Twelve Diseases
THAT CHANGED OUR WORLD

IRWIN W. SHERMAN

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Preface

The literature on the impact of disease on history is large. It chronicles how illness has affected Western civilizations: in the 14th century plague broke the Malthusian stalemate and provided the impetus to restructure European societies; during the past two centuries genetic diseases altered the fates of the British, Spanish, and Russian royal families and contributed to the rise of Lenin, Franco, and Hitler; in the last 100 years we have witnessed how increased opportunities for disease transmission have decimated populations, created panic, and fostered discrimination. We continue to be painfully aware of the power a disease can wield in effecting social and political changes on a grand scale and how it can reveal and exacerbate social tensions. In the past, disease played a role in colonial expansion in the Americas and Africa and, through demographic pressure and starvation, forced a mass migration of the Irish people; tomorrow in different places and in different ways, another disease may do the same.

Historical perspectives of disease can be valuable for a better understanding of how we, and our forebears, survived the onslaught of "plagues" and how we might avoid some of their consequences: confrontations between immigrants and nativists, discrimination against those with different lifestyles, and the social and political disruptions due to incapacitation and death. Of equal value, and much needed, is an examination of the attempts to control disease and how it was possible to improve the public health. In short, this book is about the lessons we have or should have learned from our past encounters with unanticipated outbreaks of disease and how such understanding can be put to use when future outbreaks occur.

The recent SARS and AIDS pandemics clearly show that our lives, as well as the political and economic fortunes of the developed world and emerging nations, can be influenced by the appearance of a contagious disease. In 2004, alarm bells went off as avian influenza spread across the globe, killing millions of domestic fowl and 113 people. The public asked what measures would be needed to stop its spread so that another 1918 to 1920 flu pandemic, which killed tens of millions of people, would not occur. In 2006 cholera swept through West Africa, striking 20,000 people, and in the United States mumps—no longer thought to be a threat because of childhood vaccination—broke out in Iowa and quickly spread to neighboring states, affecting 1,000 people.

These unanticipated epidemics provoke questions. What is needed to curtail the transmission of a disease? What will it take to contain a disease so that protective measures can be instituted? These questions, perplexing and complex, need answers. To simply catalog past diseases and tell of their historic consequences would not be of lasting value to the general public. Rather, it was my feeling that the answers to how we might deal with "coming plagues" could be better obtained by an examination of how past encounters with disease allowed for better control and improved health.

Our world has experienced so many diseases that it would be pointless to deal with all of them. In fact, it would be a nearly impossible task, and, if achieved, it would be numbing to read. Instead, I have selected a dozen diseases that have shaped our history and illuminated the paths taken in finding measures to control them. Porphyria and hemophilia (chapter 1) influenced the political fortunes of England, Spain, Germany, Russia, and the United States; late blight (chapter 2) spawned a wave of immigration that changed the politics of the United States; cholera (chapter 3) stimulated sanitary measures, promoted nursing, and led to the discovery of oral rehydration therapy; smallpox (chapter 4) led to a vaccine that ultimately eradicated the disease; plague (chapter 5) promoted quarantine measures and attenuated vaccines were the result of outbreaks of tuberculosis (chapter 6); syphilis (chapter 7) provided the impetus for cure through chemotherapy; and malaria and yellow fever (chapters 8 and 9) provided the basis for vector control. However, despite these successes, two pandemics—influenza (chapter 10) and HIV/AIDS (chapter 11)—continue to elude control. In this book I try to answer why this is so.

The message of this book is simple: understanding past outbreaks of disease can better prepare us for those in our future. The twelve diseases

chosen have influenced the way we look at sickness and show how they resulted in public health measures and other interventions to stem the spread of that disease and others. To eliminate the fear and confusion surrounding "coming plagues," I describe the ways we have succeeded in bringing certain diseases under control and, in other cases, our failures. My purpose in writing this book for the general reader is to show that despite the challenges which an unanticipated illness may place before us, the future is not without hope or remedy.

