

1 An Introduction to Hemophilia

This chapter provides answers to these questions:

- What is hemophilia?
- When was hemophilia first recognized?
- Why is hemophilia called “The Royal Disease”?
- What is the history of hemophilia in the 20th century?
- What causes hemophilia?
- What are other names for hemophilia A and B?
- How common is hemophilia?
- Who is affected by hemophilia?
- How serious is hemophilia?
- Are there effective treatments for hemophilia?
- How does blood clot normally?
- What is the clotting problem in hemophilia?
- How can parents recognize bleeds in the first year?
- What do parents need to know in the first year?

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NOTES

■ What is hemophilia?

The word *hemophilia* derives from two Greek words: *haima*, meaning blood, and *philia*, meaning affection.

The blood of a person with hemophilia does not clot normally. He does not bleed more profusely or more quickly than other people; however, he bleeds for a longer time. Such bleeds are also called *hemorrhages*.

His blood is lacking a protein that is needed for normal clotting. Some people with hemophilia lack a protein called *factor VIII* (pronounced “factor eight”). This is *hemophilia A*. Others lack a protein called *factor IX* (pronounced “factor nine”). Their disease is called *hemophilia B*.

Many people believe that people with hemophilia bleed a lot from minor cuts. This is a myth. External wounds are usually not serious. Far more important is internal bleeding. This occurs in joints, especially knees, ankles and elbows; and into tissues and muscles. When bleeding occurs in a vital organ, especially the brain, the person’s life is in danger.

MYTH:

**BLEEDING IS
CAUSED BY FRAGILE
BLOOD VESSELS.**

REALITY:

The blood vessels of a person with hemophilia are no less fragile than anybody else’s. However, once broken, they bleed for a longer time. This is because the protein, factor VIII or IX, needed to solidify the clot, is missing.

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■ When was hemophilia first recognized?

Hemophilia was recognized, though not named, in ancient times. The Talmud, a collection of Jewish Rabbinical writings from the 2nd century AD, stated that male babies did not have to be circumcised if two brothers had already died from the procedure.

The Arab physician Albucasis, who lived in the 12th century, wrote of a family whose males died of bleeding after minor injuries.

In 1803, a Philadelphia physician, Dr. John Conrad Otto, wrote an account of “a hemorrhagic disposition existing in certain families.” He recognized that the condition was hereditary and affected males. He traced the disease back through three generations to a woman who had settled near Plymouth, New Hampshire, in 1720.

The word “hemophilia” first appears in a description of the condition written in 1828 by Friedrich Hopff, a German medical student at the University of Zurich.

■ Why is hemophilia called “The Royal Disease”?

Hemophilia has often been called *The Royal Disease*. This is because Queen Victoria, Queen of England from 1837 to 1901, was a carrier. Her eighth child, Leopold, had hemophilia and suffered from frequent hemorrhages. These were reported in the *British Medical Journal* in 1868.



Even more important to history was how hemophilia was passed on to the other royal families of Europe. Two of Queen Victoria’s daughters, Alice and Beatrice, were also carriers of hemophilia. They passed the bleeding disorder on through marriage into the German and Spanish Royal Families.

Alexandra, Alice’s daughter and Queen Victoria’s granddaughter, was also a carrier of hemophilia. She married Nicholas, the Tsar of Russia in the early 1900s. Alexandra, the Tsarina, passed hemophilia on to her first son, the Tsarevich Alexei. Nicholas and Alexandra were pre-occupied by the health problems of their son at a time when Russia was in turmoil. The monk Rasputin gained great influence in the Russian court, partly because he was the only one able to help the young Tsarevich. He used hypnosis to relieve Alexei’s pain. The use of hypnosis not only relieved the boy’s pain, but may have also helped slow or stop his hemorrhages. The illness of the heir to the Tsar’s throne, the strain it placed on the Royal Family, and the power wielded by the mad monk Rasputin were all factors leading to the Russian Revolution of 1917.



