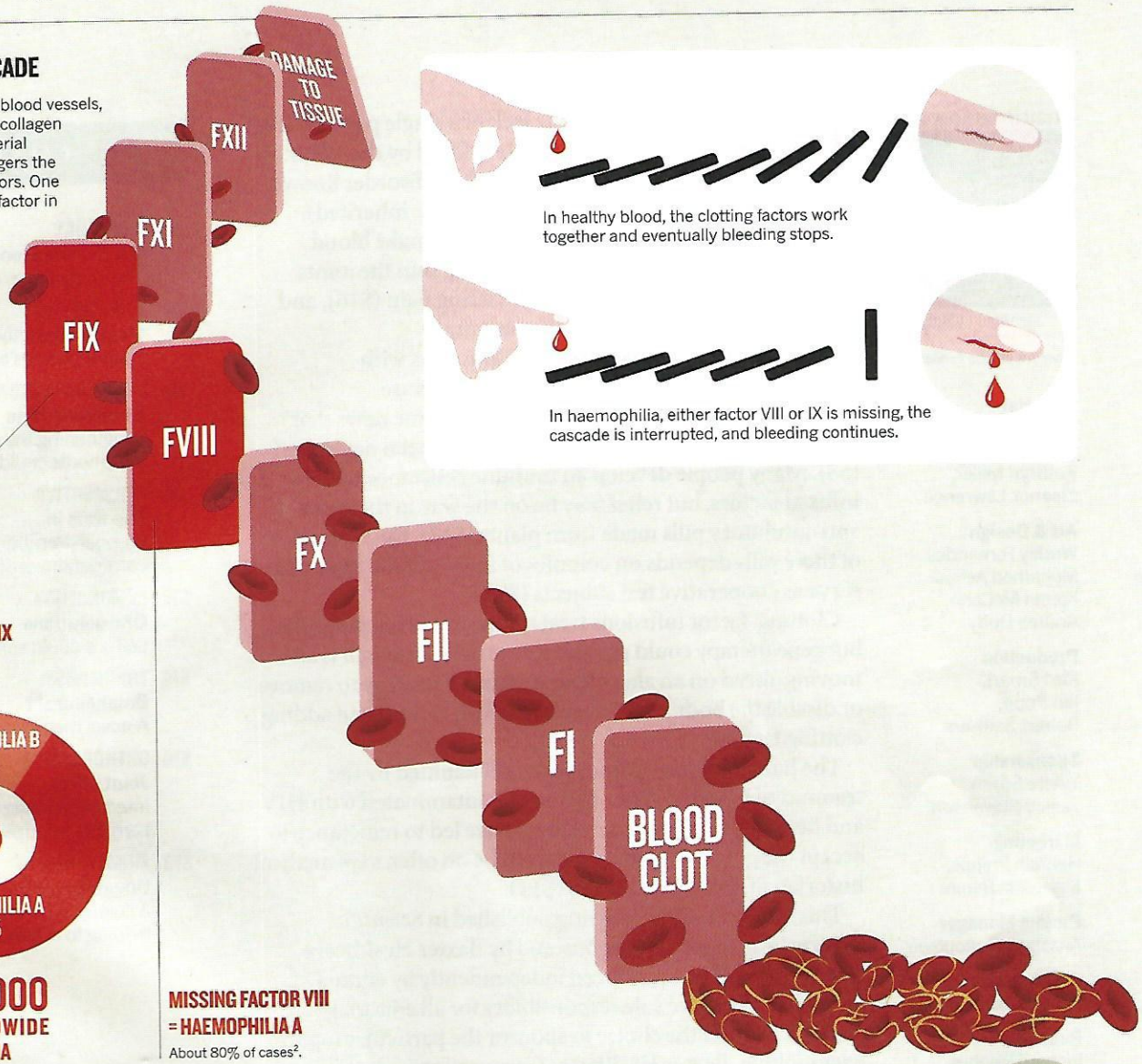
# BORN IN THE BLOOD

*People with the inherited bleeding disorder haemophilia lack factors that cause the blood to clot. The disease affects thousands of people around the world and has even played a part in historic events. By* **Neil Savage.**

## COAGULATION CASCADE

When damage occurs to blood vessels, exposure of the blood to collagen in the cell walls and material released by the cells triggers the activation of clotting factors. One factor activates the next factor in a series of events (some not depicted here) that eventually produces fibrin. Fibrin forms a mesh to hold together a plug of platelets to form a clot (platelets are a type of cell that circulates in the blood to help coagulation)[1].



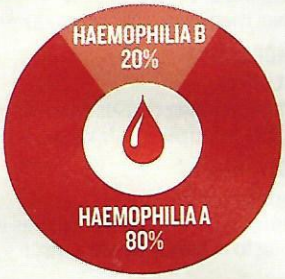



In healthy blood, the clotting factors work together and eventually bleeding stops.

In haemophilia, either factor VIII or IX is missing, the cascade is interrupted, and bleeding continues.

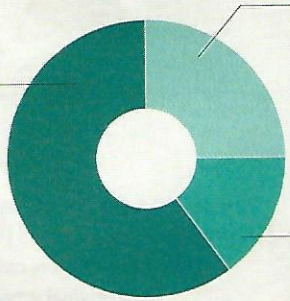
**MISSING FACTOR IX = HAEMOPHILIA B**
About 20% of cases[2].