1

The Legacy of Disease: Porphyria and Hemophilia

In 1962 the U.S. President John F. Kennedy said, "Life is unfair. Some people are sick and others are well." He, of course, was referring to himself and the persistent rumors about his ill health. Forty years later, an examination of his medical records revealed that he had Addison's disease, a life-threatening lack of adrenal gland function, as well as osteoporosis and persistent digestive problems. He was given pain killers (demerol and methadone), stimulants, and antianxiety agents, as well as hormones (hydrocortisone and testosterone) to keep him alive, especially during times of stress. Although doubts linger whether President Kennedy's physical ailments influenced the manner by which the Cuban missile crisis was handled or whether they affected other political decisions, it is clear that for many world leaders, including Great Britain's King George III, several of Queen Victoria's children and grandchildren, Tsar Nicholas II of Russia, and Alfonso XIII and Generalissimo Franco in Spain, as well as, indirectly, the leaders of Nazi Germany, sickness was the seed for historical change.

Porphyria

Madness in the monarchy

Mary Queen of Scots (1542 to 1587) had a mysterious ailment. At the age of 24 she wrote, "Oftentimes I have great pains . . . ascending unto my head . . . it descends to my stomach so that it makes me lack an appetite . . . and there is sickness with great vomit . . . excuse my writing, caused by the weakness of my arm . . . wherewith we are tormented." In 1570, when

she had another attack, her symptoms were described by her physician: "terrible pains in the side made worse by every movement, even breathing. She vomited continuously, more than 60 times, and eventually brought up blood. She became delirious, and two days later she lost her sight and speech, had a series of fits, remained unconscious for some hours and was thought to be dead. Yet within 10 days she was up and about again. She had unquiet and melancholy fits, convulsions, shivering, difficulty in swallowing, altered voice, weakness of arms and legs so that she could neither write, walk or even stand unaided." The onset of her symptoms was rapid and suggested to some in her court that she was being poisoned. Others judged her to be hysterical. It is most likely, however, that Mary Queen of Scots was neither hysterical nor the victim of poisoning. Instead, she and many of her descendants probably suffered from an inherited disorder—a curse of British royalty—that would alter the course of world history.

Mary Stuart, Queen of Scotland since birth, was engaged at the age of 3 to Prince Francis, heir to the throne of France; at age 15, when she married him, he was already King Francis II, so she became Queen of France as well as of Scotland. Such glory did not last very long. Francis II died unexpectedly a year after the marriage, and Mary returned to Scotland, where she later married Henry Stuart, Lord Darnley, a relation of the English royal family who was described by historians as a drunkard and an imbecile. Mary did not trust Darnley with affairs of state, and she had several male secretaries who advised her. One of her favorites was David Rizzio, who provoked such jealousy in Mary's husband that he arranged for Rizzio to be murdered. Darnley himself was murdered a year later, and it was widely believed that James Hepburn, 4th Earl of Bothwell, had conspired with the Queen to kill her husband. Shortly thereafter, Mary married Bothwell. This, together with Mary's episodes of blindness, depression, and inability to speak or stand, so disturbed the Scottish nobility that they forced her to abdicate the throne. Mary sought refuge and protection in England, where her cousin Elizabeth I was queen. Mary was an ungrateful and tormented guest in England and became involved in plots to kill Elizabeth. The plots were discovered, and in 1587 Mary was beheaded.

When Elizabeth I died in 1603, Mary's son, James VI of Scotland, succeeded her as James I of England. The King had a disease similar to that of his mother. According to his physician, Sir Theodore de Mayerne, "He was afflicted with pain . . . under his ribs . . . he glows with heat, and his

appetite falls off; he sleeps badly; he readily vomits, at times so violently that his face is covered with red spots for two or three days . . . very often he suffered from painful colic . . . with vomiting and diarrhea, preceded by melancholy and nocturnal rigors . . . he had such pain and weakness in the foot that it was left with an odd twist when walking . . . In 1616 . . . for 4 months he had to stay in bed or in a chair . . . In 1619 . . . he sweats easily . . . often suffers bruises . . . he is of exquisite sensitiveness and most impatient of pain . . . He often passed urine red like Alicante wine." Although diagnosis of medical conditions in persons living so long ago is uncertain, it is very likely that the mysterious disease suffered by Mary Queen of Scots, her son King James, and many of their descendants was porphyria, derived from the Greek word "porphuros," meaning "purple," with its telltale sign of red-purple urine.

