

Hemophilia: “The Royal Disease”

by

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Hemophilia is an X-linked recessive disorder characterized by the inability to properly form blood clots. Until recently, hemophilia was untreatable, and only a few hemophiliacs survived to reproductive age because any small cut or internal hemorrhaging after even a minor bruise were fatal. Now hemophilia is treated with blood transfusions and infusions of a blood derived substance known as antihemophilic factor. However, the treatment is very expensive and occasional problems can arise because of a patient's allergic reactions or other transfer complications.

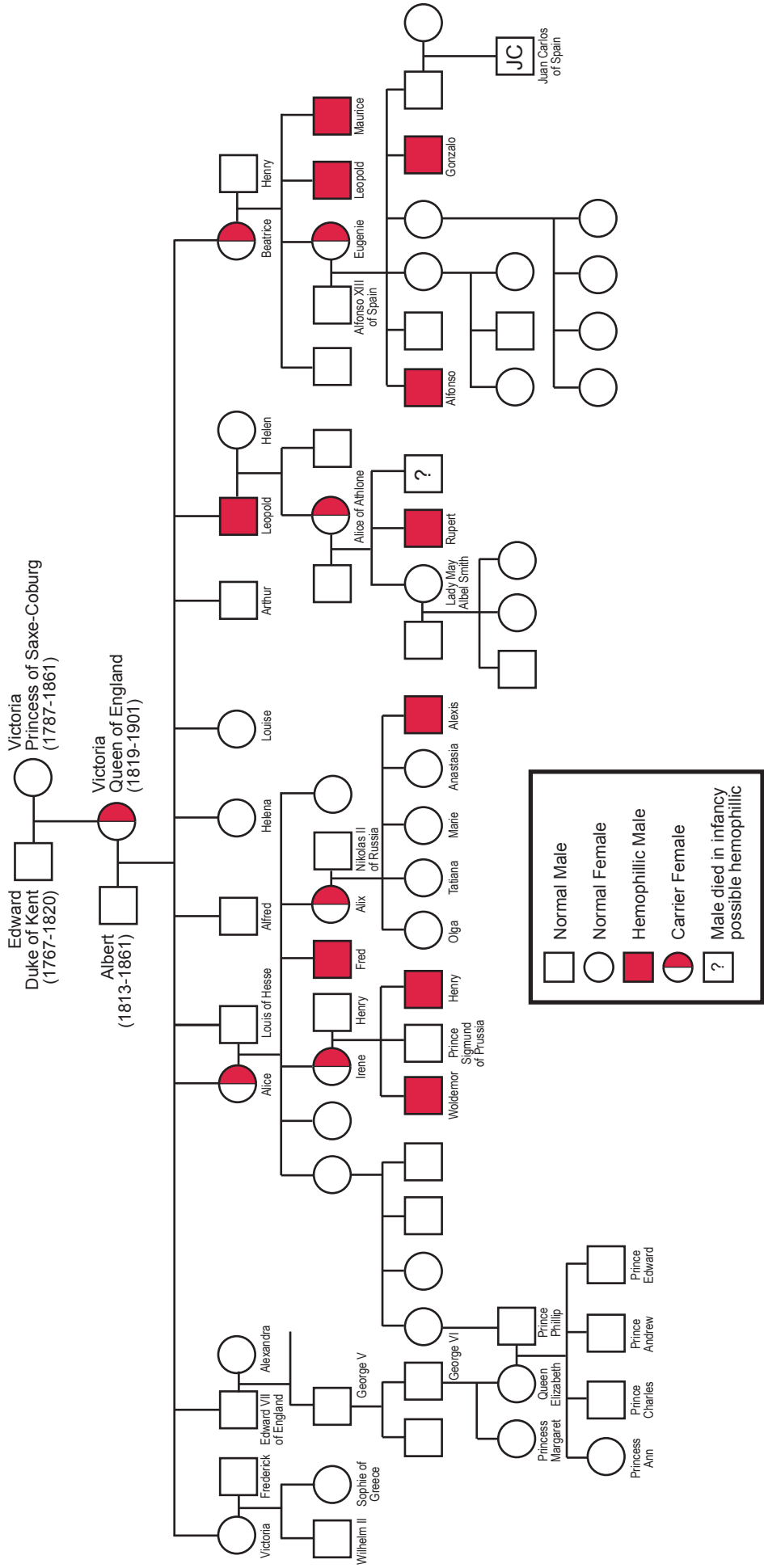
Hemophilia affects males much more frequently (1 in 10,000) than females (1 in 100,000,000). This occurs because a critical blood clotting gene is carried on the X chromosome. Since males only carry one X chromosome, if that is defective, hemophilia will immediately show up. An early death is likely. Females, on the other hand, carry two X chromosomes. If only one is defective, the other normal X chromosome can compensate. The woman will have normal blood clotting; she will simply be a carrier of the recessive defective gene. This fact will be discovered if some of her children are hemophiliacs. Naturally, women hemophiliacs are rare because it takes two defective X chromosomes in order for the condition to be seen.

