BIO 186 GENERAL PATHOLOGY
Final Examination

May 13, 2002
2:00-5:00 PM

This examination consists of four sections. 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. Slide Identification (15 points)

1. **Figure 1** (A and B) shows a biopsy from a 20 year old male. The morphology of this lesion is MOST CONSISTENT with what disease?
   - Sickle cell anemia ✓

   Explain the basis of your diagnosis.
   - We see an area of expanded red pulp w/ red blood cells in abnormal sickle shapes. We are in the spleen.
   - What is/are the molecular change(s) that produce(s) this disease?
     - Cytoskeleton of the proteins of the RBC are damaged.
     - Mutation in B-globin.
   - How do/does this/these alteration(s) lead to disease?
     - This damage causes the sickle shape - RBC cannot perform function.
     - You see anemia, b/c spleen traps them and kills them.

2. **Figure 2** (A, B) illustrates a biopsy from a 60 year old man that has been sent to you for pathological examination.

   What is your diagnosis?
   - Adenocarcinoma in the colon ✓

   Is this lesion benign or malignant?
   - Malignant

   Justify your diagnosis.
   - You know you're in the colon because you can still see some goblet cells. You know it's malignant b/c the cells are pleomorphic, nucleus/cytoplasm ratio is higher, nuclei are hyperchromatic & situated at all levels of cell (not just basal) and there is mucus in center of gland.

   What molecular changes would you expect on DNA analysis of this tissue sample?
   - APC mutations + many other mutations such as ras, p53 etc.

3. **Figure 3** A, B, C is a malignant cancer from a 35 year-old farmworker.

   What is your diagnosis?
   - Malignant melanoma ✓

   Describe the morphology of this lesion.
   - First expanding radially (horizontally) & then down-deep to adjacent tissue. Cells are pleomorphic w/ large nuc/cytoplasm ratio, hyperchromatic nuclei, prominent nucleoli, nuclei are disorganized in cell.

   What is the cause of this cancer?
   - Pesticide exposure on skin ✓

   How does this agent interact with DNA, producing cancer?
   - Probably gets absorbed through the skin & gets into cell.
Section 2. Multiple choice questions. Each question is worth 3 points (Total 27 points)

1. The biopsy in Figure 4 is from a 45 year old woman with cervical cancer. Many years ago she recalls having been diagnosed with HPV infection but subsequent Pap smears were negative. Her doctor explains that HPV can remain latent for many years. Based on your assessment of this biopsy, what would you tell your patient about her cancer?
A. The cancer is well-differentiated and her prognosis is good if she is Stage I
B. The cancer is well-differentiated and her prognosis is poor, regardless of stage of disease
C. The cancer is anaplastic and her prognosis is poor
D. The cancer is anaplastic and her prognosis is good
E. The cancer has definitely metastasized

2. Cell culture models of carcinogenesis have been crucial in understanding the development of cancer. You are a researcher interested in studying the carcinogenicity of tobacco smoke. What is the MOST stringent criterion of carcinogenicity in a cell culture model?
A. The morphology of the cells is altered in culture
B. The cells produce foci in culture
C. The cells require a lower concentration of serum to grow
D. The cells form colonies in soft agar
E. The cells produce tumors in nude mice

3. A young woman whose mother, aunt, and grandmother died of breast cancer wants to be tested for mutations in BRCA-1 and BRCA-2. What is the proposed mechanism by which mutations in these genes contribute to the development of cancer?
A. Inhibition of cyclin activity is lost
B. There is over-expression of the BRCA-1/2 protein
C. DNA repair is defective
D. There is interference with signal transduction by ras
E. Cell adhesion is altered

4. Avian leukemia virus is an slow transforming retrovirus that produces tumors in chickens. The oncogene that this virus alters is functionally active as a:
A. MAP kinase
B. serine kinase
C. G-protein
D. transcription factor
E. tyrosine kinase

5. Exposure to 6-10 Gy induces severe diarrhea and infections due to depletion of stem cells in the gastrointestinal tract. Recent experimental evidence in a mouse model indicates that the mechanism of cell death is due to:
A. direct targeting of stem cells by radiation
B. indirect effects on stem cells mediated by severe bone marrow toxicity at this dose of radiation
C. direct effects of radiation on endothelial cells in the intestine
D. indirect effects of radiation on endothelial cells in the intestine
6. Cyclin D is overexpressed in several cancers, including breast, liver, and esophageal cancers. What is one common mechanism by which increased levels of cyclin D are produced?
   A. Gene amplification
   B. Point mutation
   C. Gene rearrangement
   D. Insertional mutagenesis
   E. Two base deletion

7. A 40 year old man presents with a recent history of weight loss, mild anemia, and extreme splenomegaly. He is ultimately diagnosed with chronic myelogenous leukemia. What genetic change is characteristic of this tumor?
   A. amplification of c-myc
   B. fusion of bcr-abl
   C. point mutation in K-ras
   D. translocation of c-myc
   E. amplification of N-myc