**MISSING FACTOR VIII = HAEMOPHILIA A**
About 80% of cases[2].




**AT LEAST 172,000 PEOPLE WORLDWIDE HAVE HAEMOPHILIA**

## OF ALL THE PEOPLE WITH HAEMOPHILIA...



**60%**
**Have severe haemophilia (clotting factor in the blood is less than 1% of the level in normal, healthy people)[3]**
Bleeding after injury, spontaneous bleeding, risk of joint damage. Median age at diagnosis is one month.

**25%**
**Have mild haemophilia (clotting factor levels of 6–30%)[3]**
Bleeding only after serious injury, accidents or surgery. Heavy menstrual bleeding in women. Median age at diagnosis is 36 months, though it is often not diagnosed until after a serious injury.

**15%**
**Have moderate haemophilia (clotting factor levels of 1–5%)[3]**
Bleeding after injury, some spontaneous bleeding, risk of joint damage. Median age at diagnosis is eight months.

## TREATMENT TIMELINE

**About two-thirds of the world's population lacks access to prophylaxis with clotting factors because the cost of treatment is too high.**

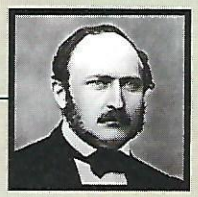
**1840**

**1840s**
First blood transfusions for bleeding episodes.

## THE ROYAL DISEASE

Queen Victoria became a carrier of haemophilia through what is believed to have been a spontaneous genetic mutation[4].

Queen Victoria
1819–1901

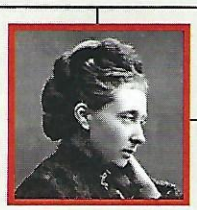


Prince Albert
1819-1861

Victoria passed it on to one son, who died of bleeding, and two daughters.

Victoria

Edward VII



Alice
1843–1878

Alfred

Helena

Louise

Arthur

Ludvig IV

Leopold
1853–1884

Beatrice
1857–1944

Haemophilia spread throughout European royalty, including Victoria's great-grandson, Alexei Romanov, son of the last Russian tsar, Nicholas II.

The 'mad monk' Rasputin claimed to be able to treat Alexei's haemophilia, and his influence with the tsar's family is credited with contributing to the Russian revolution.

In 2009, DNA tests on Alexei's remains showed that Victoria carried haemophilia B.

Alexandra
1872–1918

Nicholas II of Russia

Alexei
1904–1918

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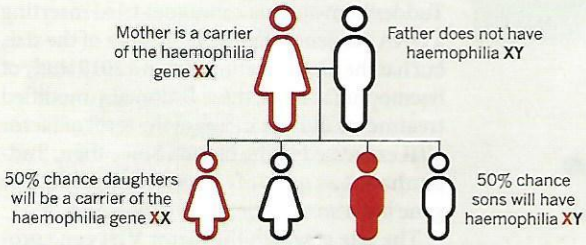
## INHERITANCE PATTERN

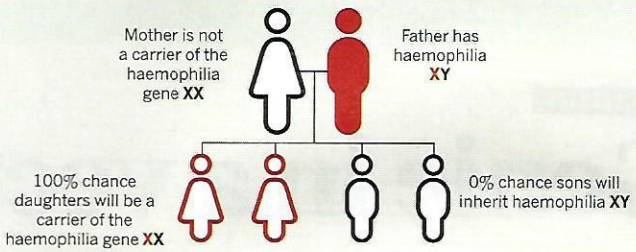
The mutations causing haemophilia are carried on the X chromosome. Woman are usually carriers, with a 50% chance of having sons with haemophilia or daughters who are carriers. Men with haemophilia will have no sons who are haemophiliacs, but all their daughters will carry the gene. In rare cases, female carriers or girls with both X chromosomes affected will have haemophilia; fewer than 10% of cases occur in females. Approximately one-third of cases arise from spontaneous mutation[5].

Does not have haemophilia

Carrier of haemophilia gene

Has haemophilia




**An estimated 40,000 haemophiliacs worldwide were infected with HIV, including 70–90% of those with severe haemophilia[6].**

40,000

**The cost of prophylaxis treatment could reach $300,000 per child per year[7].**

$300,000

**1900**

**1923** — First use of plasma replacement therapy

**1950s–1960** — Fresh frozen plasma requires large volume transfusions

**Mid-1960s** — Cryoprecipitate (a concentrate of blood components made from frozen plasma) allows smaller transfusions

**1970** — Freeze-dried clotting factors allow home-based prophylaxis

**1970s–early 1980s** — Haemophiliacs contract hepatitis and HIV from blood products

**1987** — Heat-treated factor VIII reduces risk of blood-born pathogens

**1989** — Genetically engineered factor VIII, no risk of HIV or hepatitis

**2000**

**1997** — Genetically engineered factor IX

**2014** — First extended-life clotting factors approved

**Future** — Gene therapy

References: 1. Pipe, S. W. (Ed.) The Hemophilia Report (2014) available at: www.hemophiliareport.com 2. 2012 World Hemophilia Foundation Survey, covering 91% of the world's population; 3. US National Hemophilia Foundation 4. Rogaev, E. I. *et al. Science* **326,** 817 (2009). 5. US Centers for Disease Control and Prevention 6. Starr, D. *Blood: An Epic History of Medicine and Commerce*, p346, Harper Perennial (2000). 7. Manco-Johnson, M. A. *et al. N. Engl J. Med.* **357,** 535–544 (2007).