Pathology Test 1 Challenges:

Regarding the extra point we received from Question #73: Our final grade is determined by the total number of points we earn. So the point everyone received goes towards our total number of points. So the 1 point vs. 1.25 points added to our grade sheet doesn't really matter, what matters is the extra point out of 80. (For example, a 100 = 81/80 points)

- **Question #6:** A 7 year-old girl develops pyoderma (an infection of the skin) of her legs because mosquito bites have been infected with streptococci. Which of the following types of cells would be most prominent in the infected areas?
    A. Eosinophil
    B. Lymphocyte
    C. Macrophage
    D. Neutrophil
    E. Plasma cell

  Challenge: The patient has an Streptococcoi infection. Since bacterial infection is exogenous, wouldn't the patient produce a humeral response (E-plasma cells) against the infecting agent?

  From Dr. Henegar: The example given in the question should be interpreted as acute inflammation because she "develops" an infection in the skin due to streptococci. There is nothing in the question that suggests that this has been chronic process. I realize that "pyoderma" is not a term that many students know yet but it is characterized by pus formation. In any case, bacterial infections nearly always lead to acute inflammation with neutrophil infiltration, liquifactive necrosis with abscess formation, and resolution. Rarely bacterial infections can cause chronic inflammation but this usually occurs in instances like Mycobacterium tuberculosis or Treponema pallidum (syphilis) infection. If a similar question is used in the future, I will probably add something about pus-filled lesions or abscess formation.

- **Question #51:** An obstetrician explains to a very concerned 24 year-old pregnant HIV-1+ woman that vertical transmission of AIDS from mother to infant may occur in utero by transplacental spread, during delivery through an infected birth canal, or after birth by ingestion of breast milk. What is the rate for perinatal transmission?
    A. 10%
    B. 25%
    C. 50%
    D. 75%
    E. 100%

  Challenge: The percentage would have been 10% if the mother had been treated. The question did not give treatment information. Without treatment, the percentage would have been 20-30% or answer B. How could we decide without knowing whether or not she had been treated?

  This is taken from the handout. Since it does not say that she was being treated, we are not to assume that she is.

- **Question #69:** Following an abnormal Pap smear, a 34 year-old woman has a cervical biopsy. The cervical eopthelium demonstrates marked hyperchromasia and an increased nuclear/cytoplasmic ratio. The changes involve the full thickness of the epithelium and do not penetrate the basement membrane. A test for a carcinogenic agent is performed. You would predict that the test will show:
    A. Epstein Barr virus
    B. Herpes simplex virus
    C. High risk human papillomavirus
    D. Human herpesvirus-8
    E. Low-risk human papillomavirus

  Challenge: I figured since the neoplastic changes had not penetrated the basement membrane, the carcinogenic agent would have been Low-risk human papillomavirus.

  *From Dr. Hughson: This question is pretty clear and was taken almost word for word from the notes. In practical terms, the students in their OB rotations will need to be able to associate **high-risk HPV** with a high risk of cervical cancer and **low-risk HPV** with very little chance of cancer. The risk mainly comes from the chance of contracting high-risk HPV because of behavioral practices that lead to additional exposure. You will be getting reports on follow-up of some PAP smears that require additional HPV testing. High risk HPV=bad: need follow-up culposcopy and biopsy. Low-risk=OK for the time being follow with annual PAP smears.*

Pathology Test 1 Challenges:

- **Question #73:** A two year boy has developed a retinoblastoma of his right eye. His 3 year-old sister had a retinoblastoma successfully treated last year and an aunt died of metastatic retinoblastoma at 4 years of age. A molecular genetic study of the tumor shows a deletion of gene sequences (loss of heterozygostiy) of a segment of chromosome 13q that includes 13q14, the locus of the retinoblastoma gene. This deletion is not present in the testing of DNA from the patient's lymphocytes. According to the Knudson hypothesis this patient has:

  A. Acquired after birth a mutated retinoblastoma gene in tumor and lymphocytes.
  B. Acquired after birth a mutated retinoblastoma gene in tumor but not in lymphocytes.
  C. Inherited a deleted retinoblastoma gene in retinal tissues but not lymphocytes.
  D. Inherited a mutated retinoblastoma gene in tumor and lymphocytes.
  E. Inherited a mutated retinoblastoma gene in tumor but not in lymphocytes.