Portrait of Queen Victoria and family painted by Franz Xavier Winterhalter in 1846. Victoria and Albert’s children include Edward VII and Princess Alice, great-grandparents of the Queen and the Duke of Edinburgh

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■ What is the history of hemophilia in the 20th century?

In the 20th century doctors looked for the cause of hemophilia. Until then, they had believed that the blood vessels of people with hemophilia were simply more fragile. Then, in 1937, researchers found that they could correct the clotting problem by adding a substance that came from the plasma in blood. This was called *anti-hemophilic globulin*. In 1944, a lab test revealed that blood from one person with hemophilia was able to correct the clotting problem in a second person with hemophilia, and vice versa. Each person was found to have a deficiency of a different protein—factor VIII and factor IX. This led to the recognition in 1952 of hemophilia A and hemophilia B as two distinct disorders.

In the 1960s the clotting factors were identified and named. An article in the prominent scientific journal *Nature*, in 1964, described the clotting process in detail. The interaction of the different factors in blood clotting was named the *coagulation cascade*.


In the 1950s and early 1960s, people with hemophilia were treated with whole blood or *fresh frozen plasma*, a major component of blood. Unfortunately, the factor VIII and IX proteins were not concentrated enough in these blood products to stop serious internal bleeding. The body's circulatory system would be overloaded before a sufficient quantity of clotting factor concentrate was administered. Many people with severe hemophilia and some people with mild and moderate hemophilia died in childhood or early adulthood. The most common causes of death were bleeding in vital organs, especially the brain, and bleeding after minor surgery or after an injury.

Those who survived childhood were usually crippled by the long-term effects of repeated hemorrhages into their joints. The complications of prolonged and recurrent bleeding into joints and muscles made hemophilia one of the most painful diseases known to medicine.

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Then, in the 1960s, *cryoprecipitate* was discovered. The sludge at the bottom of a bag of thawing plasma was found to be rich in factor VIII. For the first time, enough clotting factor VIII could be infused to control serious bleeding. Even surgery became possible.

In the late 1960s and early 1970s, hemophilia treatment centres (HTCs) were established to provide *comprehensive care*.  For more information, see **Chapter 3, Comprehensive Care for Hemophilia**. People with hemophilia began to enjoy improved health and quality of life, and missed fewer days from school and work.

Starting in 1968, *factor concentrates* containing factor VIII or IX, made from human plasma, began to be available. These freeze-dried powdered concentrates could be kept at home and used as needed. They revolutionized hemophilia care. People with hemophilia were now independent of hospitals. They could travel, hold steady jobs and hope to lead nearly normal lives. Life expectancy began to approach that of the general population. Tragically, these same blood products were eventually found to carry blood-borne viruses such as HIV and hepatitis C. Many people with hemophilia were infected before blood safety measures such as viral inactivation were introduced to pharmaceutical manufacturing processes in the mid- and late 1980s to make factor concentrates safer.

Finally, in the early 1990s, genetically engineered factor called recombinant factor concentrates came on the market. Recombinant factor concentrates are not made from plasma and contain little or no human proteins.

As a result of these advances, children born with hemophilia in Canada today can look forward to long, healthy, active and productive lives.

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■ What causes hemophilia?

Hemophilia is a *genetic disorder*. This means that it is caused by a gene that does not work normally. Like other genetic health problems, hemophilia can be passed from generation to generation. In almost all cases, the gene responsible for hemophilia is passed from a parent to the child at the time of conception.

However, in about 3 out of 10 cases, a son is born to a family that has no history of hemophilia. There are 3 reasons why this might happen:

1. It could be that hemophilia has been in the family for generations. Because no male showed signs of bleeding problems, no one knew hemophilia was present. The family may have had females who were hemophilia *carriers*. But if none of these women had sons, or none of their sons had hemophilia, no one would know that hemophilia was being passed on—until a boy was born with hemophilia.
2. It could be that the boy's mother developed the gene with the hemophilia mutation when she was conceived. The mother would be the first person in the family to carry hemophilia. Her daughters could be carriers; her sons could have hemophilia.
3. It could be that the mutation that causes hemophilia happened when the boy was conceived. In this case, the egg from his mother developed a mutation and as a result, the boy has hemophilia. In such a case, the mother is not a carrier but some of her other eggs could also develop the mutation.

