions of the course. When answering the short answer and essay 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. Histopathology (20 points)

1. A 50-year-old man presents with symptoms of slowly increasing dyspnea (shortness of breath) that has worsened over the past year. Bronchoscopic biopsy of the lung revealed diffuse pulmonary interstitial fibrosis, and the findings shown in Figure 1A. Results of an iron stain are shown in Figure 1B.

![Figure 1A](image1)

**Figure 1A.**

These findings are most consistent with what disease? What related diseases might you be concerned about? (3 points)

This is **asbestosis.** I would be concerned about lung cancer and mesothelioma because asbestos is a risk factor for both. Mesothelioma is a cancer of the pleural lining that usually starts happen with asbestos.
Explain the basis of your diagnosis. (Describe the findings present in Figures 1A and 1B).

2 points
The major finding is the asbestos body seen in block in the iron stain - this is a fiber of asbestos that has lodged in the lung. There are also eosinophilic inclusions, and fibrosis around the asbestos fiber.

What questions (pertinent to the diagnosis) might you ask this patient about when taking his past history? (2 points).

Has he ever worked in a factory or served in the military or worked in any other place where he could have been exposed to asbestos? Did he wear any protective gear?

Has he ever or does he now smoke? How many packs a day?

For how long? Does anything worsen or lessen the symptoms?

Does he have a family (like a wife who washed his clothes) who might have been exposed?

Long latency period for this disease.

What additional risk factor might you warn this patient about, and why? (2 points).

He should not smoke because the risk of developing bronchogenic lung cancers when one smokes and is exposed to asbestos is much higher than either risk factor alone. Smoking won't increase his chances of mesothelioma but he doesn't want to take the risks of other types.

2. A 60-year-old man presented to his physician with symptoms of fatigue and "lightheadedness". He was found to be severely anemic, and had a positive test for occult blood in a stool specimen. A biopsy was performed, and revealed the findings shown in Figures 2A, B, C, and D.
What is your diagnosis? Is this lesion benign or malignant? (3 points)

Colonic adenocarcinoma. It is malignant
Justify your diagnosis. (2 points) The cancer cells have penetrated deep into the mucosa, they are disorganized and anaplastic (undifferentiated), pleomorphic. The nuclei are hyperchromatic. The cells appear to be trying to form glands which should not be happening in the mucosa.

What molecular changes would you expect to see in this tissue sample? (3 points) All of these lesions have mutations in the APC gene. Point mutations were likely followed by k-ras, loss of p53 and loss of heterozygosity at 18q 21. All of these genetic changes generally make the normal mucosa or a colonic tumor progress to polyp to carcinoma.

3. An 18-year-old college student presented to her physician with a 1.5 cm nodule in the upper inner quadrant of her right breast. The surgeon who removed the lump described it as a well-encapsulated mass that was very readily "shelled out". Biopsy revealed the findings in Figures 3A and B.

Figure 3A (1x)

Figure 3B (4x)
Section 2. Multiple choice questions. Each question is worth 2 points (Total 16 points)

1. A 60-year-old man presents to his doctor with extreme fatigue. He is found to have a markedly elevated white blood cell count of 189,000/ul. Peripheral blood smear demonstrated the presence of mature and immature myeloid cells. Cytogenetic analysis on a bone marrow sample reveals a translocation that resulted in the formation of a chimeric protein with greatly enhanced tyrosine kinase activity. What was the translocation?

   A. t (13;14) bcl/Rb
   B. t (17;11) NF-1/myc
   C. t (9;22) bcr/ras
   D. t (18;14) Ig promoter/myc
   □ E. t (9;22) bcr/abl

2. Of the following types of tumors, which is the best example of viral oncogenesis in humans?

   ✓ A. Bronchogenic lung carcinoma
   B. Retinoblastoma
   C. Prostatic adenocarcinoma
   D. T-cell leukemia – Adult HTLV
   E. Hepatic angiosarcoma

3. A 60-year-old man with a strong past history of smoking was found to have a right upper lobe mass lesion on chest X-Ray. The mass is removed by wedge resection and is sent to Surgical Pathology for evaluation. The mass is consistent with a neoplasm. All of the following pieces of information would be important for you to know, to determine further therapy and prognosis EXCEPT:

   ✓ A. Is the neoplasm invading the margin of resection?
   B. What is the degree of atypia and pleomorphism of the neoplastic cells?
   C. How much inflammation is present in the neoplasm?
   D. Is the neoplasm primary or metastatic?
   E. What is the size of the neoplasm?
4. A 76-year-old man has hematuria. Evaluation by a urologist reveals a 3 cm mass in the dome of the bladder. Biopsy reveals a transitional cell carcinoma. In this malignancy, a single point mutation resulted in a protein's inability to hydrolyze GTP, thus resulting in cellular transformation. Which of the following oncogenes is most likely implicated in this case:
   - A. c-abl
   - B. c-neu
   - C. c-sis
   - D. K-ras
   - E. N-myc
   \[\checkmark\]

