Post-lecture reading for CHM 109 introductory (PKU) lecture

Loss-of-function genetic diseases illustrate the requirement all living things have to perform specific chemical and physical jobs. Failure to perform these jobs results in ill health or death. The first subject we will discuss in CHM 109 this semester is phenylketonuria (PKU). This is a loss-of-function genetic disease that occurs when a person produces insufficient phenylalanine hydroxylase (PAH) activity. PAH is an enzyme. (The -ase suffix indicates that the compound in question is an enzyme.) Please let me know if I forget to define “new” words.

Enzyme: a catalyst produced by a living thing or virus (So what is a catalyst?)
Catalyst: a substance that increases the rate of a chemical (or physical???) change Chemists usually confine this to chemical changes, but......

We must answer three questions to be able to understand PKU: 1) What is the nature of the PAH reaction? 2) How do living things make proteins (Central Dogma)? 3) How much redundancy is present in the human genome (Humans are diploid, sort of)?

The PAH Reaction
PAH increases the rate of conversion of the amino acid L-phenylalanine (Phe) to the amino acid L-tyrosine (Tyr). Amino acids are the building blocks you use to make proteins. The oxidant (not shown structurally below) is molecular oxygen, $O_2$:

$$\text{phenylalanine} + \text{oxidant} \xrightarrow{\text{PAH}} \text{tyrosine}$$

If you do not have PKU that means your body produces enough PAH to convert Phe to Tyr fast enough to meet your needs to remain healthy. If you do not produce enough PAH two “bad” things happen. First, Phe builds up in your body. This built-up Phe is converted to phenylketones, and there is evidence that phenylketone buildup damages your body. Second, if your diet is not sufficiently rich in Tyr, you will not have enough Tyr for protein synthesis. Since most (but not all) of the jobs your body does are carried out by proteins, insufficient Tyr will cause problems in many areas of your body. We will discuss the pathophysiology of and treatment options for PKU during lecture.

PAH is an average sized enzyme. The smaller enzymes in your body are roughly one-tenth its size, while the larger ones are more than ten times as large as PAH. A stick model derived from an X-ray crystal structure of a PAH dimer is shown at the top of p. 2.

Dimer: a molecule that is composed of 2 subunits
This structure has the PDB accession code 2pah. Each native (naturally occurring) PAH subunit contains 452 amino acid units. The chemists who prepared the structure shown below used a modified form of PAH that contained only 335 amino acid units per protein subunit.

My guess is that you will consider the structure shown above to be quite complicated compared to other chemical structures you have seen (ex.: H₂O?). How is it that your body can produce millions of such large, complicated molecules so flawlessly? The answer is that your cells contain a detailed set of instructions that code for production of PAH. The instructions are contained in the DNA present in your cells.

The conversion of this DNA (nucleic acid language) information into protein (amino acid language) is part of the Central Dogma of molecular biology.

The Central Dogma

How is the information in a linear DNA sequence converted into the linear amino acid sequence found in a protein? Most simply: DNA codes for RNA, which codes for protein:
We will consider the Central Dogma in much greater detail near the end of the course.

The final item needed to understand the basic elements of the PKU comes from examining the redundancy present in the human genome. (I’ll let you look up redundancy.)

Humans are (sort of) Diploid

The relationship between the sequence of bases in human DNA (which determines our genotype) and the way our bodies function (which is described by the term phenotype) is slightly more complicated than you might think.

**phenotype:** the “...biological appearances, including chemical, structural, and behavioral attributes that we can observe about an organism...”

**genotype:** “...the particular genetic material that an organism inherits from its parents.”

These definitions are from p.102 of *Genetics* by M. W. Strickberger (1968).

Most biologists would describe humans as being diploid, which means that we have two copies of the information needed to carry out the various chemical and physical jobs necessary to sustain our health and well being. However, not all humans are equally diploid. Put another way, some of us are more diploid than others.

More explicitly, most of the cells in your body are diploid. However, human reproductive cells (eggs and sperm) are haploid, meaning that they have only one copy of all of the necessary information. When the nuclei of the egg and sperm unite after fertilization, the zygote that results is diploid. How does this haploid vs. diploid issue relate to PKU?

A picture of the chromosomes in a haploid human genome (as would be present in an egg or sperm cell) is shown below (but XYY?). Your non-reproductive cells are diploid, and so would contain two versions of each chromosome, one of which came from your mother and one from your father. If unfamiliar with meiosis, see: [http://www.youtube.com/watch?v=D1_-mQS_FZ0](http://www.youtube.com/watch?v=D1_-mQS_FZ0)


![Chromosome Diagram](http://www.ncbi.nlm.nih.gov/mapview/w/map_search.cgi?taxid=9606)

The gene for PAH is on chromosome 12, slightly more than half-way down the long arm (at the two red bars). For PKU, like most loss-of-function genetic diseases, if an individual has one gene that codes for a functional PAH, the individual’s phenotype is normal (a.k.a.: wild type). However, if neither copy of the PAH gene codes for a functional PAH molecule, the individual then has PKU. We could also say that they display the PKU phenotype. To make sure you understand this system, fill in the boxes and tables on p. 4.
Punnett Squares for PKU inheritance. The + symbol indicates a functional PAH gene while the – indicates a non-functional PAH gene. The two different entries shown for the heterozygous mom and dad (either + or –) show the different types of eggs or sperm that could form. What do hetero- and homo- mean? (The are many [>520] different ways to have a non-functional PAH gene.) The first two possible mating outcomes (offspring) have been filled in for you. Fill in the other blanks. Is there another interesting Punnett Square to consider?

Complete the table below:

<table>
<thead>
<tr>
<th>genotype</th>
<th>phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/+</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>-/+</td>
<td></td>
</tr>
<tr>
<td>-/-</td>
<td></td>
</tr>
</tbody>
</table>

During lecture questions: Which genotype and phenotype were Irene and her sister? The husband? (Maybe a guess?) Stephanie???
Questions
1. What must living things be able to do to stay alive and healthy?
2. What (at the molecular level) causes PKU?
3. Phe and Tyr are in what class of biomolecules?
4. What are the building blocks of proteins?
5. Where in your body are the instructions for producing PAH?
6. Are you either completely haploid or completely diploid?
7. If you are not either completely haploid or diploid, are you mostly haploid or diploid?
8. Explain why you are not completely haploid or diploid.
9. Does a person with a heterozygous genotype for PKU “show” the trait? That is, what is their phenotype?
10. What are the odds of mating between a +/+ father and a −/− mother producing a child with a PKU phenotype? If the answer is not obvious, go back to p. 4 and construct the appropriate Punnett Square in the lower right box.