

Historical Review

THE HISTORY OF HAEMOPHILIA IN THE ROYAL FAMILIES OF EUROPE

On 17 July 1998 a historic ceremony of mourning and commemoration took place in the ancestral church of the Peter and Paul Fortress in St Petersburg. President Boris Yeltsin, in a dramatic eleventh-hour change of heart, decided to represent his country when the bones of the last emperor, Tsar Nicholas II, and his family were laid to rest 80 years to the day after their assassination in Yekaterinberg (Binyon, 1998). Prince Michael of Kent expressed his sadness over the controversy surrounding the burial which he described as 'a great opportunity to heal divisions in Russian society'. He described it as 'ironic that the Orthodox Church, for so long the bedrock of the people's faith, should find it difficult to give this blessing the country had expected'. 'I have studied the results of DNA testing carried out in England and abroad and am convinced that the remains are those of the Tsar and his family' (*The Times*, 1998a). Unfortunately, politicians and the hierarchy of the Russian Orthodox Church had argued about what to do with the bones previously stored in plastic bags in a provincial city mortuary. Politics, ecclesiastical intrigue, secular ambition, and emotions had fuelled the debate. Yeltsin and the Church wanted to honour a man many consider to be a saint, but many of the older generation are opposed to the rehabilitation of a family which symbolizes the old autocracy. Yeltsin's sudden decision to attend the funeral sets him at odds with the Russian Church, which remains sceptical about the authenticity of the bones and insists that the recent DNA tests are fallible. The scientific evidence regarding the remains seems overwhelming, but the historical drama continues.

What has this got to do with haematology and haemophilia in particular? Most of us are aware that Tsar Nicholas II's son, Alexei, had haemophilia. What is not always appreciated is the impact that haemophilia has had on the Royal Houses of Europe for over 100 years. The interest has only been heightened by the unknown whereabouts of Alexei and one of his sisters. As we shall see, there is even now a possibility that the mystery may be solved.

Haemophilia and the Royal Family of Russia

Queen Victoria. Our story starts, almost inevitably, with Queen Victoria of England who had nine children by Albert, Prince of Saxe-Coburg-Gotha. Victoria was certainly an obligate carrier for haemophilia as over 20 individuals subsequently inherited the condition (Figs 1 and 2). Princess Alice (1843–78) was Victoria's third child and second daughter. Having married the Duke of Hesse at an early age,

Alice went on to have seven children, one of whom, Frederick ('Frittie') was a haemophiliac who died at the age of 3 following a fall from a window. Alexandra was the sixth child and was only 6 years old when her mother and youngest sister died. 'Sunny', as she became known, was a favourite of Queen Victoria, who as far as possible directed her upbringing from across the channel: Alexandra (Alix) was forced to eat her baked apples and rice pudding with the same regularity as her English cousins. Alix visited her older sister Elizabeth (Ella) on her marriage to Grand Duke Serge and met Tsarevich Nicholas for the first time: she was 12 and not impressed. Five years later they met again and Alix fell in love, but by now she had been confirmed in the Lutheran Church and religion became the solemn core of her life.

Victoria had other aspirations for Alix. She hoped that she would marry her grandson Albert Victor (The Duke of Clarence) and the eldest son of the Prince of Wales (later Edward VII). The Duke was an unimpressive young man who was somewhat deaf and had limited intellectual abilities. If this arrangement had proceeded then Alix's haemophilia carrier status would have been introduced into the British Royal Family and the possibility of a British monarch with haemophilia might have become a reality; however, the Duke died in 1892.

Nicholas and Alexandra. Alix and Nicholas were married in 1894 one week after the death of Nicholas's father (Alexander III). In the same way that Victoria, with her personal aspirations of a marriage between Alix and the Duke of Clarence, had not considered the possibility of haemophilia, neither did the St Petersburg hierarchy consider a marriage to Nicholas undesirable. Haemophilia was already well recognized in Victoria's descendants. Her youngest son, Leopold, had already died, as had Frittie her grandson. The inheritance of haemophilia had been known for some time since its description by John Conrad Otto (Otto, 1803). However, it was as late as 1913 before the first royal marriage was declined because of the risk of haemophilia, when the Queen of Rumania decided against an association between her son, Crown Prince Ferdinand, and Olga, the eldest daughter of Nicholas and Alexandra. The Queen of Rumania was herself a granddaughter of Queen Victoria and therefore a potential haemophilia carrier!