Challenge:
In Dr. Hughson's handout, it states that Hereditary neuroblastomas occur in the germline and (the mutation) is present in all cells, which corresponds with answer D. However, the Second is Acquired in somatic cells of the retinal tissue developing the tumors, which would correspond with answer B. To me, it seems that there are two correct answers.

From Dr. Hughson: This is a badly constructed question. All answers will be considered right. I obviously didn't make the point I wanted to make. I've changed the notes. (see below) Let me know if that clarifies the concept. The practical aspect of understanding the problem is how to test a patient for a genetic abnormality if you think they have an inherited cancer syndrome. If there is a family history of cancer and you wish to test the patient for an inherited mutation, you would collect a blood specimen, DNA would be extracted from lymphocytes, and the gene of interest would be sequenced for a point mutation. The second "hit" (the deletion) only occurs in tumor.
If, on the other hand, you are interested in studying genetic changes in a sporadic malignancy, all the action is in the tumor. Both mutations ("hits") are found in tumor and not in normal cells. The patients lymphocytes will be normal.

MUTATIONS: Mutations are of two types: 1) point mutations in which there is a change in the nucleotide sequence of a gene; and 2) chromosomal mutations in which there are changes in the structure or number of chromosomes. Point mutations are detected by molecular genetic techniques such as gene sequencing. Chromosomal mutations are identified by growing tumor cells in tissue culture and cytogenetically analyzing chromosomes. Mutations may be present in the germline in which case they will be found in all cells of the individual from the beginning of embryonic development. Germline mutations are inherited or passed from one generation to the next and are responsible for a relatively small proportion of human cancers. Inherited or germline cancer causing mutations are virtually always point mutations. Only very rare instances of familial cancer syndromes have been associated with inherited structural chromosomal mutations (chromosomal translocations). The great majority of cancers are not inherited but are the result of acquired mutations that occur in the somatic cells of developed organs. Acquired, cancer causing mutations are found only in the neoplasm and not in normal tissues (this will be discussed further in the section on tumor suppressor genes).

Retinoblastomas are rare childhood tumors that develop in neuroretinal cells of the eye. 60% of the tumors are sporadic, and 40% are familial. It was noticed that the karyotypes of tumor tissue from some patients with retinoblastomas showed a deletion of the long arm on chromosome 13, where the Rb gene was localized and cloned at 13q14. On the basis of the deleted gene sequences and the identifications of familial and sporadic cases of the tumor, Knudson proposed the "two hit" theory of oncogenesis as it applies to recessive cancer genes (tumor suppressor genes). The theory states that two mutations ("hits") are required to develop a tumor. ***In hereditary neuroblastomas, which develop before 2 years of age, the first "hit" is inherited in the germ line as a point mutation in the Rb gene and the point mutation is present in all cells of the body (peripheral blood lymphocytes as well as retinal tissues). The second "hit" is acquired in somatic cells of the retinal tissue developing the tumors. The second hit is most commonly a structural chomosomal abnormality resulting from an abnormal mitotic event that causes a deletion of the chomosomal segment containing the remaining normal or wt Rb gene. This chromosomal deletion will only be present in tumor and not in normal retinal cells or in other cells of the body including lymphocytes.*** Genetic testing of the patients will find the inherited point mutation in the Rb gene by sequencing of DNA from lymphocytes obtained as a blood sample. The deleted gene segment can be identified by a PCR test for LOH in the tumor but will not be present in normal cells of the body and will not be seen in either normal retinal cells or lymphoctyes.

Pathology Test 1 Challenges:

In sporadic neuroblastomas, which develop between 2 to 4 years of age, both "hits" or mutations are acquired in somatic cells of the retinal tissue. The two "hits" are most commonly a point mutation in one Rb gene combined with a deletion of the chromosomal segment as the result of an abnormal mitotic event that gets eliminates or "inactivates" the opposite allele. Genetic testing of peripheral blood lymphocytes or normal retinal cells will show only normal results. Both the point mutation and LOH showing the deleted chromosomal segment will only be seen in tumor tissue.