 For more information on inheritance, see **Chapter 2, How a Child Gets Hemophilia.**

Still a Mystery...

Some cases of hemophilia are caused by new genetic mutations. The gene that causes hemophilia was not present in any family member up to that point. Why does this extremely rare event happen?

It's still a mystery.

■ What are other names for hemophilia A and B?

Hemophilia A is called by two other names:

- *classical hemophilia*, because it is the most common of the factor deficiencies; and
- *factor VIII deficiency hemophilia*, because it is the lack of the factor VIII protein in the blood that causes the clotting problem.

Hemophilia B also goes by two other names:

- *Christmas Disease*, named after Steven Christmas, a Canadian who in 1952 was the first person to be diagnosed with this distinct form of hemophilia; and
- *factor IX deficiency hemophilia*, because factor IX is the blood protein that is lacking and whose absence slows down the normal clotting process.



■ How common is hemophilia?

Both hemophilia A and B are very rare disorders. Hemophilia A affects fewer than 1 in 10,000 people, or about 2,500 Canadians. Hemophilia B is even less common, affecting approximately 1 in 50,000 people, or about 600 Canadians.

“Mom says hemophilia is only in one of my genes and that I have lots more. It is a little piece of who I am. You should know lots of other stuff about me too. I like riding my bike and watching BMX racing on TV.”

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■ Who is affected by hemophilia?

Hemophilia affects people of all races, colours and ethnic origins around the world.

The most severe forms of hemophilia affect almost only males. Females can be seriously affected only if...

- the father has hemophilia and the mother is a carrier.
- the female experiences *lyonization*, also called *X-inactivation*. In this case, she has one abnormal X chromosome with the hemophilia gene and one normal X chromosome; however, the normal X chromosome is inactive in the production of the clotting protein.

Both these situations are extremely rare.

However, many females who are carriers have symptoms of mild hemophilia. We are only now fully recognizing that carriers can have bleeding problems and that this can affect their quality of life.  For more information on being a hemophilia carrier, see **Chapter 14, Symptomatic Carriers of Hemophilia**, and the CHS publication **All about Carriers**, available from the Canadian Hemophilia Society or hemophilia treatment centres.

As hemophilia is an inherited disorder, children are affected from the moment of birth. In fact, hemophilia is often diagnosed in the first year of life. It is a lifelong condition. At the moment, there is no way to correct the genetic defect.

Did you know...

that people with hemophilia are less likely to suffer from Economy Class Syndrome (the formation of blood clots in the legs due to inactivity on long cramped flights)? This is because clots are less likely to form in their bloodstream.

■ How serious is hemophilia?

Hemophilia A and B can be divided into three classifications.

Table 1

Classification of Hemophilia		
Classification of hemophilia	Level of factor VIII or IX in the blood*	Percentage of children with hemophilia in each classification
Severe	Less than 1 percent	40 percent of cases
Moderate	1 to 5 percent of normal	20 to 25 percent of cases
Mild	5 to 30 percent of normal	35 to 40 percent of cases

* Clotting factor activity in a normal person is said to be 100 percent, ranging anywhere from 50 percent to 150 percent.


People with *severe hemophilia* have less than 1% of the normal level of factor VIII or IX in their blood. Without preventative treatment, they can have hemorrhages several times a month. Sometimes there is no apparent cause for the bleeding.

People with *moderate hemophilia* usually bleed less often. Their hemorrhages are frequently the result of minor trauma, such as a sports injury. However, some people with moderate hemophilia, especially those whose level of factor VIII or IX is 2% or less, can have frequent bleeds just like a person with severe hemophilia.