5. Which of the following characteristics of a neoplasm would imply the best prognosis?
   - A. Increased expression of laminin receptors
   - B. Decreased apoptosis
   - C. Presence of tumor giant cells
   - D. Increased nuclear/cytoplasmic ratio
   - E. Increased E-cadherin expression
   \[\checkmark\]

6. A 2 year-old boy is admitted to the hospital for evaluation of an abdominal mass and hematuria. A biopsy of the kidney demonstrated blastema (renal primordial cells), immature stroma, and tubules. Frequent mitotic figures are observed. These findings are most consistent with what diagnosis?
   - A. Retinoblastoma
   - B. Wilm's tumor
   - C. TORCH syndrome
   - D. Osteogenic sarcoma
   - E. Neurofibromatosis
   \[\checkmark\]

7. During a routine examination of a male born recently, you notice unilateral cryptorchidism and hypospadias. Knowing that exposure to endocrine disruptors may result in these congenital anomalies, you are concerned about the mother's exposure to potential teratogens during what "window of development"?
   - A. 1-2 weeks post-conception
   - B. 3rd trimester
   - C. 6-8 weeks
   - D. 7-12 weeks
   - E. 3-6 weeks
   \[\checkmark\]

8. A 40-year-old male who works at a nuclear reactor plant in his hometown was brought to the ER within 1-2 hours of a "minor" nuclear accident that occurred at the reactor. He was found to be disoriented and lethargic. He expired within the hour, while undergoing evaluation. What caused his death?
   - A. Metabolic imbalance due to radiation exposure
   - B. Internal bleeding due to thrombocytopenia
   - C. Irreversible brain swelling
   - D. Neutropenia and acute infection
   - E. Sepsis and Disseminated Intravascular Coagulation (DIC)
   \[\checkmark\]
Section 3. Short answers. (41 points)

1. A 40 year-old woman had a firm nodule palpable on the dome of her uterus six years ago on routine pelvic examination. Since then, the nodule has gradually increased in size – it is now approximately twice as large as when it was initially discovered. She has no symptoms from this mass and is healthy.

A. What is the likely diagnosis for this uterine nodule? Is this benign or malignant? (2 points)

- ovarian cyst. It is likely benign because it is slow growing and firm. leiomyoma

B. What four major tumor characteristics would allow you to make the distinction between a benign and a malignant tumor (describe the differences, briefly)? (4 points)

- Degree of differentiation: Benign tumors should be well differentiated and resemble the tissue of origin. Malignant tumors are anaplastic, undifferentiated, and often do not look like the tissue of origin.

- Presence of mitotic figures: Both will have mitotic figures but there will be more in malignant tumors than in benign. In addition, mitotic figures in malignant tumors are often abnormal (atypical mitotic figures).

- Invasion and metastasis: Invasion refers to the tumor spreading locally inside the same organ while metastasis is spread to distant sites. Benign tumors do not do either, they are encapsulated. Malignant tumors almost always invade and they have a chance of metastasizing.

- Tumor giant cells: should only be present in malignant tumors, they will not be in benign ones, like a growth - benign-slower, malignant-erratic - can be fast

2. Figure 4 shows the biopsy results of an anterior neck mass that arose in a 17-year-old boy who was born in Chernobyl at the time of the nuclear accident.

![Figure 4. (10x)](image)

What is the diagnosis? (2 points)

Papillary thyroid cancer
C. What is the inheritance pattern for this disease? Explain how this genetic defect could be recessive at the cellular level. (3 points)

B. Cytogenetic analysis of a tumor that arose in this child stated that there was a "loss of heterozygosity" at chromosome 13q14. What is meant by the term "loss of heterozygosity"? (2 points)

A. What neoplasms are likely to arise from this mechanism? (2 points)

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Excellent!
4. What is the difference between anaplasia and dysplasia? Define each term. (4 points)

Anaplasia means undifferentiated while dysplasia means altered and unregulated growth. Both have hyperchromatic nuclei, ↑ nuclear/cytoplasmic ratios, pleomorphic cells, prominent nucleoli, and an increase in mitotic figures. Anaplastic growths have tumor giant cells and atypical (tripolar) mitotic figures. Dysplastic growths do not and that's how main way to tell them apart. Anaplastic growths are more aggressive while dysplasias may regress, persist or progress.