Alix was received into the Russian Orthodox Church, taking the name of Alexandra Fedorova. The first duty of a Tsarina was to maintain the dynasty and produce a male heir, but between 1895 and 1901 Alix produced four princesses, Olga, Tatiana, Maria and Anastasia. Failure to produce a son made Alix increasingly neurotic and she had at least one false pregnancy. However, in early 1904 she was definitely pregnant. Nicholas had provoked Japan who

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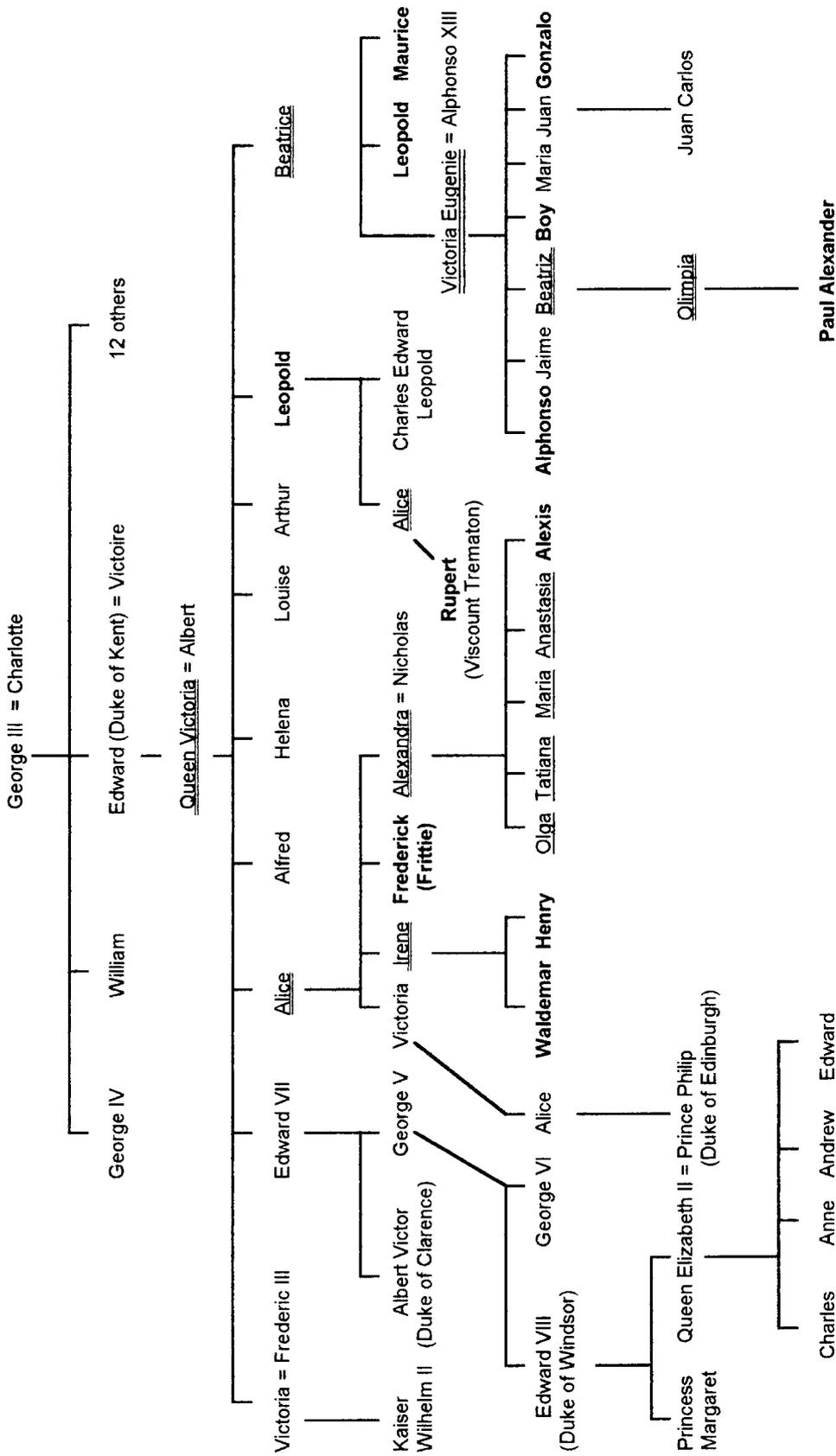


Fig 1. Haemophilia and the Royal Families of Europe. Bold, haemophilic male; double underline, carrier female; single underline, possible carrier female.