People with *mild hemophilia* have even fewer hemorrhages. They may be aware of their bleeding problem only in the case of surgery, a tooth extraction or a serious injury. The danger for


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people with mild hemophilia is that, having so few bleeds, they often do not know what to do when one occurs. Women who are carriers of hemophilia may bleed more during their menstruations. For these reasons people with mild hemophilia and carriers of hemophilia, too, need to be followed at a *hemophilia treatment centre (HTC)*.  For more information, see **Chapter 9, Mild and Moderate Hemophilia**.

■ Are there effective treatments for hemophilia?


Yes, there are. Current treatments for hemophilia A and B are very effective. The key treatment for hemophilia is *clotting factor therapy*. This therapy involves the *infusion* (injection into a vein) of the clotting factor that is low or missing in the blood of the person with hemophilia. It is both safe and effective in stopping bleeding. This therapy is also used in a preventative way—to prevent bleeding from happening at all. Preventative treatment with factor concentrates is called *prophylaxis*. Children with hemophilia born in Canada today can look forward to long, healthy and active lives because of these effective treatments.

 For more information on care and treatment, see **Chapters 3, 4, 5, 6 and 7**.

Complications are possible. The most serious of these is the development of an *inhibitor*. In some people with hemophilia, the immune system reacts to the clotting factor concentrate that is infused to stop or prevent a bleed. The factor concentrate is seen as a foreign substance. The body's defences do not recognize it so the immune system fights the factor concentrate by producing antibodies, natural chemical substances that circulate in the blood. The antibodies eliminate the infused factor concentrate and thus prevent it from doing its job of stopping or preventing bleeding. These antibodies are called inhibitors. Fortunately, there are effective treatments for people with hemophilia who develop inhibitors.  For more information on inhibitors, see **Chapter 8, Complications of Hemophilia**.

“I don’t have enough factor VIII in my body, so I have to have needles. I don’t like getting needles. It would be good if someone could find a medicine that tasted like bubble gum, or maybe they could just make it go away.”

■ How does blood clot normally?

Blood is carried throughout the body within a network of blood vessels. When tissues are injured, damage to a blood vessel may result in leakage of blood through holes in the vessel wall. The vessels can break near the surface of the skin, as in a cut. Or they can break deeper inside the body, causing a bruise or an internal hemorrhage.  For more information on recognizing different kinds of bleeds, see **Chapter 4, Management of Bleeds**.

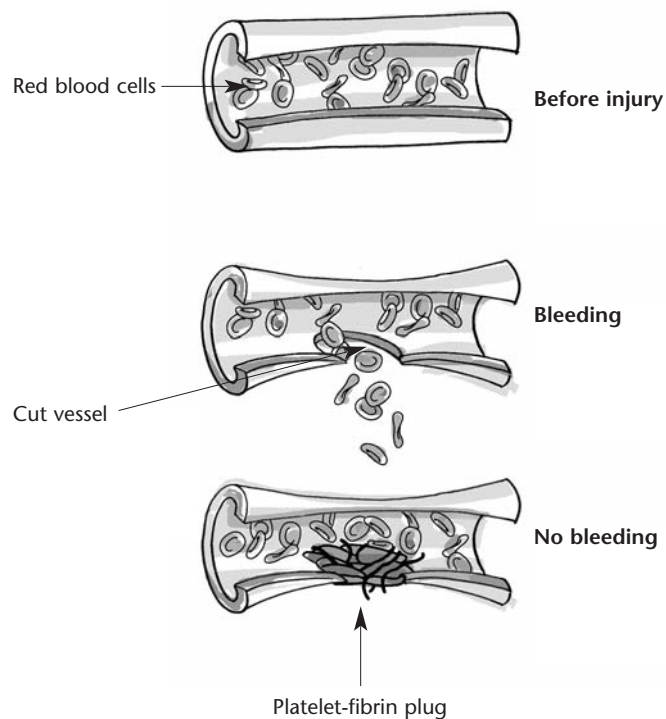


Figure 1

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Clotting, or *coagulation*, is a complex process that makes it possible to stop injured blood vessels from bleeding. As soon as a blood vessel wall is torn, the proteins that work together to form the clot come together to form a plug at the tear. There are several steps involved in forming this plug.