5. A 70-year-old man is found by abdominal CAT scan to multiple 2-5 cm masses in both lobes of the liver. He tells his children that he has “liver cancer.” Based on what you know about cancer, is this likely to be accurate? How might this statement be made more accurate, and how would that affect prognosis? (2 points)

This is not very accurate. He probably has cancer that has metastasized to his liver from another site of origin. Cancer that is in multiple locations in one organ has invaded and when the mucosal sites in the liver it is almost always metastasis. The statement would be more accurate if he said I have cancer that has metastasized to my liver so now I have cancer in multiple locations. This makes the prognosis very bad because already metastasized cancers are very hard to treat.

What are the four mechanisms by which proto-oncogenes can be activated to oncogenes? Give one example of an oncogene activated by each mechanism, and an example of a type of cancer that can occur as a result. (6 points)

1. Point mutations: This occurs in ras. Follicular thyroid cancer occurs as a result (it is one of the many) yep.
2. Translocations forming chimeric proteins: Occurs with Chrom. 9 and 22 translocating to form bcr/abl on the so-called Philadelphia chromosome. This leads to chronic myeloid leukemia.
3. Translocations causing overexpression: occurs when chromosomes 8 and 14 translocate and c-myc causes over expression of the T-cell receptor. Hence ↑ in B cells and Burkitt's Lymphoma is a result.
4. Gene amplification: occurs when N-myc is amplified. ↑ cause Neuroblastoma.

7. A 10-year-old boy has extreme sun sensitivity and has extensive skin damage in sun-exposed sites. He has already had several basal cell skin carcinomas removed. He was diagnosed with Xeroderma pigmentosum. What is the defect in this disease? Why does he have lesions in sun-exposed areas of his body? (2 points)

He can not do nucleotide excision repair so everytime he is exposed to UV light (sunlight) he get pyrimidine dimers that he cannot repair. People with the problem excise the damaged area but this
8. What three (mechanistic) factors can play a role in determining an individual's susceptibility to skin cancer? (3 points)

The amount of melanin in their skin because melanin absorbs UV so if you have more your risk is less. Ability to do nucleotide excision repair which repairs the tandem mutations caused by UV. Ability to undergo apoptosis of badly damaged cells, if you can kill them off they won't grow and produce cancers. Need good p53 ligand expression for this.

Excellent!

9. A 27-year-old woman who underwent allogeneic bone marrow transplantation for treatment of Acute Myelogenous Leukemia (AML) is experiencing chronic graft-vs-host disease. Her doctor is considering the possibility of using an immunosuppressive drug - thalidomide - to treat her graft-vs-host disease. Her doctor expresses concerns about serious potential consequences of this medication. The patient finds the following information in the PDR (Physicians Desk Reference):

"Effective contraception must be used for at least 4 weeks before beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks following discontinuation of thalidomide therapy. Reliable contraception is indicated even when there has been a history of infertility, unless due to a hysterectomy or because the patient has been postmenopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual contact is the chosen method..."

Why are these recommendations made? Why the emphasis on using effective contraception for at least 4 weeks before beginning therapy? Address potential side effects of this medication, and timing issues. (4 points)

These recommendations are made because thalidomide causes severe birth defects when women take it while pregnant. The most obvious defect is phocomelia (seal-like limbs - usually the arms are very short and the hands are close to the chest). The period that is of most concern is 23-38 days post conception. At this point the woman often doesn't know that she is pregnant and hence it is important that she be on contraception a full menstrual cycle before taking thalidomide to ensure that she isn't pregnant from the start. The drug poses no threat to the mother you just want to ensure that there is absolutely none in her system while she is pregnant (hence recommendation). Even the smallest dose can cause an defect in the fetus so no chances should be taken.

Excellent!

10. Evasion of normal apoptosis is one of the ways by which malignant cells overcome normal restraints on proliferation. Give two examples of mechanisms by which malignant cells can overcome apoptosis. (2 points)

They can have a mutation in p53 which decreases apoptosis or another mechanism to degrade p53 like the E6 protein produced by HPV 16 and 18 which degrades p53 and apoptosis. Or they could have a mutation in bcl-2 which decreases...
Section 4. Matching. (0.5 points each x 12 = 6 points).

Match the exposure/risk factor to the associated malignancy. Note that each letter can be used more than once or not at all.