Fig 2. Queen Victoria and Prince Albert with their children (1857). Left to right: Prince Alfred, Prince Albert, Princess Helena, Prince Arthur, Princess Alice, Queen Victoria with Beatrice, Princess Victoria, Princess Louise, Prince Leopold and Prince Edward. (The Royal Archives © Her Majesty the Queen.)

promptly sank a large part of the Russian Far Eastern Naval Fleet and the Tsar ordered the Baltic Fleet to sail around the world to the North China Sea. On 12 August 1904 Alix gave birth to the long-awaited prince, but even this event was tainted by the news that the Japanese had destroyed more of the Russian Fleet and the commander had been killed in his bombarded flagship the *Tsarevich*.

For a month or so all seemed well with little Alexis, but it was then noticed that the Tsarevitch was bleeding excessively from the umbilicus (a relatively uncommon feature of haemophilia). At first the diagnosis was not admitted by the parents, but eventually the truth had to be faced although even then only by the doctors and immediate family. Alix was grief stricken: 'she hardly knew a day's happiness after she realized her boy's fate'. As a newly diagnosed haemophilia carrier she dwelt morbidly on the fact that she had transmitted the disease. These feelings are well known to

some haemophiliac mothers but the situation was different in Russia in the early twentieth century. The people regarded any defect as divine intervention. The Tsar, as head of the Church and leader of the people, must be free of any physical defect, so the Tsarevich's haemophilia was concealed. The family retreated into greater isolation and were increasingly dominated by the young heir's affliction (Fig 3).

In the summer of 1907 Nicholas and Alexandra met Anna Vyrubova, a girl of little importance but who had a particular attraction for Alix and who shared a common Faith, and in particular a faith in a holy man, the stare, the country priest who had already been an occasional visitor to the Imperial Palace for 2 years: Rasputin.

From the mass of anecdotes and conjecture that surrounds Gregorii Rasputin, one surprising probability emerges: that he was basically an honest man. His appearance and demeanour may have been akin to a



Fig 3. Empress Alexandra at the Tsarevich's bedside during a haemophiliac crisis in 1912. (Radio Times Hulton Picture Library.)

dishevelled vagrant, but the Orthodox Church had different views on sin from other Christian Churches, to the extent that the Khlysty sect (which influenced Rasputin) believed that one should sin as much as possible so that one's repentance would be the greater and one's salvation the more resounding. For all that he was a drunken, coarse, treacherous and offensive rapist. Although he did not lack native shrewdness, the indications are that he believed profoundly that the universe was a holy mystery, that life was for living, and that God was not mocked.

It is easy to understand what Alix saw in Rasputin. He met the Tsarina's fascination for the Russian spirit and her desire to be the soul-mother of its simple people. In a unique way he also offered the royal couple the only therapy for their son's bleeding episodes. Rasputin was able to soothe and calm an often distressed and sometimes hysterical child. There is little doubt that Rasputin was a source of 'complementary medicine'. He was undoubtedly a great hypnotist and the influence he exerted over the Tsarevich may have had little effect on physical bleeding but it certainly did something. The Grand Duchess Olga (his older sister) witnessed an episode when 'the poor child lay in pain, dark patches under his eyes and his little body all distorted and the leg terribly swollen. The doctors were just useless more frightened than any of us just whispering among themselves. Alicky then sent a message to Rasputin he reached the palace around midnight. The following morning I just could not believe my eyes. The little boy was not just alive but well. He was sitting up in bed, the fear gone, his eyes clear and bright, not a sign of swelling in the leg. Later I learned from Alicky that Rasputin had not even touched the child, but merely stood at the foot of the bed and prayed'. Perhaps clinical responses like this were not to be seen until the introduction of modern-day replacement therapy.