Hemophilia has played an important role in Europe's history, for it suddenly cropped up in the children of Great Britain's Queen Victoria. It became known as the "Royal disease" because it spread to the royal families of Europe through Victoria's descendants. Queen Victoria had always been worried about the quality of the blood of the British royal family. Her feelings about the necessity of revitalizing what she called the "lymphatic" blood of their houses are reflected in her letter to her daughter Vicky: "I do wish one could find some more black eyed Princes and Princesses for our children! I can't help thinking what dear Papa said—that it was in fact when there was some little imperfection in the pure Royal descent that some fresh blood was infused... For that constant fair hair and blue eyes makes the blood so lymphatic... it is not as trivial as you may think, for darling Papa—often with vehemence said: 'We must have some strong blood.'"

It is doubtful that at the time of writing this letter, the Queen knew exactly what was wrong with her family's blood. Hemophilia first appeared in Victoria's family in her eighth child, Prince Leopold, Duke of Albany. Throughout his short life, Leopold had suffered severe hemorrhages, and always was described as "very delicate." Leading the life of a normal child was impossible for Leopold because any cut or bump could lead to death and it was necessary to keep him always under strict surveillance. However, in spite of all the protection, Prince Leopold died at the age of thirty-one as the result of a minor fall.

The appearance of hemophilia in one of Victoria's sons upset and confused the Queen, who could only protest that the disease did not originate in her side of the family. Yet, a whisper about the "curse of the Coburgs" was spread about. This curse was supposed to have dated from the early nineteenth century, when a Coburg prince had married a Hungarian princess named Antoinette de Kohary. A monk, a member of the Kohary family, envied the wealth inherited by the happy couple from the bride's father, and cursed future generations of Coburgs with the disease. Of course, hemophilia affecting Victoria's offspring had nothing to do with the curse. The traditional view is that there was a mutation in either her or in a sperm of her father, Edward Augustus, Duke of Kent. From there it spread through the Royal Houses of Europe as monarchs arranged marriages to consolidate political alliances. We can trace the appearance of hemophilia as it popped up in Spain, Russia, and Prussia by looking at the family tree (Figure 1 next page).

Figure 1. Royal Houses of Europe



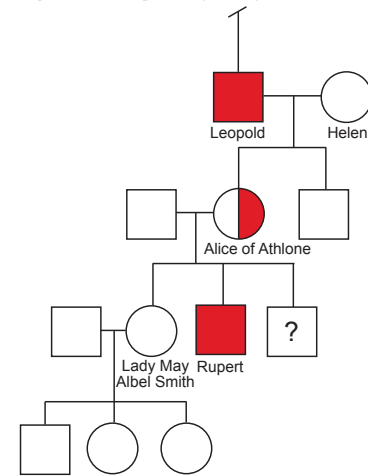
- First, let's take a look at Queen Victoria's son Leopold's family (see Figure 2). His daughter, Alice of Athlone, had one hemophilic son (Rupert) and two other children—a boy and a girl—whose status is unknown.

Questions

- What is the probability that her other son was hemophilic?
- What is the probability that her daughter was a carrier? Hemophilic?
- What is the probability that both children were normal?

Fortunately, Leopold was the only one of Victoria's sons who suffered from hemophilia. Her other three sons, Edward, Alfred, and Arthur, were unaffected. Since the present royal family of England descended from Edward VII, the first son, it is free from hemophilia. Louise, Queen Victoria's fourth daughter and sixth child, did not have children and her status as a carrier cannot be assessed. Vicky, the first child, and Helena, the fifth child, had children, none of whom was hemophilic, indicating that the mothers probably were not carriers.

Figure 2. Leopold's family

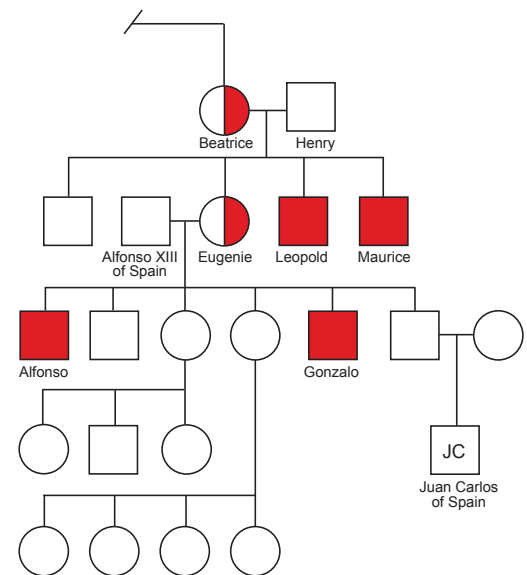


- Now for the Spanish connection: Victoria's youngest child, Beatrice, gave birth to one daughter, one normal son, and two hemophilic sons (see Figure 3).