- a. hepatic angiogenic sarcoma
- b. bronchogenic carcinoma
- c. osteogenic sarcoma
- d. melanoma
- e. transitional cell carcinoma of the bladder
- f. cervical cancer
- g. Burkitt’s lymphoma
- h. stomach (gastric) cancer
- i. hepatocellular carcinoma
- j. T cell leukemia/lymphoma
- k. mesothelioma
- l. glioblastoma

(Please give only ONE answer per blank):

Polyvinyl chloride  a
Cigarette smoking  b
Epstein Barr Virus  g
β-naphthalamine  c
eultraviolet rays  d
HPV  f
Helicobacter pylori  e
Hepatitis B virus  h
HTLV I  k
asbestos  b
radon  c
radium  l
Section 5. Essay Questions (9 points total for each of two major essay questions = 18 points for this section).

1. A 30-year-old woman is concerned that she has a very high risk of breast cancer, and wishes to have genetic testing done. She has read about the "breast cancer gene", and is sure that her family is affected. Her sister was recently diagnosed with recurrent breast cancer at age 34, and her mother died of breast cancer at age 45. Her physician discussed the "pros" and "cons" of genetic testing with her, and she has decided to proceed with testing. However, she is confused because her physician has encouraged her to ask her sister with breast cancer to be tested first.

A. Delineate two "pros" and two "cons" of being tested (4 points).

Pros:
- Since she has two first degree relatives who have had breast cancer, she is at greater risk and so she has a mutation in BRCA 1 or 2. She might consider a mastectomy to remove the "potential time bomb" as some call them. And thus lessen her chances of breast cancer.
- If she does not have the same mutation as her sister (see B), she will be less at risk for familial breast cancer and this might take a weight off her.

Cons:
- BRCA 1 and 2 mutations are only found in 5-10% of breast cancers. So just because she does not have the mutation does not mean that she will not get sporadic breast cancer. It may make it less likely that she would get familial (the same mutation as her sister).
- Even if she gets a radical mastectomy, there is no way she can get rid of every single cell of breast tissue and she could still get breast cancer, though the risk would be less.

B. Why was it recommended that her sister be tested first? (1 point)

Even though we have many different possible mutations of BRCA 1 and 2, we don't know what they all mean at this stage or which ones will develop cancer. However, if they know which mutation to look for, they can give her a better answer. If she has that mutation, her chances are greatly increased. If not, her chances of familial cancer are decreased.

C. What type of cancer-causing genes are the "breast cancer genes", and how do they cause cancer? (4 points)

BRCA 1 is involved in DNA repair and as a "gatekeeper." This means that BRCA 1 arrests the cell before mitosis to allow it time to repair. Both BRCA 1 and 2 are involved in homologous recombination and allowing the DNA to repair double strand breaks in an "error-free" way. Thus without these two genes the cell is unable to do homologous repair and if it loses BRCA 1 it will be less likely to arrest before mitosis and repair. As a result, damaged DNA will propagate and...
2. Read the attached excerpts from an article entitled: “Contamination of drinking water by arsenic in Bangladesh: a public health emergency”. Although you haven’t learned specifically about arsenic, apply the information you’ve learned in class and in your research on phthalate toxicity. Here’s the task: Describe the key questions you would ask (or steps you would take) in order to learn more about arsenic toxicity that would enable you to assess the magnitude of the risk of chronic arsenic exposure to the Bangladeshi population. You need only formulate the questions – you obviously don’t have the information you need to be able to answer them. Include in your essay, principles of toxicology and relevant scientific questions. Finally, speculate briefly about what might be done to lessen the risk to the Bangladeshi population.

(6 points)

1. The first toxicology principle is to identify the toxicant. This has clearly been done in the case of arsenic. It has been known for many years that arsenic is a dangerous compound.

2. But how did we come up with that? Are there animal studies? What did they show? What animals were used? Do they metabolise arsenic in the same way that people do? How was the arsenic given to them (eat it, drink it, placed on skin)?

3. Was a dose response curve developed? How much of arsenic is needed to cause an effect? Was LD50 (dose at which 50% of the animals died) discovered? What is Bangladesh’s standard higher?

4. Were any cell culture studies done to determine the mechanism by which arsenic causes damage?

5. What about epidemiologic studies? These are hard because it is hard to get exposure and health data that is accurate. Also you can’t control exposures so it is hard to prove that the damage was due to arsenic. However, you get real world data which the other two don’t. Are humans exposed to many factors which may contribute compound differently. This real world data can tell you what happens in humans and then you use the other two to find mechanism and dose.

6. Exposure levels need to be done, which it seems like this article has already done, saying that 35-77 million people are in regions where some wells are contaminated. How much is the average person consuming? How much do they need to consume before they get sick?

7. Do any protection/filtration methods work? Can the water be treated to remove arsenic? Does boiling or iodine do anything? Is water safe for swimming/washing dishes clothes?

8. I would try to find answers to the above protection questions in an essay.