The start of the Russian Revolution. On 28 June 1914 the heir to the throne of the Austro-Hungarian Empire, Franz Ferdinand, and hismorganatic wife Sophie were shot dead in their car in Sarajevo by Gavrilo Princip, a young member of a gang called the Serbian Black Hand. Three days before the assassination the Tsarevich had slipped on a ladder on his father's yacht which resulted in a severe haemarthrosis in his ankle. To make matters worse, a few hours before the events in Sarajevo, Rasputin had been stabbed in his home village in Siberia. Rasputin sent a telegram from his sick bed: 'Let Papa not plan war, for with war will come the end of Russia and yourselves and you will lose to the last man'. Nicholas unfortunately ignored Rasputin's words and ordered partial military mobilization. His generals opted for full mobilization without telling the Tsar. Nicholas was at war with his cousin-in-law, Wilhelm II, who was at war with his cousin, George V.

In the first full year of the war Nicholas lost 4 million of his subjects. He took over the reins of Commander-in-Chief, with disastrous results. With the persuasion of Rasputin, the Tsarina increased her influence over government and a series of incompetents were placed in office. Throughout Russia Alexandra was hated only less than Rasputin. In December 1916 Prince Youssouпов and Grand Duke Pavlovitch, a nephew of the Tsar, assassinated Rasputin in a crude and

protracted fashion (Potts, 1996): he was first poisoned with cyanide, then shot twice in the chest, twice in the head, beaten with a candlestick, and finally pushed through the ice into a canal where he finally drowned. It has been postulated that Rasputin may have had achlorhydria thereby failing to produce hydrocyanic acid (which is rapidly absorbed and toxic) from the ingested cyanide (Potts, 1996).

Through the early months of 1917 the situation deteriorated in St Petersburg. Food and fuel became scarce and revolution was in the air. Nicholas responded with the demand, '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'. But the troops were no longer on his side and the capital garrison were fraternizing with the workers. Rebellious crowds had taken over the city.

The provisional government wished to maintain the Romanov dynasty but demanded that Nicholas abdicate in favour of Alexis with his brother, Grand Duke Michael, as regent. Whilst the army commanders begged the Tsar to stand down, Nicholas questioned his physician, Dr Federov, about his son's future. Federov summed up the state of haemophilia in the early twentieth century. 'Science teaches us, Sire, that this is an incurable disease. Yet those who are afflicted will sometimes reach an advanced old age. Still, Alexis Nicolaivich is at the mercy of an accident'. Nicholas decided to assign the throne to Grand Duke Michael. The love and humanity which he reserved for his family prevented him from handing on the Romanov burden to the ailing Alexis: 'You will understand a father's feelings'. The new government was prepared to accept Alexis as a constitutional monarch but feared that the Grand Duke might prove as autocratic as his elder brother. Michael realized that his situation was untenable and abdicated immediately. The Romanov dynasty, which had lasted for over 300 years, had come to an end.

The fate of the Imperial Royal Family. The provisional government approached Britain to grant asylum to the Imperial Family, but the Tsar's cousin, George V, rather than the British Prime Minister, Lloyd George, declined and the family were sent initially to Tobolsk in Siberia. The following year they were transferred to the more revolutionary city of Yekaterinberg in the Urals when the communists seized power.

The Royal Family remained confined to the Ipatiev House in Yekaterinberg until the summer of 1918. The Ipatiev House is now a car park having been demolished in 1977 by the then governor of Yekaterinberg, Boris Yeltsin. In the early hours of 17 July, Nicholas, Alexandra, their five children, their physician and three servants were executed by firing squad, a hail of bullets ricocheting off the Grand Duchesses' jewel laden corsets (Massie, 1995). The local newspaper proclaimed that Nicholas had been 'shot without bourgeois formalities but in accordance with our new democratic principles'.

Six months later a Russian investigator named Nikolai Sokolov recovered valuable pieces of physical evidence from the probable grave site, but found no skeletons. His conclusion that the bodies had been doused in sulphuric acid and burned to ashes was seldom questioned during the

next 70 years of communist rule. But in April 1989 the *Moscow News* published an exclusive interview with the filmmaker Geli Ryabov, who announced that he knew where the Romanovs were buried. Ryabov and geologist Alexander Avdonin had actually located the grave 10 years earlier, 5 miles from the Sokalov site. Working from photographs and the Kremlin report of Yakov Yurovsky, the executionist leader, they had retrieved three skulls, only to return them fearfully to the ground the following year.