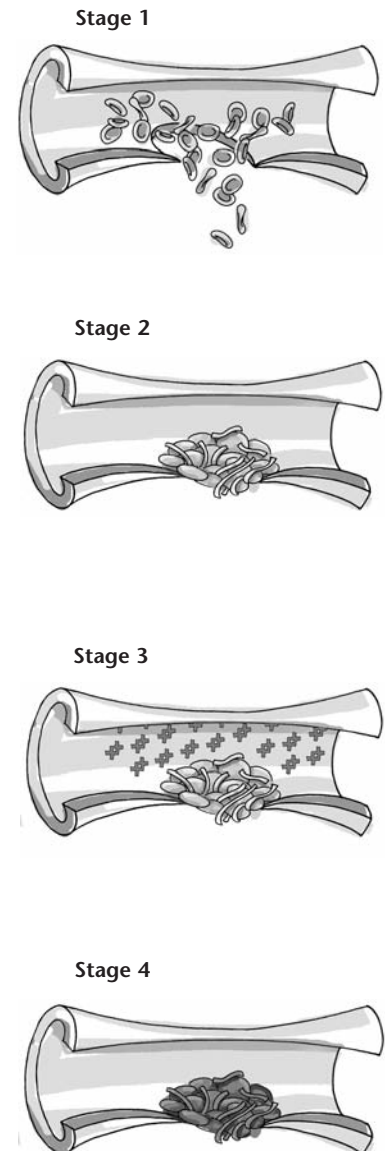
- **Stage 1:** The blood vessels constrict to slow the flow of blood to the injured area. This is called *vascular constriction*, or *vasoconstriction*.
- **Stage 2:** *Blood platelets*, which are very tiny cells circulating in the blood, are the first to arrive at the tear in the blood vessel wall. Each platelet is less than 1/10,000 of a centimetre in diameter. There are 150 to 400 billion platelets in a normal litre of blood. The platelets play an important role in stopping bleeding by clumping together, thereby beginning the repair of injured blood vessels. This is called *platelet adhesion*.
- **Stage 3:** These platelets then emit chemical signals calling for help from other platelets and from clotting factors, such as *von Willebrand factor*. These spreading platelets release substances that activate other nearby platelets, which then clump at the site of injury to form a platelet plug. This is called *platelet aggregation*.
- **Stage 4:** The surface of these activated platelets then provides a site for blood clotting to occur. Clotting factors, which are tiny plasma proteins, link to form a chain, called *fibrin*. The strands of fibrin join together to weave a mesh around the platelets. This prevents the platelets from drifting back into the bloodstream. These proteins (factors I, II, V, VII, VIII, IX, X, XI, XII and XIII) work like dominoes, in a chain reaction. This is called the *coagulation cascade*.  See **Figure 3**.