Gene failure

Porphyria, a hereditary error of metabolism, is linked to the body's production of the pigment hemoglobin, which gives color to our red blood cells and grabs oxygen molecules as blood courses through the lungs. Hemoglobin consists of a protein, globin, coupled to a nonprotein molecule, heme. Heme, an iron complex within a ring structure called porphyrin, is synthesized in the red cells and liver. The reverse of this process, that is, the breakdown of heme to salvage the iron, results in the formation of bile pigments which are stored in the gallbladder and function as a detergent to emulsify fats for easier digestive action; bile pigments also color the feces brown. If there is a block anywhere in the eight-step pathway of heme formation, heme is not produced and the porphyrin intermediates accumulate in a variety of tissues in the body.

The pathway of heme manufacture can be thought of as if it were a river flowing downstream with a series of eight waterwheels along the way; each waterwheel is a cellular factory for making heme intermediates, i.e., porphyrins. To allow for control of water flow, a series of sluice gates are positioned ahead of each waterwheel. For a waterwheel to turn, each sluice gate must be opened by a gatekeeper. When a gatekeeper cannot open a gate, the flow of water is interrupted; water accumulates behind the waterwheel and spills over. Similarly, in the pathway for the synthesis of heme, the gatekeepers are the eight biological catalysts, called enzymes, that allow a controlled flow of intermediates in the pathway. If a gatekeeper "falls asleep at the wheel," i.e., a particular enzyme does not function properly (or is absent), the normal pathway to heme is blocked

and porphyrins accumulate in front of the block. These increased amounts of porphyrins do their dirty work, causing abdominal pain and neuropsychiatric symptoms (such as those seen in Mary and James), although the precise molecular basis for this is not known. The porphyrins in the skin, when exposed to UV light, become "excited" and in this state react with molecular oxygen to form activated oxygen, which can lead to cell death, with redness and blistering of the skin and scarring. The porphyrin intermediates also spill over into the urine during an attack. In an individual with porphyria, fresh urine is colorless, but on exposure to air and light for several hours it turns the color of port wine.

How did James I get porphyria from his mother, Queen Mary? The disease was transmitted through inheritance, not by contagion. Porphyria is transmitted as an autosomal dominant; that is, it is not carried on either the X or Y chromosome but on one of the other 44 chromosomes. The presence of a single copy of the defective gene has noticeable effects on the body. If one parent carries the defective gene, then, on average, half the children will bear the defective gene; this gene encodes a defective enzyme and causes porphyria. Most often the disease arises from a partial deficiency in a liver enzyme in the third step (or sometimes the seventh step) of heme synthesis. Porphyria is often more prevalent in females than in males, but in both sexes the symptoms rarely occur before puberty. These days, there are treatments for the disease symptoms, and dietary measures can reduce overproduction of porphyrins; however, in the time of Queen Mary and King James there was no such help.

The curse of the British royal family

The pedigree of porphyria can be traced back as far as Mary Queen of Scots. Her grandson Henry Frederick, Prince of Wales (the eldest son of James I), is believed to have inherited porphyria. His younger brother Charles was next in line for succession to the throne (he reigned as Charles I from 1625 to 1649); he did not have symptoms suggestive of porphyria. Charles I had a daughter named Henrietta Anne, who married a brother of Louis XIV of France and became the Duchess of Orleans. She had symptoms of porphyria and died unexpectedly at the age of 26. The eldest surviving son of Charles I, Charles II, did not appear to have porphyria. However, he had no legitimate children and was succeeded by his younger brother, James II, whose daughter Mary had married William of Orange, ruler of the Netherlands. In 1688, King William was invited to

invade England, and James II was forced to leave the country for France. In effect, Mary (the daughter of James II) and William ruled both Britain and the Netherlands. Mary appeared not to suffer from porphyria. She died of smallpox in 1694, leaving William as the sole ruler. After his death in 1702, Mary's younger sister, Anne, became Queen. Queen Anne suffered from indigestion, hysteria, fits of depression, convulsions, and muscular weakness. Indeed, this royal invalid was so weak at age 39 that she had to be carried to her own coronation. She died in a coma at the age of 49, having outlived her longest-surviving child, William Henry, Duke of Gloucester. Her death left the country without a Protestant heir in the direct line of descent. Succession to the throne then passed from the House of Stuart to the House of Hanover through descent from Elizabeth, daughter of James I (and granddaughter of Mary Queen of Scots), who had married the King of Bohemia. Although Elizabeth showed no signs of porphyria, she must have transmitted the defective gene to her daughter Sophia, who married the Elector of Hanover, Ernst August, the father of King George I of Britain. Both George I and George II were healthy, but the grandson of George II, George III, manifested many symptoms of porphyria.