Possibly as a belated gesture to appease his conscience, Boris Yeltsin authorized the exhumation at Yekaterinberg. Almost 1000 bone pieces were assembled into five female and four male skeletons. This meant that two bodies were missing, consistent with the executioner's account that he had burnt two of the bodies, those of Alexis and one of the princesses. There was, however, some disagreement as to which were the remaining bodies. Using photographic superimposition, Russian scientists concluded that the Tsarevich and the dowager Princess Marie were missing. However, an invited American forensic team, led by William Maples from the University of Florida, analysing the dental and bone specimens, believed that the missing Grand Duchess was Anastasia.

Genetics: the final answer?

At a conference during the summer of 1992 a Russian expert in DNA fingerprinting, Pavel Ivanov, announced that DNA tests on the boney remains would be conducted in collaboration with Peter Gill at the British Forensic Science Service. On 15 September 1992 Ivanov was welcomed to the U.K. and escorted (with his invaluable possessions) in a funeral hearse as it was felt 'inappropriate to carry the Russian Imperial Family in the boot of a Volvo'.

Gill carried out nuclear and mitochondrial (mt) DNA tests on the nine bone samples (Gill, 1994). Five of the bodies were clearly related, and three were those of female siblings. Furthermore, a sample of maternally inherited mtDNA suspected of belonging to Tsarina Alexandra matched a sample generously donated by her grandnephew, Philip Duke of Edinburgh. However, despite calling on the ultimate arbiter of DNA screening, the analyses left a slight doubt as to whether some of the other remains were truly those of Tsar Nicholas.

Finding a reference sample for Nicholas proved more difficult. Ivanov suggested the exhumation of the Tsar's younger brother, Grand Duke Georgij Romanov, who had died before his brother of tuberculosis. This initially proved financially and politically impossible. The Tsar's nephew, Tikhon Kulikovskiy, refused to donate a sample, citing his contempt for the British (and perhaps George V in particular) for not offering asylum for his uncle's family after the revolution. Eventually, however, two more distant relatives from the same matrilineage, Xenia Cheremeteff-Sfiri and the Duke of Fife, agreed to help.

As expected, the mtDNA sequences of the Tsar's two relatives were identical to each other, but where the relatives had a T at nucleotide 16169, the bone mtDNA of Nicholas surprisingly had a C. Further analysis revealed a chimaeric mixture of mtDNAs in the bone differing at this one position.

Gill and his colleagues therefore concluded that the Tsar exhibited 'heteroplasmy' and must have had two populations of mitochondria within his cells that contained either a C or a T at this position. Gill estimated the probability of the remains belonging to the Tsar as being 98.5% (Gill, 1994). But critics, including Maples, alleged that the discrepancy could be due to contamination (Maples, 1993). If this mitochondrial sequencing discrepancy could be resolved, then the exact nature of the bones could be confirmed.

With the Russian Orthodox Church demanding more evidence, the exhumation of Grand Duke Georgij finally took place in July 1994. On this occasion Ivanov took the bone samples to the Armed Forces Institute of Pathology DNA Identification Laboratory in Maryland. Analysis was carried out at the request of the Russian Federal Government. The results showed that the mtDNA of both Grand Duke Georgij and Tsar Nicholas had the same heteroplasmy, showing the same mixture of C and T at position 16169; the first time that heteroplasmy had been applied in human identification. Ivanov calculated a likelihood ratio for the authenticity of the remains in excess of 100 million to 1 (Ivanov *et al.*, 1996), not including other anthropological and forensic evidence.

Most of us would accept that the mtDNA sequencing data alone are compelling and would convince even the greatest sceptic that the bones have been correctly identified. However, the events of 17 July 1998 only emphasized the gap between church and science. Patriarch Alexsi II insisted that DNA tests were fallible and held a rival ceremony at a monastery outside Moscow. Nor did the Archbishop of St Petersburg attend.

What about the absentees?