Questions

- Looking at the pedigree of the royal family, identify which of Beatrice's children received the hemophilic gene; why can you make this conclusion?
- Notice that Beatrice's daughter, Eugenie, married King Alfonso XIII of Spain and had six children, one of whom was the father of Juan Carlos, the current King of Spain. Would you predict that Juan Carlos was normal, a carrier, or a hemophilic?

Figure 3. Beatrice's family



- Queen Victoria's third child, Alice, passed hemophilia to the German and Russian imperial families (see Figure 4, next page). Of Alice's six children, three were afflicted with hemophilia. At the age of three, her son Frederick bled for three agonizing days from a cut on the ear. Eventually, the flow of blood was stanchied. But a few months later, while playing boisterously in his mother's room, the boy charged headlong through an open window and fell to the terrace below. By the evening he was dead from the internal bleeding.

Alice's daughter Irene, a carrier, married her first cousin, Prince Henry of Prussia, and gave birth to two hemophilic sons. Every attempt was made to conceal the fact that the dreaded disease had shown itself in the German imperial family, but, at the age of four, Waldemar, the youngest of the princes, bled to death. The other prince, Henry, died at the age of fifty-six.

Alice's other daughter, Alix, was also a carrier. Had she accepted the offer of marriage from Prince Eddy, or his brother George, hemophilia would have been re-introduced into the reigning branch of the British royal family. But Alexandra (Alix) married Tsar Nikolos II instead and carried the disease into the Russian imperial family. She had four daughters, Olga, Tatiana, Marie, and Anastasia, before giving birth to the long-awaited son, Alexis, heir to the Russian throne. These children, along with their parents, were eventually murdered during the Russian Revolution.

Within a few months of his birth, his parents realized that their precious and only son, Alexis, had hemophilia. The first sign had been some unexpected bleeding from the navel, which had stopped after a few days. Much more serious,

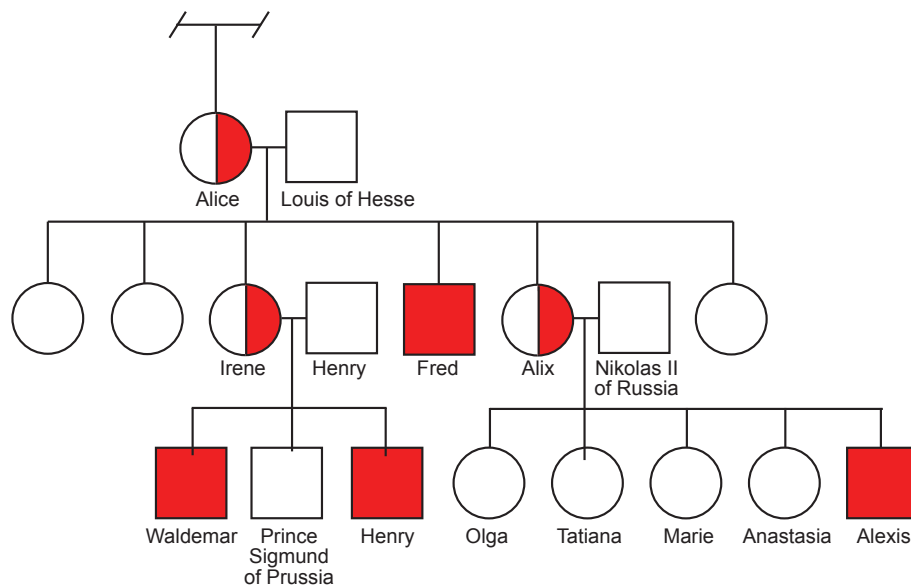
however, were the dark swellings that appeared each time the child bumped an arm or a leg. And worst of all was the bleeding into the joints. This meant a crippling of the affected limbs in addition to excruciating pain. As the boy grew older, he was obliged to spend weeks in bed, and after he was up, to wear a heavy iron brace.