In his play "The Madness of George III," Alan Bennett gives the King a voice:

> "Why do you shiver? I am not cold. I am warm. I am burning. No, I am not burning. It is my body that is burning. And I am locked inside it . . . Well give me my shirt then. What shirt is this? No. It's rough. Feel. It's like calico. Sailcloth. It's a hairshirt . . . These are not my proper stockings. They itch, too. I burn all inward. My limbs are laced with fire. But I will not give into it . . . Oh God, my blood is full of cramps, lobsters crack my bones, there are stones in my belly." Then the King's two servants remark, "Look. What? It's blue. I'd call it purple. You and me, we piss plain. Kings piss purple . . . It has been blue since His Majesty has been ill." The King continues: "Peace of mind! I have no peace of mind. I have had no peace of mind since we lost America . . . All ours. Mine. Gone. A paradise lost. The trumpet of sedition has sounded. We have lost America. Soon we shall lose India, the Indies, Ireland even, our feathers plucked one by one, this island reduced to itself alone, a great state moldered into rottenness and decay. And they will lay it at my door . . . I am not going out of my mind; my mind is going out of me . . . I don't know. I don't know. Madness isn't such a torment. Madness is not half blind. Madmen can stand. They skip. They dance. And I talk. I talk. I hear the words so I have to speak them. I have to empty my head of words. Something has happened. Something is not right. Oh . . . God, please restore me to my senses, or let me die directly for Thy Mercy's sake."

King George III was stubborn and unpredictable in his behavior. Although he did have an attack of ill health in 1765, at age 26, there is no indication that this was accompanied by a fit of madness, and it is not certain whether this disease was porphyria or some other malady. Thus, the American War of Independence in 1775 was precipitated not so much by the King's porphyria as by his inflexible attitude and because he backed the policies of his Prime Minister, Lord North, in the passage of the unpopular Stamp Tax in 1765. "The king's bad judgment may have prevented an amicable settlement, but his faults were shared by his ministers, the majority of the House of Commons and a large proportion of the British public."

Although the loss of the American colonies in the War of Independence between 1775 and 1781 appears not to be attributable to the "royal malady," the same cannot be said for the hostile relations between the Irish and the English. During this period, Protestant settlers and native Catholics lived amicably in Ireland, but in 1798 the Catholics, who were not allowed to sit in the Dublin Parliament, began to revolt, encouraged by France. The uprising was suppressed, and William Pitt, the Prime Minister, suggested that the Dublin Parliament abolish itself and declare union with Britain, with the understanding that Catholics would be eligible to sit in Parliament. In short, Pitt had committed himself (and Britain) to Catholic emancipation. However, Pitt did not inform George III, who regarded himself as "Defender of the Protestants." The King objected to Catholic emancipation, and Pitt resigned. Ten days later, George III suffered an acute attack of what was almost certainly porphyria, and when he recovered a month later, he called back Pitt, who gave the King his solemn promise that Catholic emancipation would never again be mentioned during George's lifetime. This shelved the subject for 28 years, and the Pitt pacification plan for Ireland was doomed to failure. In consequence, the Irish Catholic union with Britain resulted in domination by the alien and oppressive Protestants. Two hundred fifty years later, the troubles in Ireland, due in part to King George's "madness," continue.

King George is thought by many to have had eight porphyric attacks between 1762, when he was 24, and 1804, when he was 66, although it has been argued that his episodes of ill health prior to 1788 did not include symptoms consistent with porphyria. In 1810 he again suffered an attack and lapsed into madness for 2 years; his son, the Prince of Wales, became Regent under the Regency Act of 1811. Because there were hopes that King George might recover, the Prince Regent did not replace his ministers;

however, the King never rebounded sufficiently to resume the throne, and he died blind and deaf at age 81.

In 1968, Ida Macalpine and Richard Hunter, a mother-and-son team of psychiatrists, carefully reviewed the clinical features shown by George III and theorized that his behavioral aberrations were not due to his being "mad" (or, in the modern sense, a manic-depressive psychotic); instead, they concluded that the King's symptoms were consistent with porphyria, a metabolic disorder that caused gastrointestinal symptoms, dermatitis, and dementia. He was, according to Macalpine and Hunter, a simple victim of his "bad," not his "mad," genes. But why the severity and late onset of the attacks of lameness, abdominal and limb pain, racing pulse, insomnia, temporary mental disturbance, and discolored urine? It has been suggested, based on a recent (2005) chemical analysis of a hair obtained from George III, that this was the result of continual exposure to arsenic and/or antimony in the medicine (emetic tartar) commonly prescribed in the 18th century to reduce fever.