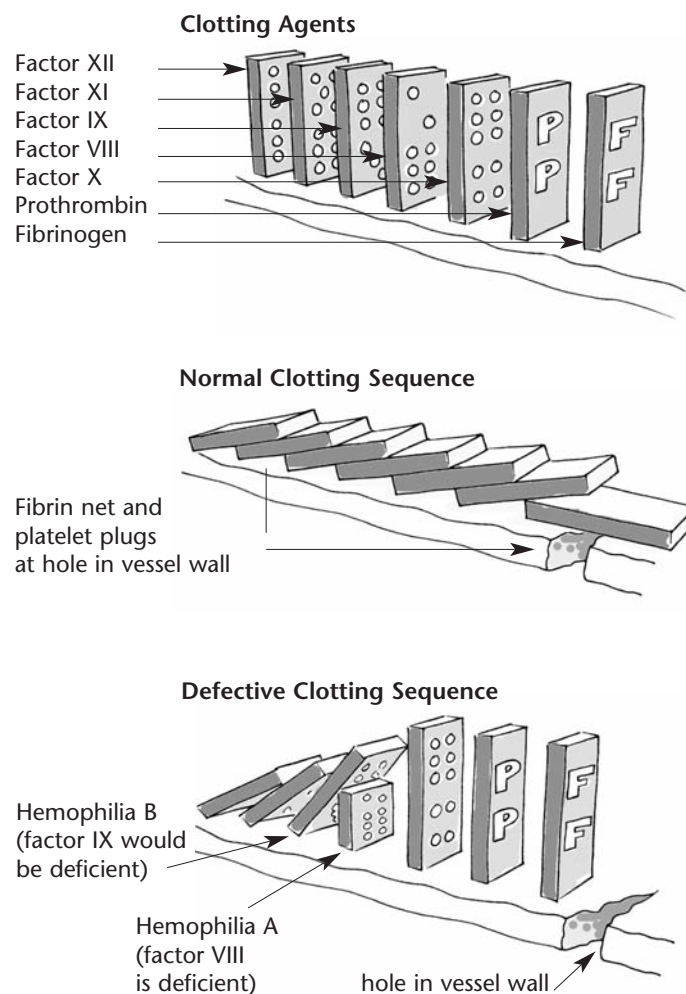
Figure 2



■ What is the clotting problem in hemophilia?

When one of the proteins, for example factor VIII, is absent, the chain reaction is broken. Clotting does not happen, or it happens much more slowly than normal. The platelets at the site of the injury do not mesh into place to form a permanent clot. The clot is “soft” and easily displaced. Without treatment, bleeding can continue for days and sometimes weeks. Re-bleeding often occurs.

Figure 3



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■ How can parents recognize bleeds in the first year?


In the first few months, a baby with hemophilia will look like all other newborns and show no sign of a bleeding problem. Gradually, parents will start to notice bruises in places like the chest and arms. These bruises are often located at pressure points where parents hold the child more and more tightly as he gets heavier. While these bruises on the child's body can be alarming, they are usually not painful and rarely require treatment. It is important not to avoid holding the baby out of fear of causing bruising. A lack of affectionate physical contact with those he loves can have psychological effects that are far more serious than a few minor bruises. You should hold and play with your baby as you would with any baby who does not have hemophilia.

After any fall or injury, the parent must look for physical or behavioural changes in the baby. These include...

- bruising
- swelling
- reluctance to use a limb or joint
- unusual crying

At first, it is not easy to know whether an injury is serious or not. That's why it is always important to contact your HTC nurse coordinator or care team as soon as an injury occurs.




It is normal to feel insecure about handling bleeds when your child is so young but, with time, you will start to gain confidence and, with experience, recognizing a bleed will become easier.

 To learn how to recognize bleeds and whether or not a child needs treatment with clotting factor concentrate, see **Chapter 4, Management of Bleeds.**

“Ultimately, you and your child will know more about hemophilia than most people.”

■ What do parents need to know in the first year?

Parents need to know about the special health and safety precautions to take with children with hemophilia. These include ...

- the recommendations on the vaccination schedule, provided by the hematologist at the HTC.  *For more information on vaccination, see **Chapter 10, Growing with Hemophilia.***
- the recommendations on protective gear for toddlers learning to walk – such as a helmet to protect his head from knocks, padding to protect his buttocks from bruising, and elbow pads and knee pads – and where to buy these items in toddler sizes.  *For more information, see **Chapter 11, Staying Healthy.***
- the medications to give if there is bleeding from the gums, which often happens when a baby is teething.  *For more information, see **Chapter 4, Management of Bleeds.***
- the appropriate type of shoes and other footwear recommended by the physiotherapist or physician at the HTC.
- the proper way to mix clotting factor concentrate in case the child has a bleed outside regular clinic hours and staff at the hospital emergency room need help with infusion.