Case File 1: Hemophilia A

The Scenario
On a recent visit to the dentist, John bled for an unusually long time after getting his tooth pulled out. He was later tested and diagnosed with Hemophilia A, a disorder where the blood fails to clot properly because of a lack of protein, Factor VIII. Interestingly, John’s grandfather Ed (his mom’s dad) also has prolonged bleeding after surgeries, injuries and tooth extractions. John’s mother and his sister, Beverly, are both healthy and seem to clot fine.

![Family History Diagram]

<table>
<thead>
<tr>
<th>Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grandfather Ed</td>
</tr>
<tr>
<td>John</td>
</tr>
<tr>
<td>Beverly</td>
</tr>
</tbody>
</table>

Legend
- Females
- Males
- Filled in symbols = affected with Hemophilia

1) What is the most likely pattern of inheritance of Hemophilia in this family?

**Hint:** To describe the genotypes for the questions below, it may be helpful to use 'X_H' to represent the functional (normal) allele and 'X_h' to represent the non-functional (mutant) allele.

John and his wife Sara would like to have children. There is no history of bleeding problems in Sara’s family.

2) What are the possible genotypes and phenotypes of the children?

3) What is the chance that any of their children would be affected with Hemophilia?

4) What is the chance that any of their children would be carriers of Hemophilia?

Beverly wonders if it’s possible that she may have children with Hemophilia.

5) What is the chance that she is a carrier of Hemophilia?

6) If she is not a Hemophilia carrier, what is the chance that she will have children with Hemophilia?

With her family history of Hemophilia, Beverly is tested and finds out that she is a carrier.

7) If she has children with a man who does not have Hemophilia, what are the possible genotypes and phenotypes of the children? What is the chance that she will have a son with Hemophilia?

**Bonus Question:** Can you name the famous historical family that was affected with Hemophilia?
Case File 1: Answers

Question 1

ANSWER: The inheritance of Hemophilia A in this family follows an X-linked recessive pattern.

EXPLANATION:
- Recall that the X and Y chromosomes are responsible for determining an individual’s gender. Females have two copies of the X chromosome and males have one copy of the Y chromosome.
- The phenotype of X-linked conditions is determined by a gene on the X chromosome.
- Because females have two X chromosomes, they have two copies of all the genes on the X chromosome. If one copy of an X-linked gene is not functional, females have a second copy of the gene (on their second X chromosome) to ‘make-up’ for the non-functioning gene. Females with one functional copy and one non-functioning copy of a gene involved in an X-linked recessive condition are called ‘carriers’ of the condition. Carrier females are usually not affected with the condition because the cells with the functional copy usually compensate for the cells with the non-functional copy. However, some females may have a less severe manifestation of the disease. For example, a carrier of the clotting disorder Hemophilia A may bruise easier because she clots less than a person with fully functioning Factor VIII.
- Because a male has only one X chromosome, if an X-linked gene is not functional, he will be affected with the X-linked condition. Males do not have an ‘extra’ X chromosome to compensate for a non-functional gene.

Key points about X-linked recessive inheritance:
- The condition is usually only seen in males and rarely in females
- Unaffected carrier females may have sons with the condition
- Unaffected males do not pass on the condition to their sons or daughters
- Affected fathers do not pass on the condition to their son (because a man always passes on his Y chromosome to create a son and does not pass on his non-functional X chromosome)

Question 2

ANSWER:
Genotypes: X_h/X_h and X_h/Y
Phenotypes: All daughters will be carriers. All sons will be unaffected.

EXPLANATION:
- Let X_h represent the non-functional (mutant) gene that causes Hemophilia A and let X_h represent the functional (normal) gene.
- We know John has Hemophilia. Therefore he must be X_h/Y.
- His wife Sara is unaffected and therefore is most likely X_h/X_h. Unless there is evidence to the contrary, we assume unaffected spouses are not carriers because the chance of 2 unrelated people having the disease is very low.
- The possible products of their mating are described in the table below. Note that John must pass on his Y chromosome to create a son, and therefore his sons will always be unaffected. John must pass on his X chromosome to create a daughter, and therefore his daughters will always be carriers of Hemophilia.

<table>
<thead>
<tr>
<th>Affected Male x Unaffected Female: X_h/Y x X_h/X_h</th>
<th>X_h</th>
<th>X_h</th>
</tr>
</thead>
<tbody>
<tr>
<td>X_h</td>
<td>X_h/X_h</td>
<td>X_h/X_h</td>
</tr>
<tr>
<td>Y</td>
<td>X_h/Y</td>
<td>X_h/Y</td>
</tr>
</tbody>
</table>
Question 3
ANSWER: There is no chance that John and Sara will have children fully affected with Hemophilia.