Although the mystery of the last Tsar and Tsarina can be laid to rest, the whereabouts of the missing two bodies remains. As recently as October 1998 *The Times* reported that the remains of Tsarevich Alexis and one of his sisters, possibly Maria, had been found (*The Times*, 1998b). An expedition has apparently found beads of the kind given to Maria on her birthday, and bones believed to be those of her and Alexis. Further samples may also be available. In 1924 the Russian Orthodox Church received a finger and bottles of congealed fat believed to belong to the Royal Family. These holy relics are buried in a church built by Russian exiles in memory of Nicholas in Brussels in 1936. However, until the true genetic identity of these remains is established, further political and religious wrangling is likely to continue.

Prior to these very recent discoveries there have been a series of claimants to the Imperial Family which have formed the basis of a multitude of books and screenplays. A certain 'Michael Gray' has made claims that he is the grandson of Nicholas and Alexandra and that his father, Tsarevich Alexei, escaped to Western Europe, dying in England as recently as 1987 (Alderson, 1998). The most famous claimant to the title of Anastasia was Anna Anderson who was even accepted as genuine by some of the Tsar's relatives and became the subject of the longest legal case in German history, which came to no conclusion. She died in 1984 and was cremated, but 4 years previously had undergone emergency surgery for an ovarian tumour which was

successfully removed together with some gangrenous small bowel which subsequently underwent genetic analysis. DNA fingerprinting by several groups on this laparotomy material has dismissed the posthumous claims of Anna Anderson (Stoneking *et al*, 1995).

Our understanding of the genetics of haemophilia has increased dramatically over the past few years and the intron 22 inversion can be used in tracking pedigrees in up to half of families exhibiting severe haemophilia A (Jenkins *et al*, 1994). Polymorphisms in introns 13 and 22 of the factor VIII gene can be identified using blood spots stored on filter paper (Goodeve *et al*, 1996). However, nuclear DNA is much more unstable than mtDNA and liable to degradation. In the case of mitochondrial DNA, successful analysis has been performed on tissue samples on mammoths and Neanderthal Man going back over 30 000 years. For nuclear DNA, the present limit appears to be in the region of 100 years using PCR technology (W. Goodwin, personal communication). We can only speculate as to the exact genetic marker associated with the Tsarevich's haemophilia and his carrier mother and sisters (whoever might have been affected).

Haemophilia and the Spanish Royal Family

Queen Victoria had nine children over a 17-year period. The youngest, Beatrice, was born in 1857 and also proved to be a carrier for haemophilia and subsequently transmitted the gene to three of her four children. Beatrice was particularly close to her mother, staying at home when her older siblings had left and reading aloud official documents when her mother's sight was failing. Her eldest son was unaffected. Her daughter, Victoria Eugenie, was a carrier. The second son, Leopold was a haemophiliac but joined the King's Rifle Corps. He was physically delicate and lame, which prevented active service. He died in 1922 following a hip operation. The third son, Maurice, was also affected but joined the King's Royal Fusiliers and died of wounds received at the first battle of Ypres.

Victoria Eugenie's carrier status had a significant effect on the political stability of Spain in the early twentieth century. Officially Spain was a constitutional monarchy based on British principles of government. In reality the political parties were weak and governments tended to come and go with great regularity. It was the king who held the responsibility of appointing his governments.

The Spanish King's choice of bride was important. The liberal Alphonso XIII favoured a British queen. At first he contemplated marrying Princess Patricia, the daughter of Queen Victoria's seventh child, Arthur. He was not a haemophiliac and therefore Patricia was not a carrier. However, the Archbishop of Canterbury suggested that Patricia was too close in succession even though more than a score of claimants would have needed to be removed for Alphonso to take up the British throne. Undeterred, Alphonso married another grandchild of Victoria, namely Victoria Eugenie.

Alphonso must have been warned that Eugenie was a possible carrier, and she had two brothers with haemophilia. However, at the beginning of this century the royal pedigree of a princess was more important than her X chromosomes.

Edward VII favoured the arrangement as it would draw Spain towards Britain and France.