8. Burkitt’s lymphoma is an aggressive cancer that occurs in young children in Africa and is associated with Epstein Barr virus infection. One possible mechanism by which this virus contributes to the production of cancer is:
   A. activation of translocation between chromosome 8 and 14
   B. binding of EBNA2 with p53
   C. transactivation of IL-2
   D. transduction of a cellular oncogene
   E. production of chronic injury to lymphocytes

9. A young woman is diagnosed with clear cell adenocarcinoma of the vagina. What is the MOST LIKELY cause of this cancer?
   A. Her mother was given thalidomide for the treatment of morning sickness
   B. Her father drank heavily before her mother got pregnant
   C. Her mother was infected with cytomegalovirus
   D. Her mother was given diethystiibesterol to reduce the risk of miscarriage
   E. Her mother drank heavily during pregnancy

Section 3. Short answers. (38 points)

1. A 60 year old woman comes to your office complaining of back pain and abnormal bleeding. You diagnose a leiomyoma. When you tell her she has a tumor, she is worried that this means she has cancer. What is the cellular origin of this tumor? What would you tell her about her risk of developing cancer? (4 points)

   Smooth muscle cells give rise to this cancer. This is a benign tumor and she has no risk of developing cancer from this particular benign tumor.
2. If normal cells were fused with malignant cells, would you expect the phenotype of the fused cells to be "normal" or malignant? Why? (3 points)

   malignant, normal tumor suppressors. 0

   malignant characteristics conferred by oncogenes are dominant. if these two cells fuse, the normal DNA can not do anything to "protect" the cell if there is one copy of an oncogene.

3. A patient comes to your office with a news article reporting on two large case-control studies on screening for neuroblastoma published in New England Journal of Medicine. Both studies showed that the incidence of neuroblastoma was higher in the screened group but that mortality from neuroblastoma was NOT decreased in children who had been screened. (In fact, mortality was higher in the screened group.) How is it possible that early diagnosis did not lead to decreased mortality? What is a biological explanation for these findings? (4 points)

   Neuroblastoma is caused by amplification of the N-myc gene. Mortality may not have differed because there is no treatment for neuroblastoma - so it makes no difference whether you screened or not. Incidence seems higher because you are probably looking for a gene mutation - this means you are counting in people whose tumors would have spontaneously disappeared as they do in stage IVs. these people would not be included in the control group.

4. Patients with xeroderma pigmentosum develop skin cancers at a 2000X greater frequency than non-skin cancers. Except for brain cancer, these patients do not have a higher risk of developing other cancers. Briefly explain this differential risk. (2 points)

   Xeroderma pigmentosum is caused because of an inability to perform nucleotide excision repair after pyrimidine dimer formation. The T-T dimers only happen in skin after exposure to UV - therefore skin cancers more likely. Other parts of the body do not use NER. excision repair - so a defect in this process would not affect them. they use base excision repair.

5. Despite the controversy over mammography, you continue to advise your patients over 50 to have a yearly mammogram. A density was detected in one of your patients that was diagnosed as ductal carcinoma in situ (DCIS) on biopsy. What would you tell your patient this means? (3 points)

   Ductal carcinoma in situ is a malignant cancer in the ductal epithelial cells of the breast. While this is bad news, the good news is that it has not metastasized yet. The proliferating duct cells have grown into the duct, not spread into mesodermal tissue. Therefore, a partial or radical mastectomy could preserve a breast.
6. How does ionizing radiation produce damage in tissues? Why is vascularized tissue more sensitive to radiation therapy? (5 points)

Ionizing radiation causes tissue damage both directly and indirectly. Direct involves actually knocking off or out of DNA molecules making them electrophilic. This can result in cross linking with other DNA or protein. Single stranded & stranded breaks in DNA. Indirect damage can result in formation of oxygen and OH radicals which will also cause similar damage. Vascularized tissue is more sensitive to radiation therapy because endothelial cells will often die before the tissue itself cause hypoxia. (as in G1 of mouse in expt mentioned in class). Tissues with higher cell content will also be more susceptible.

7. Invasion and metastasis are critical events in carcinogenesis. Describe the mechanisms by which malignant cells invade, drawing on what you know about the specific molecules involved. Propose a reasonable therapeutic approach to inhibiting invasion and briefly discuss the advantages and disadvantages of this approach. (6 points)

Invasion involves 4 steps - detachment is mediated by down regulation of adhesion molecules. Attachment is mediated by fibronectin and collagen receptors. Digest ECM - matrix metalloproteases & collagenase III & catherpsin D. Mobility factors - matrix degradation products, BstII, macrophages & hepaqueptide GF.

* disadvantages include inability to design one that can block mobility factors well & delimiting correct area may also be a problem. Mobility factors could be blocked somehow - maybe using target tumor cells. One most other normal body cells would not need and do not produce mobility factors - so there wouldn't be many adverse effects on regular body tissue.