Question 4
ANSWER: All of John and Sara’s daughters will be carriers of Hemophilia. None of their sons will be carriers.

EXPLANATION:
(Refer to diagram in answer to question 2). We know that Sara is unaffected and therefore will always pass down a functional gene ($X_H$) to her children. We know that John has Hemophilia and is $X_h/Y$. For him to have a daughter, he must pass down his X chromosome with the nonfunctional allele ($X_h$). Therefore all of his daughters will be carriers. For John to have a son, he must pass down his Y chromosome. Because all of his sons inherit his Y chromosome, none of his sons inherit his X chromosome with the non-functional allele.

Question 5
ANSWER: Beverly has a $\frac{1}{2}$ (or 50%) chance of being a Hemophilia carrier.

EXPLANATION:
Beverly’s mother is an ‘obligate carrier’ of Hemophilia. That is, we assume Beverly’s mom is a carrier because she has a father and a son with Hemophilia. Therefore Beverly’s mom’s genotype is $X_HX_h$.

- Beverly's mom had a $\frac{1}{2}$ (50%) chance of passing down the working gene ($X_H$) to Beverly, in which case Beverly would not be a carrier (diagramed as ‘Path A’ below).
- She also had a $\frac{1}{2}$ (50%) chance of passing down the non-working gene ($X_h$) to Beverly, in which case Beverly would be a carrier (diagramed as ‘Path B’ below).

<table>
<thead>
<tr>
<th>Path A</th>
<th>Path B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beverly’s Mom</strong></td>
<td><strong>Beverly’s Mom</strong></td>
</tr>
<tr>
<td>$X_HX_h$</td>
<td>$X_HX_h$</td>
</tr>
<tr>
<td>Beverly’s Dad</td>
<td>Beverly’s Dad</td>
</tr>
<tr>
<td>$X_HY$</td>
<td>$X_HY$</td>
</tr>
<tr>
<td>Beverly</td>
<td>Beverly</td>
</tr>
<tr>
<td>$X_H$</td>
<td>$X_H$</td>
</tr>
<tr>
<td>Beverly</td>
<td>Beverly</td>
</tr>
<tr>
<td>$X_HX_H$</td>
<td>$X_HX_H$</td>
</tr>
</tbody>
</table>

Result: Beverly is not a Hemophilia carrier

Result: Beverly is a Hemophilia carrier

Question 6
ANSWER: If Beverly is not a carrier of Hemophilia, the chance of her having a child with Hemophilia would be incredibly small. (Recall the chance of an unaffected spouse carrying...
the same disease is very small. Plus, her husband would have to be affected if he carried the nonfunctional copy).

**Question 7**

**Answer:**

Genotypes: \(X_H/X_H\) and \(X_H/X_h\) and \(X_H/Y\) and \(X_h/Y\)

Phenotypes: All daughters will be unaffected (\(\frac{1}{2}\) daughters will be carriers, \(\frac{1}{2}\) daughters will not be carriers), \(\frac{1}{2}\) of sons will be affected, and \(\frac{1}{2}\) of sons will be unaffected.

**Explanation:**

- We know that Beverly is a carrier of Hemophilia. Therefore her genotype must be \(X_H/X_h\).
- Her partner is unaffected and therefore his genotype must be \(X_H/Y\).
- Note that each time Beverly creates a child, she has a \(\frac{1}{2}(50\%)\) chance of passing on her functional \(X_H\) allele and a \(\frac{1}{2}(50\%)\) chance of passing on her non-functional \(X_h\) allele.

<table>
<thead>
<tr>
<th>Carrier female (X_H/X_h)</th>
<th>Unaffected male (X_H/Y)</th>
<th>Daughters: (\frac{1}{2}) will be carriers, (\frac{1}{2}) will not be carriers. All will be unaffected.</th>
<th>Sons: (\frac{1}{2}) will be unaffected. (\frac{1}{2}) will be affected.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X_H)</td>
<td>(X_H/X_H)</td>
<td>(X_H/X_h)</td>
<td></td>
</tr>
<tr>
<td>(X_h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Y)</td>
<td>(X_H/Y)</td>
<td>(X_h/Y)</td>
<td></td>
</tr>
</tbody>
</table>

**Bonus Answer:**

Hemophilia is sometimes called ‘The Royal Disease’ because it was thought to occur among descendants of Britain’s Queen Victoria, who was a hemophilia carrier.

**Reference:**