Name: _____ Date:_____

The Blue People of Troublesome Creek

In 1820, a French orphan named Martin Fugate settled on the banks of eastern Kentucky near Troublesome Creek. He married his American redheaded sweetheart, Elizabeth Smith. They had seven kids and lived happily ever after. Oh, yeah, and four of their kids were blue.

Six generations later in 1975, Martin's great great-great-great grandson, Ben Stacy was born blue, and was immediately rushed from the maternity ward to the nearest city hospital by ambulance. There he stayed for two days receiving tests but no one could explain why baby Ben was blue. Then Ben's grandmother brought up the "Blue Fugates of Troublesome Creek". That's when Ben's father admitted that his grandmother, Luna, was a blue Fugate. After this information was revealed, doctors concluded that Ben Stacy was blue due to an inherited condition known as methemoglobinemia. Over time, the blue appearance of Ben's skin diminished as he aged. Today he is a normal looking man, though his fingernails still have a tinge of blue.

Decades before Ben's birth, the legend of the "Blue Fugates of Troublesome Creek" caught the attention of a hematologist (someone who studies blood) from the University of Kentucky named Dr. Madison Cawein. Dr. Cawein decided to investigate the Blue people of Troublesome Creek. At the time, no one knew much about them- least of all why these people were blue. He worked closely with a local nurse who was also interested in finding out more about the blue people. However, as soon as Dr. Cawein spotted a blue person from afar, they would soon disappear. Most of these people were older and were born in their childhood homes, not in a hospital. Their condition went undetected and they were very private, not wanting to be seen by any outsiders.

Then, one day, seemingly out of nowhere, two blue people walked into the clinic. As Dr. Cawein described, "They were bluer than heck". The pair of blue people that showed up to the clinic was a brother and sister, Patrick and Rachel Ritchie. They were very embarrassed about their appearance. Dr. Cawein examined them and ruled out heart and/or lung disease. They seemed perfectly healthy other than their blue skin. When Dr. Cawein asked them if they had any blue relatives, Patrick and Ritchie admitted they had quite a few blue relatives that were deceased or living in the hills near Troublesome Creek. Dr. Cawein decided to chart out their family to help better understand the blue people.

After doing so, it was quite apparent that this was an inherited condition. Also, many family members married cousins, aunts and uncles because there weren't any railroads or ways of coming and going in and out of Troublesome Creek. The Blue People of Troublesome Creek did not have much opportunity to mix with others for many generations. So, they married the girl next door, even if that happened to be their cousin.

Now the question was what exactly caused their skin to be blue? Dr. Cawein took many samples of the Ritchie's blood and brought it back to his lab at the University of Kentucky. In order to understand his discoveries, you must first understand what makes normal blood red. The answer to that is hemoglobin, it is a molecule in your blood consisting of proteins and iron.

Hemoglobin is responsible for carrying oxygen in your blood stream (oxygen bonds with the iron, giving the blood a red color). Hemoglobin is actually converted into a slightly different molecule called methemoglobin. Methemoglobin is bluish or purplish in color, not red. The methemoglobin gives oxygen-depleted blood a purple hue, which appears blue through the skin as seen in veins. This is because methemoglobin has a slightly different ion of iron different than that of hemoglobin (it has one less electron) and it does not effectively bond with oxygen.

If all of our hemoglobin were converted to methemoglobin, it would be useless. However, the conversion is a natural process that happens over time. So, how is it that all our hemoglobin doesn't just turn into methemoglobin? An enzyme known as diaphorase is responsible for converting methemoglobin back into hemoglobin. Dr. Cawein suspected that the blue people did not have the enzyme diaphorase, which would mean that their (red) hemoglobin was turning into (blue) methemoglobin and not turning back into (red) hemoglobin, like in normal people.

Rachel and Patrick Ritchie must have spread the word of Dr. Cawein to their blue family because their 76-year-old uncle, Zach Fugate (who happened to the Patriarch of the Blue Clan), as well as Zach's 84-year-old Aunt Bessie, also agreed to give blood. Cawein studied the blood of the blue Fugates and found that none of them had the enzyme diaphorase just as he thought!

After more research, Dr. Cawein discovered a piece of older medical literature from the late 1800's in which a doctor by the name of E.M. Scott had researched and explained a condition known as "methemoglobinemia", a condition in which patients lacked the enzyme diaphorase and were, in fact, blue. That condition perfectly described the Blue Fugates of Troublesome Creek, and a diagnosis was finally reached. They had accumulated so much of this molecule in their blood, that it overwhelmed the normal red hemoglobin. Instead of showing through as pink as it does in most Caucasians, it showed through as blue, similar to the blood that you may see in your veins.