8. A 25 year old worker at a manufacturing plant comes to your clinic complaining of asthma-like symptoms that disappear on the weekend. What might you suspect is the problem based on this history? How would you go about diagnosing this patient's condition? (5 points)

This worker is exposed to some kind of exposure at work that is blocking off his airways partially. I am not sure what the exact compound or material is (it is not asbestos or mesothelioma - b/c they have a long latency period). I would ask him the following questions:

1) all jobs in lifetime (although the current one seems to be the one causing)
2) work exposure - what don't he / work with? similar
3) other workers - do they have symptoms?
4) non-work exposure - anywhere else he is during the week he is not at during weekends.
9. Physicians are often involved in health education, either directly or indirectly. In Cancer in the Community, the following statements were described by the health promotion team as "misconceptions" that the people in Tannerstown held that were not "accurate" from a scientific point of view. Based on what you have learned about the biology of cancer, pick ONE of the "misconceptions" and explain whether or not would you dismiss these notions as mere "myths" with no physiological basis? (6 points)

- "There is cancer hidden in everybody. It is a matter of time until it becomes activated."
- "Cancer is inherited. You can be born with it in your body."

**#2** - Cancer is inherited in some ways — this is not a total myth. It is not that you are born with a cancerous mass — but you could be born with genes that pre-dispose you to having cancers.

**eq1** Rb gene: 40% of retinoblastomas are inherited. You first inherit one mutated Rb in all your cells. All you need is a second hit to one of those cells to develop retinoblastoma. 2 hits mean both tumor suppressors are inactivated.

**eq2** APC — those who inherit an APC mutation (also a tumor suppressor) are sure to get another hit and develop adenomatous polyps in the colon. This condition is called FAP. Eventually these polyps can progress to colon cancer.

**eq3** Littre's syndrome — inherit one p53 mutation - 25% more likely to develop cancers.
Section 4. Essay Question (20 points) Please respond in complete sentences in the space provided.

Read the attached discussion from your textbook on lead poisoning. Write an essay in which you compare the health consequences of phthalates that of lead, drawing on the discussion in class, your research and the assigned reading. Compare the issues raised by phthalates to those raised by lead poisoning. Include in your essay, principles of toxicology, including the steps in hazard identification, relevant basic science questions, and the clinical relevance of both exposures for your future patients. Be concrete.

Phthalates and lead both seem to be substances that affect young children the most. Therefore, it is very important to carefully consider the health effects of both. I will use the principles of toxicology to talk about each substance. They include (1) identification, (2) toxicokinetics, (3) dose response, and (4) risk characterization.

(i) Compared to lead, which was discovered as a hazardous material over 150 years ago, phthalates have only recently come into the spotlight. DEHP, an older version of phthalates, was changed to DINP because the latter was thought to be less toxic. However, the debate continues as to exactly how toxic DINP really is.

(ii) Dose response information for lead is not provided in this article. However, it implies that 15 μg/dL, as found in >10% of urban preschool children, is unacceptable. Dose response studies ask the question of whether an increase in dose results in increased pathology or vice versa. In the case of phthalates, it was found that at high levels of phthalate exposure, mice developed spongy liver. A dose response curve extrapolated from this and other research tells us that ADI is 1.2 mg/dL/day for children <18 mos.

(iii) Exposure assessment involves understanding where susceptible populations are being exposed to this hazardous material. In the case of lead, it seems to be everywhere—petroleum, paint, pipes, ceramics, cans, soil, water. It can either be inhaled or ingested. Exposures seem like they could happen anywhere, especially in the home for children. Phthalate exposure is also ubiquitous—phthalates are used in all flexible plastics, including baby toys. Ingestion is the only known route of transmission through skin are unclear at this point.

(iv) Risk characterization asks the question—so what happens after exposure—what are the consequences to the body? Because lead has had such a long history, we know a lot more about it. High affinity for sulfhydryl groups and affects

(v)
and developmental delay, and intellectual impairment. Not so much is known about phthalates, they are thought to cause cancer & endocrine disruption, but the evidence is not so solid. Animal tests have shown that phthalates, while non-genotoxic, are peroxisome proliferators and indirectly cause DNA damage through increased 
H2O2 production. The endpoint or outcome used to measure risk was spongy liver in mice. Children who

brush on toys for more than 150 min/day are thought to be at increased risk. But, with the present evidence, it is hard to say how applicable the results of animal studies are in humans. For example, humans don’t really react to peroxisome proliferators do. Also, mice are exposed to much higher levels in artificial, controlled envts. than humans—so can that data be applied? age, sex, exposure & species will affect outcome of a toxin. More clinical & basic science questions regarding these factors need to be asked & answered in order to further determine the real risk of phthalates to young children.

Overall, the research on phthalates is still in its beginning phases and we know a lot more about lead at this point. If phthalate is truly toxic, then we need to put in the same advocacy efforts that went into getting unleaded gasoline on the market, clean up lead paint from old buildings and establish the lead-safe advocacy center in order to protect children from the harmful effects of phthalates.

Socially, it seems like lead is a much more difficult problem to deal with because it is so intertwined with race & class conditions. Phthalates could pose similar problems if replacing phthalates with something else makes toys more expensive and only rich people could afford them. We could look to Europe to learn some lessons b/c they have already banned phthalates there.

Both phthalates & lead are going to be an issue in my clinical practice—not only in children but adults, especially industrial workers. It is important to recognize the symptoms & know how to assess exposure in order to make accurate diagnoses.