Alphonso and Eugenie. Things didn't start well for Alphonso and Eugenie. A bomb was thrown at the couple's carriage after their wedding, killing several people. Their first son, Alphonso, was a haemophiliac, having inherited it from his great grandmother. Their second son, Jaime, was a congenital deaf mute. The third son died young and may well have had haemophilia. Only the fourth son, Juan (the father of the present King Juan Carlos) was unaffected. It is not surprising that anti-British opinion in Spain was fuelled by these clinical catastrophes and there was widespread opinion that the British had defiled the royal blood of Spain by imposing a genetically defective wife on the Spanish monarchy. Under Spanish law a physically compromised son cannot succeed. The increasing list of inadequate heirs discredited the marriage between Eugenie and Alphonso and the liberal democracy which had initiated it.

It is probably untrue that haemophilia in the Spanish Royal Family led directly to the Civil War in the same way that it is equally untrue that a young Spanish soldier was sacrificed daily to provide fresh blood for the haemophiliac princes. Nevertheless, the tragedies in the Royal family undoubtedly weakened the position of the monarchy. After the Great War, strikes, assassinations, and the military disaster in Morocco led to further destabilization, and Primo de Rivera seized dictatorship power. Rivera and the King lost support in the early 1930s and the King went into voluntary exile. Revolts from the right and strikes and murders from the left resulted in the death of over one million, either in battle or executed in reprisals following Franco's rise to power.

The tragedies of the Spanish Royal Family continued after the Civil War. Alphonso, the eldest haemophiliac son, blamed his mother for his troubles and had two unsuccessful marriages outside royalty. In 1938 he was involved in an accident in a car driven by a Miami night-club singer and died of uncontrolled haemorrhage. Don Jaime, the deaf mute, died leaving two sons who could not have been affected. The fifth son, Gonzalo, was involved in a car accident while being driven by his sister Bertriz and died later of uncontrollable haemorrhage. Fortunately the healthy fourth son, Don Juan, survived and his son, Carlos, was returned as King after 30 years of dictatorship.

The life of a British Royal haemophiliac

We have already considered the lives of some imperial haemophiliacs. Alexei was heavily protected and suffered increasing isolation by his increasingly neurotic parents. Alphonso and Gonzalo broke away from family circles with the abdication of their father and had chequered lives before dying as a result of road traffic accidents.

When asked to name the most famous haemophiliac, many would nominate Tsarevich Alexis. During his lifetime his affliction was kept a close secret, which compares differently with his present notoriety. When asked whether Queen Victoria had an affected son, many would be less certain.

Leopold was born on 7 April 1853 and was the eighth child (and fourth son) of Victoria. He was the only boy to be



Fig 4. Prince Leopold with Sir William Jenner at Balmoral in 1877. (Hulton Deutsch Collection Ltd.)

affected. His birth was a landmark for other reasons. Dr John Snow (who later identified the water pump in Broad Street as the source of the London cholera outbreak) administered chloroform to Victoria in childbirth with Leopold and created a breakthrough in anaesthesia. Leopold was clinically a severe haemophiliac and suffered excessive bruising and frequent haemarthroses. He soon became a chronic invalid with an abnormal stance almost certainly due to chronic arthropathy. What is more disturbing is the way the monarch perceived her son. Victoria considered him unattractive and a poor speaker. 'He is tall, but holds himself worse than ever, and is a very common looking child, very pale in face, clever but an oddity – and not an engaging child though amusing'. Could these be the sentiments of a mother struggling with the knowledge of transmission of a debilitating disease who also became a widow when her affected son was only 8 years old? The Queen was so ashamed of the invalid that Leopold was often left behind when the rest of the family went on holiday to Balmoral. Perhaps because of his incapacity and confinement to bed for protracted periods he read widely and was undoubtedly the most intelligent and intellectual of Victoria's children.

When 15 years old the Queen bestowed the Order of the Garter on Leopold in acknowledgment of his 'valour and fortitude having faced so many privations and difficulties'. Ceremonial commemorations do not, however, make up for maternal deprivations. At the age of 17 he wrote to his sister Louise. 'I go on suffering frightfully, at this moment I am in agonies of pain; my knee gets worse daily and I get more desperate daily. If this continues long, I shall be driven to Bedlam or to Hanwell, where I shall soon be fortunately able to terminate a wretched existence by knocking out my brains (if I have any) on the walls: that is the brightest vision that I can picture to myself as a future. But I must stop on account of the *awful* pain, which is torturing me. Your wretched brother Leopold'.