Now, Dr. Cawein just needed a cure, and suddenly he thought of a molecule called methylene blue. We use methylene blue to dye cells in the classroom. It's looks just like a little bottle of blue ink. And yes, Dr. Cawein was suggesting that the Blue Fugates allow him to inject blue dye into them, and assured them that it would turn them a normal color. They thought he was crazy, trying to fight blue with blue, but decided to give it a try. Within minutes, the Blue Fugates were slowly turning a normal color. Methylene blue serves as an electron donor, which is required to turn methemoglobin back into hemoglobin (it donates an electron to the methemoglobin molecule, creating the correct ion of iron in order for hemoglobin to form). It brought many of the Blue Fugates to tears of joy, including old Aunt Bessie, who finally after 84 years was no longer blue.

ANALYSIS

1. What is hemoglobin?

_____
_____.

2. What molecule does hemoglobin decay into over time? _____

3. How is this molecule different from hemoglobin?

_____
_____.

4. What is the role of the enzyme diaphorase?

_____
_____.

5. Explain why the Blue People of Troublesome creek were blue in as much detail as possible:

_____
_____
_____
_____.

6. What was the cure for methemoglobinemia? (Extra points if you can explain why it was "ironic" ☺).

_____
_____
_____
_____.

7. What is the reason that methemoglobinemia was isolated to Troublesome Creek area of KY? (In other words why was the disorder only prevalent in KY; why didn't other states see cases like this?)

_____
_____.

On the following page, there is an excerpt of a *partial* pedigree for the Blue Fugates of Troublesome Creek. Read the excerpt carefully, and use it to construct a pedigree tracing methemoglobinemia in the space provided.

Be sure that your pedigree is clearly labeled.
USE NAMES WHEN GIVEN.
Use the key at right to depict males, females and affected individuals.

DO IN PENCIL! A rough draft on a piece of scrap paper is encouraged.

Martin Fugate married Elizabeth Smith, who had red hair and was described to be "as pale as Mountain Laurel". It is unknown as to whether or not Martin Fugate was blue or not. Together they had seven children: Eleanor, Charles, John, Zachariah, William, Hanna and Levi. John, Zachariah, Hanna and Levi were blue. Zachariah married a woman with the last name Ritchie (her first name is unknown, but she was actually Zachariah's aunt), she was normal. Together they had 6 children, 4 sons and 2 daughters. 2 of the sons were blue.

One of their sons named Levy was NOT blue, and he also married a Ritchie woman named Mahala. He and Mahala had 8 children, 4 boys and 4 girls. Only 1 of their children was blue, her name was Luna. Luna married a man by the name of John Stacy. Together they had 13 children, 6 boys and 7 girls. NONE of their children were blue. One of their sons was named Bill. Bill married Mary Ritchie. They had a son named Alva who was not blue, either. Alva married a woman named Hilda Godsey. Alva and Hilda are Ben Stacy's parents. Ben was born blue, but outgrew his bluish tint without medical intervention, suggesting he is a carrier of methemoglobinemia.

Draw your pedigree in the space provided:

ANALYSIS and CONCLUSIONS

8. How many generations are seen in this pedigree? Go back and label them using Roman numerals.

9. Is methemoglobinemia recessive or dominant? Provide examples to back up your answer.

_____
_____
_____.

10. Assuming John Stacy does not carry the methemoglobinemia allele, do a Punnett square between Luna Fugate and John Stacy to show the possible genotypes of their children.

11. Can you tell for certain if Eleanor is a definite carrier for methemoglobinemia? Why or why not?

_____
_____
_____.

12. Review your pedigree and determine which individuals are carriers by shading in half the shape (circle or square). Only do this for carriers that you have enough information to do so.

13. Review Luna Fugate's family. Do a Punnett Square showing the possible crosses among Luna Fugate's parents (Mahala and Levy). List possible phenotypes and genotypes using percentages. Compare the actual scenario to the predictions in your Punnett square.

ANALYSIS and CONCLUSIONS

14. Why didn't Bill Stacy have blue skin even though his mother did?

_____
_____.

15. What advantages does a pedigree have over a written passage?

_____
_____
_____.

Bonus

16. Is methemoglobinemia sex-linked or autosomal (non-sex linked)? Give evidence to support your answer

_____
_____
_____.