George IV, son of George III, also had symptoms consistent with porphyria. While Prince of Wales, he married his cousin Caroline of Brunswick, who was also very probably porphyric. Their only child, Princess Charlotte, also very probably suffered from porphyria. She died in childbirth at the age of 21, possibly partly as a result of this condition. When George IV died, he was succeeded by his brother William Duke of Clarence, who ruled as William IV. Since William had no legitimate children, his heir was his younger brother Edward Duke of Kent, who was most probably porphyric. Edward predeceased the King, and his daughter, Princess Victoria of Kent, became heir. She succeeded her uncle in 1837. Queen Victoria was not porphyric, but she had another hereditary disease, which is discussed later in this chapter. Subsequent British monarchs have shown no signs of porphyria, although in 1968 two living female descendants of the House of Hanover were reported to be porphyric. Thus, although the present House of Windsor appears to be free of porphyria, the disease has persisted in the House of Hanover into the 21st century.

The medical treatment of George III included methods popularly employed to handle the insane: straitjackets, coercion, cupping, and bleeding. However, it is now clear that the "mad King" was misdiagnosed. The illness from which George III presumably suffered, porphyria, and its attendant consequences such as melancholia, depression, sweats, and fits of mania led to the establishment of psychiatry (at that time called the "mad business") as a branch of medicine. The hereditary "madness" due

to porphyria has afflicted the British monarchy and the House of Hanover and affected world history for over 500 years!

Hemophilia

Blood will tell

Queen Victoria (born in 1819), who reigned as Queen of the United Kingdom from 1837 to 1901, was in part responsible for bringing the Bolshevik Party into power, contributed to the demise of the House of Romanov, influenced the rise of Generalissimo Franco in Spain, and even arguably played an unwitting role in the ascendancy of the Third Reich in Germany. She did this not through her politics or her armies but through her genes, for she sowed the seeds of a debilitating and potentially fatal disease among the crowned heads of Europe by marrying off her daughters and granddaughters to them, with devastating effects on some of the royal houses concerned.

The disease that Queen Victoria passed on to her offspring was hemophilia or "bleeders' disease." Hemophilia (literally "love of blood") involves a failure of the blood to clot within a normal time. The defect is caused by a missing protein in the plasma, the liquid part of the blood, which is necessary for clot formation. Normal blood may take 5 to 15 min to clot, but in persons with hemophilia (hemophiliacs) the process may take hours or even days. The danger for a person with hemophilia is that even a small wound or bruise may lead to severe and uncontrolled internal bleeding and death.

Without clot formation, the blood flows freely from a wound until the circulatory system collapses—the afflicted person hemorrhages to death. Blood clotting is a complex affair involving a cascade of protein-protein interactions that converts a soluble protein of blood plasma, fibrinogen, into insoluble protein fibers of fibrin. The clotting cascade is like the Mother Goose rhyme "This is the house that Jack built": This is the cat, that killed the rat, that ate the malt, that lay in the house that Jack built. In the clotting cascade: This is the break in the skin, so factor VIII can begin, converting prothrombin to thrombin; when thrombin converts fibrinogen to fibrin, the cross-linked result produces clottin'.

Eighty-five percent of all persons with hemophilia lack factor VIII, one of the clotting factors; the remainder lack factor V. In the absence of such factors, the individual may suffer internal hemorrhages after a minor bump or may die at an early age due to a bleeding crisis. It is possible to

diagnose hemophilia as early as the eighth week of pregnancy by DNA hybridization techniques, but in the time of Queen Victoria no such test was available. In recent years, hemophiliacs could be treated with intravenous transfusions of a concentrated form of factor VIII that had been prepared from normal plasma. This form of treatment dramatically lengthened the life expectancy of hemophiliacs from about 20 years to more than 60. However, this therapy was unavailable before 1960, and even when it did become possible to correct hemophilia with transfusion of factor VIII, the dangers of the recipient becoming infected with human immunodeficiency virus and hepatitis virus from such preparations were great indeed. This complication of virus-contaminated preparations has been avoided since 1986, when the gene for factor VIII was cloned, making it possible to synthesize large quantities of "pure" factor VIII in virus-free tissue culture cells.