At the age of 24 Leopold became one of his mother's private secretaries and had access to state papers. His oldest

brother, Edward Prince of Wales, did not achieve this until the death of his mother. His acute bleeds seemed to subside somewhat in frequency, a feature not unusual in haemophilia with increasing age (Fig 4). In 1879 Victoria refused to allow Leopold to represent her at the Centenary Exhibition in Australia because of his fragile and delicate existence. The following year he nearly became Governor-General to Canada, but was too valuable to leave British shores because of his skills as an intermediary between Victoria and her government. Leopold could not realize when he opened a new wing at the Radcliffe Infirmary in Oxford that he was close to the site of the future Churchill Hospital which would become the centre for much pioneering research into haemophilia.

In 1881 Victoria created Leopold Duke of Albany and the following year he married Princess Helena of Waldeck, sister of the Dutch Queen. On his wedding day he was somewhat incapacitated after slipping on orange peel in a French hotel and suffering a severe traumatic haemarthrosis. Leopold had two children. Princess Alice was an obligate carrier and had a haemophiliac son (Rupert, Viscount Trematon) who died in 1928 at the age of 21. Charles Edward Leopold was born posthumously, as his father had died at the age of 31 having fallen down a staircase in Cannes and died of a cerebral haemorrhage.

Charles Edward Leopold could not inherit haemophilia from his father, but he did inherit the old dukedom of Saxe-Coburg-Gotha (the same ancestry as Prince Albert) when 16 years old and rose to the rank of General in the German Imperial Army. With the collapse of Germany in 1918 he was forced to abdicate his dukedom, but later gave his support to the German National Peoples Party (DNVP) and helped bond an alliance between the DNVP and the National Socialist Party (Nazi). In 1933 Hitler was elected chancellor and the DNVP was dissolved. Charles Edward Leopold, a grandchild of Queen Victoria, became a group leader in the Brownshirts. Perhaps it would have been better if Charles Edward Leopold had been affected by haemophilia; his influence on the Third Reich might have been less.

The family allele(s)

Up to a third of haemophilic males do not have a family history of the condition. This is usually thought to be the result of a relatively high mutation rate occurring in either affected males or female carriers. None of Queen Victoria's ancestors, for many generations, showed any evidence of haemophilia. Victoria was therefore either a victim of a mutation, or the Duke of Kent was not her father. The mutation is unlikely to have been in her mother, Victoire, who had a son and daughter by her first marriage, and there is no sign of haemophilia in their numerous descendants.

Victoire was under considerable pressure to produce an heir. The year before Victoria was born, Princess Charlotte, the only close heir to the throne, had died and the Duke of Kent had somewhat reluctantly agreed to marry Victoire with the aim of producing an heir. The postulate that the Queen's gardener had a limp has not been substantiated!

The Duke of Kent had no evidence of haemophilia (he was 51 when Victoria was born) but did inherit another condition from his father (George III): porphyria. While a young man in Gibraltar he suffered bilious attacks which were recognized as being similar to his father's complaint. Had Queen Victoria carried the gene for porphyria we might expect that she would have at least as many descendants with this condition as had haemophilia. Until recently only two possible cases of porphyria have been suggested amongst Victoria's descendants: Kaiser Wilhelm's sister and niece (MacAlpine & Hunter, 1969), but they could have inherited it from their Hohenzollern ancestor, Frederick the Great. A recent television programme (*Secret History*, 1998) claims to have identified two more cases in Victoria's descendants, Princess Victoria, the Queen's eldest daughter, and Prince William of Gloucester, nephew of George V. If these two cases are correct then they would tend to confirm that Victoria was indeed the daughter of the Duke of Kent, but the apparent lack of more cases in Victoria's extended family is difficult to understand. The gene for acute intermittent porphyria has been isolated on chromosome 11. It consists of 15 exons spread over 10 kb of DNA (Sassa, 1996). There is still plenty of scope for further genetic analysis on the European Royal Families!

Conclusion

We can only speculate as to the impact on European events over the last 150 years if the marriages within the Royal houses had been different. What is evident is the dramatic effect of haemophilia on the Royal Princes and their families.

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