

Biochemistry 461, Fall 2007

Homework 1: Biochemistry of Nucleotide Metabolism. Questions relate to lecture notes and references as indicated.

Purine Salvage Diseases: These questions relate to references 1a-d. [Note figure 1 in reference 1a]

1) Lesch-Nyhan is an X-chromosome-linked recessive disease. Give a brief explanation of what this terminology means in your own words. Lesch-Nyhan Syndrome affects 1/380,000 males at birth. The chance of a woman having Lesch-Nyhan disease is many orders of magnitude lower than it occurs in men. Explain the basis of this difference and suggest how a woman could be afflicted with this disease? [2 pts]

Answer: The gene that determines Lesch-Nyhan disease is found on the X-chromosome. Thus, since the HGPRT gene and therefore its Lesch-Nyhan associated defect is X-linked, girls may carry the disease on one X-chromosome but would have to inherit 2 defective genes to have only defective mutant genes for HGPRT. Since boys die early, and most likely don't mate, they are very unlikely to pass this gene on to a son or a daughter, who might also receive a defective gene on the X-chromosome inherited from her mother. Thus, heterozygous women are more likely to be carriers with only one mutant X-chromosome than they are to develop the disease. However, some female carriers develop gout symptoms as they age.

2) Do you think that Lesch-Nyhan disease will someday be cured? Why or why not? [2 pt]

Answer: Give some kind of general impression of the disease, which may not really test understanding of the basis of the disease, but will show that you have read the New Yorker article and gotten a significant message from it.

3) Do you expect Lesch-Nyhan patients to develop gout. Why or why not? [1pt]

Answer: Though they have elevated levels of uric acid, most affected males may not live to an age at which they would develop gout. Some probably do develop gout.

4) How do the following affect the probability of men developing gout: [4 pts]
[See reference 1a, Figure 1 for the data]

Body Mass Index (BMI)
alcohol consumption
dietary dairy foods
dietary meat vs dietary seafood.

Answers:

- Men with a BMI>25 who eat lots of meat and seafood have a higher risk of developing gout than men who are alcohol consumers.
- But, in both groups (hi BMI and + or – alcohol use), diets high in dairy protein sources had the least (less than ½ or better) risk of developing gout.
- Finally, the no alcohol drinking, dairy protein consumers had the lowest risk among the groups studied.
- In both groups, seafood seems to increase the risk more than meat eaters.

5) Why might premenopausal women be less likely to develop gout than men?
[1 pt]

Answer: They have lower serum uric acid levels. This is because estrogen stimulates uric acid excretion in the urine.

Roles of folic acid: Questions relate to reference 2 [Note especially Figure 1 and Box 2]

6) Describe two different ways that a lack of folate might increase one's risk of developing cancer. [2 pts]

Answer: Low folate prevents *de novo* purine nucleotide synthesis (needed in 2 reactions to make purine ring), Defective DHFR leads to reduced supply of T-nucleotides for DNA replication, and prevent CpG methylation (therefore, preventing gene silencing in cancer cells).

7) Folate deficiency can lead to uracil being incorporated into DNA instead of thymine. DNA that contains uracil is unstable. Why might folate deficiency lead to the incorporation of uracil into DNA? What long-term health consequences would this have for an individual and why? [3 pts]

Answer: Low folate would lower the synthesis of dTMP and limit its availability for DNA synthesis. Cells would have very high levels of dUTP that could be used by mistake in DNA synthesis during chromosome replication in cell division. Uracil would base-pair with cytosine and be misincorporated into the new chromosomal DNA. The unstable DNA might break down and prevent normal cell functions or induce cells to become cancerous.

8) If DHFR (dihydrofolate reductase) activity is 100% inhibited by, for instance by the drug methotrexate, would you expect a person's cells to be able to divide at all? Also, would you expect the need for dietary or supplemental folic acid to increase or decrease with no DHFR activity? [3 pts]

Answer: Dihydrofolate can ONLY be reutilized if DHFR is active. After all the THFA is used up, cells couldn't recycle dihydrofolate and would only be able to divide if they have an active thymine salvage system to utilize thymine from degraded DNA or from food sources. One would expect an increase to very high needs for supplemental folic acid.

9) Summarize in one paragraph how insufficient folic acid intake can cause human diseases. [2 pts]

Answer: Any reasonable discussion of the subject that indicates having read the paper and integrated some of the information.