This chapter provides answers to these questions:

- What is hemophilia?
- 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?
- When was hemophilia first recognized?
- Why is hemophilia called “The Royal Disease”?
- What is the history of hemophilia in the 20th century?

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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.

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 will be born to a family that has NO history of hemophilia. There are 3 reasons why this might happen:

1. It could be that hemophilia was in the family for generations. Because no male showed signs of increased bleeding, no one knew hemophilia was present. The family may have had girls who were hemophilia carriers. But if none of these girls had sons, or none of the 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 got the mutant gene at the time she was conceived. The mother is the first person in this family to carry hemophilia. Her daughters may be carriers; her sons may 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 that was passed on to him. In such a case, the mother is not a carrier. None of her other children will be affected by hemophilia. *(For more information on inheritance, see Chapter 2, How a Child Gets Hemophilia.)*

### 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 1 in 10,000 people, or about 3,000 Canadians. Hemophilia B is even less common, affecting approximately 1 in 35,000 people, or about 800 Canadians.

### 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. This is extremely rare.

However, many women 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.

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.
How serious is hemophilia?

Hemophilia A and B can be divided into three classifications.

**Table 1**

<table>
<thead>
<tr>
<th>Classification of hemophilia</th>
<th>Level of factor VIII or IX in the blood*</th>
<th>Percentage of children with hemophilia in each classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Less than 1 percent</td>
<td>40 percent of cases of normal</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 to 5 percent of normal</td>
<td>20 to 25 percent of cases</td>
</tr>
<tr>
<td>Mild</td>
<td>5 to 30 percent of normal</td>
<td>35 to 40 percent of cases</td>
</tr>
</tbody>
</table>

*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. There is often no obvious cause for the bleeding—it just happens. This is called spontaneous 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 spontaneous bleeds in the same way as 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 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, too, need to be followed at a hemophilia treatment centre. (For more information, see Chapter 7, 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 of the clotting factor which is missing in the blood of the child with hemophilia. It is both safe and effective in stopping bleeding. This therapy can even be used in a preventative way—to stop bleeding from happening at all. Children born today in Canada can look forward to long, healthy, active lives. (For more information on care and treatment, see Chapters 3, 4, 5 and 6.)

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 defenses do not recognize it so the immune system fights 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 the bleeding. These antibodies are called inhibitors. Fortunately, there are effective treatments for children who develop inhibitors. \( \text{For more information on inhibitors, see Chapter 8, Complications of Hemophilia.} \)

**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, making a bruise or an internal hemorrhage. \( \text{For more information on recognizing different kinds of bleeds, see Chapter 5, Management of Bleeds.} \)
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 breaks, the proteins that work together to form the clot come together to form a plug at the break. 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 cell fragments, are the first to arrive at the break. Platelets are small cells circulating in the blood. 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, like *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 and XIII) work like dominoes, in a chain reaction. This is called the *coagulation cascade*. See **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.

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 by Hopff at the University of Zurich in 1828.
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. Leopold died of a brain hemorrhage at the age of 31, but not before he had children. His daughter, Alice, was a carrier and her son, Viscount Trematon, also died of a brain hemorrhage in 1928.

Even more important to history was the existence of hemophilia in the Russian Royal Family. Two of Queen Victoria’s daughters, Alice and Beatrice, were also carriers of hemophilia. They passed the disease on to the Spanish, German and Russian Royal Families. (See Queen Victoria’s family tree on p. 1-14)

Alexandra, Queen Victoria’s granddaughter, married Nicholas, the Tsar of Russia in the early 1900s. Alexandra, the Tsarina, was a carrier of hemophilia and her first son, the Tsarevich Alexei, had hemophilia. 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 pain, but may have also helped slow or stop the boy’s 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.
An Introduction to Hemophilia

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. In the 1930s, doctors looked at defective platelets as the likely cause. Then, in 1937, Patek and Taylor, two doctors at Harvard, found 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, Pavlosky, a doctor from Buenos Aires, Argentina, did a lab test which showed that blood from one person with hemophilia could correct the clotting problem in a second person with hemophilia, and vice-versa. He had stumbled upon two individuals, each with a deficiency in a different protein—factor VIII and factor IX. This led to the recognition in 1952 of hemophilia A and hemophilia B as two distinct diseases.

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 or 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 was administered. Most people with severe hemophilia and some people with mild or 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 were usually crippled by the long-term effects of repeated hemorrhages into the joints. The pressure of massive bleeding into joints and muscles made hemophilia one of the most painful diseases known to medicine.

Then, in the 1960s, cryoprecipitate was discovered by Dr. Judith Pool. Dr. Pool found that the sludge on top of thawing plasma was rich in factor VIII. For the first time, enough factor VIII clotting factor 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. \textit{(For more information, see Chapter 3, Comprehensive Care for Hemophilia.)} People with hemophilia began to enjoy improved health, and missed fewer days from school and work.

Starting in 1968, factor concentrates containing factor VIII and IX, made from 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 normal lives. Life expectancy began to approach that of the general population. Tragically, these same blood products carried blood-borne viruses like HIV and hepatitis C. Many people with hemophilia were infected.

In the mid and late 1980s, ways were found to make factor concentrates manufactured from plasma safer. Viruses like HIV were inactivated using heat or chemical processes. This again
improved the outlook. Finally, in the early 1990s, genetically engineered (recombinant) clotting factor concentrates came on the market. These concentrates are not made from plasma and contain little or no human proteins. As a result of these advances, most children born with hemophilia in Canada today can look forward to long, healthy, active and productive lives.

(See Table 2, The Major Milestones of Hemophilia Care in Canada.)

Unfortunately, less than 25% of the people with hemophilia around the world enjoy this level of care. The ones who do not have access to modern hemophilia care face the same fate as Queen Victoria’s offspring in the 1800s—a life of pain and crippling, and an early death.
Table 2
The Major Milestones of Hemophilia Care in Canada

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>Whole blood and fresh frozen plasma became widely available in Canada. This marked the beginning of factor replacement therapy for people with hemophilia.</td>
</tr>
<tr>
<td>1953</td>
<td>The Canadian Hemophilia Society was founded in Montreal.</td>
</tr>
<tr>
<td>1964</td>
<td>Cryoprecipitate was discovered. Effective treatment for hemophilia A became possible.</td>
</tr>
<tr>
<td>1968</td>
<td>The first factor VIII and IX concentrates were introduced. The first experiments with home infusion began.</td>
</tr>
<tr>
<td>1969</td>
<td>The first hemophilia treatment centre offering comprehensive care was opened in Montreal.</td>
</tr>
<tr>
<td>1980</td>
<td>The Winnipeg Conference, organized by the Canadian Hemophilia Society, was held to discuss comprehensive care. The conference served as the springboard for the creation of a network of hemophilia treatment centres across Canada.</td>
</tr>
<tr>
<td>1985</td>
<td>Heat-treated factor concentrates, effective in eliminating HIV, were introduced in Canada.</td>
</tr>
<tr>
<td>1988</td>
<td>Factor concentrates, manufactured with enhanced viral inactivation methods, effective in eliminating hepatitis C, began to be used in Canada.</td>
</tr>
<tr>
<td>1993</td>
<td>Genetically engineered (recombinant) factor VIII concentrates were introduced in Canada.</td>
</tr>
<tr>
<td>1997</td>
<td>Genetically engineered (recombinant) factor IX concentrates were made available in Canada. Canada became the first country where all people with hemophilia A and B had access to recombinant factor concentrates.</td>
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