What is the cause of defective factor VIII? It can be the result of mutations (a change in a single nucleic acid base in the DNA) that produce a shortened version of factor VIII, leading to severe hemophilia, or there can be a complete absence of factor VIII, also leading to severe hemophilia. However, if the mutation results in the insertion of a "wrong" amino acid in factor VIII, the resulting hemophilia is mild.

"Catching" hemophilia

How did Queen Victoria transmit hemophilia to some of her children and grandchildren? Indeed, how did she herself come to be a carrier? Our gender is determined at the moment of fertilization. Each of our somatic (body) cells contains within its nucleus 44 autosomes and one pair of sex chromosomes. During the formation of sperm and eggs, two kinds of sperm are possible (one with an X and one with a Y chromosome) but only one kind of egg occurs (with an X chromosome). Determination of the gender of an offspring depends on the sex chromosome of the fertilizing sperm. If the fertilizing sperm carries an X chromosome, the offspring will be female, and if the fertilizing sperm carries a Y chromosome, the offspring will be male. Genes that are carried on either the X or Y chromosome are called sex-linked genes. The defective gene for hemophilia is carried only on the X chromosome. Since males have only one X chromosome, they have symptomatic hemophilia if they carry the defective form of the gene for factor VIII. However, females, having two X chromosomes, would have to have a double dose of the defective gene to show signs of hemophilia. This is unlikely since the chance of a person having both a hemophiliac

father and a carrier mother is quite remote, and females who are hemophiliac die before maturity because the onset of menstruation is fatal.

Hemophiliac fathers pass on the recessive gene to all their daughters but not to any of their sons, because the son receives a Y chromosome, not an X chromosome, from the father. Carrier mothers, i.e., those who carry one normal and one defective gene, have a 50% chance of passing the defective gene to their offspring; affected sons are hemophiliacs, and affected daughters are carriers.

Since there is no record of hemophilia in Queen Victoria's ancestors, it is presumed that either she developed a mutation in the gene for factor VIII in her embryonic cells or a mutation occurred in the X chromosome of one of her parents' germ cells. An alternative possibility, although one for which no real evidence exists, is that she was the illegitimate daughter of a hemophiliac father. Queen Victoria had nine children by her husband, Albert, Prince of Saxe-Coburg and Gotha. Princess Alice (1843 to 1878), Victoria's third child and second daughter, married Prince Louis of Hesse at an early age and had seven children, one of whom, Frederick, was a hemophiliac who died at the age of 3 after falling out of a window. Princess Alice, along with her youngest daughter, May, died of diphtheria in 1878. Her sixth child, Alix, was only 6 years old when her mother died. Alix was a favorite grandchild of Queen Victoria, who hoped that Alix would marry Albert Victor (Duke of Clarence and Avondale), the Queen's grandson and the eldest son of the Prince of Wales (later Edward VII). Alix, however, did not take to the unimpressive Albert Victor, who was rather deaf and somewhat retarded. Had such a union been consummated, Alix's carrier status for hemophilia could have introduced the disease into the British royal family. Instead, she introduced the defective gene into the House of Romanov, the royal family of Russia, and thus contributed to its downfall.

Death of the House of Romanov

Alix first met the Tsarevich Nicholas when she was 12 years of age; 5 years later, they met again and fell in love; they married in 1894, 1 week after the death of Nicholas' father, Tsar Alexander III. Although hemophilia had already been recognized in Victoria's descendants (her son Prince Leopold Duke of Albany died of hemophilia, as did her grandson Frederick of Hesse), the risk was largely unappreciated and/or the value of marrying into a powerful royal house (and a potential ally) took precedence over prudence. On her marriage to the 26-year-old Tsar Nicholas II, Alix took