Neither well-experienced doctors nor numerous prayers to God by desperate parents seemed to help the suffering child. Distressed over their son's condition, his parents, the Tsar and Tsarina, turned to the monk Rasputin, a spiritualist who claimed he could help Alexis. Rasputin received an unlimited trust from Alexandra because he was the only person who was able to relieve her son's sufferings. How he managed to do this is uncertain. "A likely explanation is that Rasputin, with his hypnotic eyes and his self-confident presence, was able to create the aura of tranquillity necessary to slow the flow of blood through the boy's veins. Where the demented mother and the dithering doctors merely increased the tenseness of the atmosphere around the suffering child, Rasputin calmed him and sent him to sleep." While Tsar and Tsarina were preoccupied with the health of their son, the affairs of state deteriorated, culminating in the Russian revolution. Alexis did not die from hemophilia. At the age of fourteen he was executed with the rest of the family. His four oldest sisters were also young and didn't have children, so we don't know whether any of them was a carrier. But we can make an estimate.

Questions

- (a) What are the probabilities that all four of the girls were carriers of the allele hemophilia?
- (b) Supposing Alexis had lived and married a normal woman, what are the chances that his daughter would be a hemophiliac?
- (c) What are the chances his daughters would be carriers?
- (d) What are the chances that his sons would be hemophiliacs?

Figure 4. Alice's family



- 4. In 1995, a sixty-three-year-old man named Eugene Romanov, a resident of the former Soviet Union, turned up. He shared both the disease and his last name with the royal family of czarist Russia. He proclaimed himself a grandson of Nikolai II's youngest daughter, Anastasia, whose body had at that time not been recovered, and who was believed by some to have managed to survive the revolution. Eugene Romanov claimed Anastasia was raised by a farmer, and later she married a nephew of her adopted parents and had a daughter, Eugene's mother.

Questions

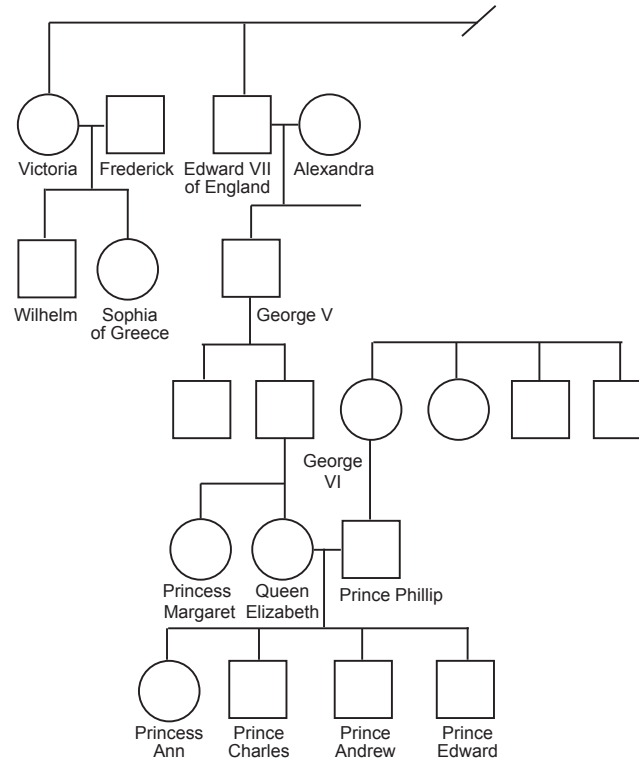
- (a) According to Eugene's argument, what was the likely hemophilic status of Eugene's mother and grandmother? What about his father and grandfather? Is this argument plausible?
- (b) How plausible is it that Eugene inherited both hemophilia and the last name from the royal family? (*Hint: Look how each of them is passed from generation to generation.*)

5. Prince Charles is the designated next king of England (see Figure 5). His well publicized marriage to Princess Diana produced two sons before it ended in an acrimonious divorce.

Question

If you learned that one of the two sons was a hemophiliac, what are the possible explanations for this event?

Figure 5. Prince Charles' family



Finally, our speculative natures compel us to mention that in 1995 two British brothers produced a new book (*Queen Victoria's Gene*) with a breathtaking suggestion. Professors Malcom Potts, an embryologist at Berkeley, and William Potts, a zoologist at Britain's Lancaster University, suggest that Queen Victoria might have been illegitimate. They point out that neither her father nor her husband was a hemophiliac. So either there was a spontaneous mutation—a one-in-50,000 chance—or Victoria is the daughter of someone other than the Duke of Kent. Think of the possible consequences to European history: no Victoria, and the current Prince of Hanover, Ernst (descendent of the brother of Victoria's father), would be King of England today. More importantly, no Victoria would mean no hemophilic son of the Czar of Russia, no Rasputin, and no revolution? What are the chances of this scenario?

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