the name Alexandra Feodorovna. Their first four children, born between 1895 and 1901, were girls; this made Alexandra increasingly neurotic since the first duty of a Tsarina was to maintain the House of Romanov by producing a male heir. In 1904, they had a son, Alexis. Alexandra soon discovered that the Tsarevich Alexis was bleeding excessively from the umbilicus and that he had inherited hemophilia. The fragile health of her longed-for son caused her to become more and more withdrawn. She dwelt morbidly on the fact that she had transmitted the disease to her heir. Alexis' condition was kept secret from everyone except close family and their physicians because such a defect would have been regarded as a sign of divine displeasure since the Tsar was both head of the Church and leader of the Russian people. In the summer of 1907, Alexandra was introduced to a "holy man," the monk Gregorii Rasputin (who was born in Siberia in about 1860 to 1865). Rasputin's appearance and demeanor were those of a disheveled vagrant; in addition, he was debauched, alcoholic, coarse, lecherous, and a rapist. He was, however, a charismatic man and a great hypnotist. He recognized and encouraged the Tsarina's fascination for the Russian spirit and her desire to be the soul-mother of its simple people. More importantly, he was able to soothe and calm the distressed and sometimes hysterical Alexis during bouts of hemophilia and hence help stop the bleeding. Increasingly the Tsar and Tsarina came to depend on him. Indeed, in 1907 Alexis recovered from a near-death experience when Rasputin simply stood at the foot of the bed and prayed; he never once touched the child. Again, in 1912, when Alexis was 8 years old, he was bruised while playing in a bathtub and hemorrhaging began. Alexandra once again contacted Rasputin, who responded by telegram that all would be well, and almost miraculously Alexis began to recover. As a result, Rasputin enjoyed increasing personal and political influence with the Tsar and Tsarina, influence which he did not hesitate to take advantage of.

The assassination of Archduke Ferdinand and his wife Sophie in Sarajevo on 28 June 1914 by a Serbian extremist signaled the beginning of the Russian Revolution and the end of the House of Romanov. Three days before Ferdinand, heir to the throne of the Austro-Hungarian Empire, was shot dead, Alexis had slipped on a ladder on his father's yacht, sustaining an injury that resulted in excessive bleeding around the ankles. To complicate matters further, Rasputin had been stabbed in his hometown in Siberia and was unable to minister to the seriously ill Tsarevich. Regarding the international situation, Rasputin wrote from his sick bed: "Let Papa [Nicholas] not plan for war, for with war will come the end of Russia and

yourselves and you will lose to the last man." For once, Nicholas ignored Rasputin's advice and mobilized the army against Austria. As a result of the Triple Alliance between Germany, Austria, and Italy, this action meant that Tsar Nicholas of Russia was at war with his cousin-in-law Wilhelm II of Germany, who in turn was at war with his cousin King George V of Great Britain. In the first year, Russia lost 4 million men. After the Tsar took over as Commander-in-Chief in 1916, the results were even more disastrous, and Nicholas was seen as personally responsible. Nicholas' position as Commander-in-Chief took him away from St. Petersburg, and Alexandra was left to govern in his absence. While she ruled the country, Rasputin ruled her. He prevailed upon her to make several government appointments, and the positions were filled by individuals who turned out to be unfit for their duties. The turnover rate among these officials was high, adding instability to incompetence. Both Rasputin and Alexandra were hated by the Russian people, not least because of Alexandra's German origins, which led to accusations that she was a traitor. An increasingly high mortality rate among the soldiers at the front, as well as Alexandra's urging that liberal reforms be abandoned and the Tsar become more autocratic, led to even further hatred of the Tsar by the Russian people. In December 1916, in an attempt to free the Tsar and Tsarina from Rasputin's influence, Prince Youssoupov and Grand Duke Pavlovitch, the Tsar's nephew, assassinated Rasputin. They were punished by being exiled, an action that drove a wedge between Nicholas and the rest of the Romanov family.

Early in 1917, conditions in St. Petersburg deteriorated even further: food and fuel were scarce, people had to queue for hours in the bitter cold to buy bread, and revolution began to brew in the streets. Nicholas ordered, "I command that the disorders in the capital shall be stopped tomorrow as they are inadvisable at the heavy time of war with Germany and Austria." The troops were no longer on his side and did not respond; the soldiers who were garrisoned in St. Petersburg were of no help since they were already consorting with the revolutionaries. The rebellious crowds took over the city, and a provisional government was established. The provisional government attempted to maintain the Romanov dynasty as a constitutional as opposed to an autocratic monarchy by demanding that Nicholas abdicate in favor of the Tsarevich Alexis, with Grand Duke Michael (the Tsar's brother) as Regent; the Army commanders also urged Nicholas to abdicate. Because of his unpopularity and recent ill health, he eventually agreed. However, instead of abdicating in favor of his son,