1 Introduction

1 History of Hemophilia

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Introduction

The word hemophilia is derived from the Greek words "*haima* – αἷμα: blood" and "*philia* – φιλος: love or tendency to". The history behind hemophilia is fascinating and complex. What is outlined here is a brief history of important events in development and discovery in this field.

History of hemophilia

Historical accounts are full of references to the disease. The first written description of hemophilia is found in the Babylonian Talmud, during the second century. In it is written "If she circumcised her first child and he died, and a second also died, she must not circumcise her third child" [1].What is fascinating is what is already understood and described from this decree. The familial nature was recognized. Rabbi Simon Ben Galaliel forbade a boy to be circumcised whose mother sisters' sons had died after circumcision. In the twelfth century the physician Moses Maimonides enforced this ruling for sons of women who had married twice, thus indicating a further understanding of the maternal inheritance of this disease [2,3].

In the United States in 1803, Otto described a family in which the males had prolonged bleeding after trauma. He noted that unaffected females pass on the disorder to a proportion of their sons, whom he described as "bleeders". In 1828 the disorder was coined "haemorrhaphilia", meaning, "love of hemorrhages" (Brinkhous *Handbook of Hemophilia*) which eventually evolved into the name hemophilia. During the nineteenth century there were continued publications describing this condition and varied family pedigrees were extensively documented.

The royal history of hemophilia is well known. Queen Victoria of England is one of the most well-known historical figures in hemophilia (Figure 1.1). She transmitted the disorder to her eighth son, Leopold, and two of her daughters were carriers. Leopold was known to have suffered from severe major bleeding episodes. He died at the age of 31 from a cerebral hemorrhage after trauma. Perhaps the most well-known descendant of Queen Victoria is Alexis, son of Tsar Nicholas II of Russia. Historically it is thought that Alexis's illness allowed for the undue influence of Rasputin. Rasputin was thought to have healing powers. Through Alexis he gained access and influence over the royal family, and this was thought to contribute in part to the eventual downfall of the empire. This fascinating history is well documented in R.K. Massie's 1968 book *Nicholas and Alexandra*.

The conclusions drawn by astute physicians and caring doctors during those early times were that (1) hemophilia caused excessive bleeding; (2) that predominantly males were affected; and (3) The disorder was passed down through females.

As one can imagine, many varied therapies were historically attempted in patients with hemophilia, from the administration of oxygen, injection of sodium citrate, to splenectomy to the use of egg white extract [4]. A more scientifically based approach was the use of coagulant snake venom by R.G. Macfarlane in the 1930s, with some success [5]. The first treatment of hemophilia occurred in 1840. Samuel Lang performed a blood transfusion to treat a hemophilia patient. It would be many years until the process of blood transfusion was developed. However by the early 1920s, it was understood that blood transfusions appeared to ameliorate bleeding by providing something that was missing in the hemophiliac patient's blood. In 1939, Kenneth Brinkhouse described something which he termed antihemophilic factor, now called factor VIII. His work was instrumental in the advancement of the understanding of hemophilia. In 1944, Edwin Cohn, a biochemist, developed a process known as fractionation, allowing

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Figure 1.1 Queen Victoria 1887. (Reproduced from http://commons .wikimedia.org/wiki/File:Queen_Victoria_1887.jpg. Accessed 4 March 2011.)

Figure 1.2 Kenneth Brinkhous. (Courtesy of UNC Chapel Hill.)

plasma to be separated into its different components. In 1952, Brinkhous developed the PTT test, which allowed for assessment of coagulation function. During this same time, it was discovered that there were two types of hemophilia. Previously it had been recognized that in certain cases the blood of two different hemophiliacs could be mixed, with correction of the clotting defect. Blood testing on Stephen Christmas, a child from Canada with hemophilia, revealed him to have a deficiency in factor IX as opposed to factor VIII. Factor IX deficiency became known as "Christmas" disease. Of great interest to note, recent investigation with novel DNA technologies have revealed the "royal disease" to be in fact, hemophilia B [6].

In 1964, Judith Graham developed cryoprecipitate. In the years that followed Kenneth Brinkhous (Figure 1.2) discovered how to purify factor VIII. Major changes in the treatment of hemophilia occurred during the 1970s. Large amounts of intermediate purity factor concentrates in lyophilized formulations became available. These concentrates were small volume, and easily injectable. This dramatically changed the face of treatment, as patients could receive treatment at home, either through self-administration or training of the caregiver. At the first sign of bleeding at home, these products could be administered, as opposed to wait for travel to a hospital. Hemophilia centers were able to focus on developing comprehensive care programs. These programs developed the concept of a team approach to care. The multi-faceted team was able to address all aspects of living with hemophilia, including the medical and psychosocial components. This was revolutionary at the time, and set the standard for the development of comprehensive care in other chronic illnesses. Orthopedic surgery became feasible in this patient population. Previously wheelchair-bound patients could have reconstructive orthopedic surgery. Great steps were made towards allowing a hemophiliac to live a fully functional life, to work, to go to school and to live.

Ongoing discovery continued in the field of hemophilia treatment. In 1977, desmopressin was discovered, which became a mainstay of treatment for patients with mild hemophilia A and von Willebrand disease, although it was not licensed for this indication until the late 1980s in the United States. In the late 1970s, production of Factor VIII by pharmaceutical companies began on a large scale. Unfortunately transmission of hepatitis B and C was a devastating consequence for many patients treated with factor concentrates produced from pooled plasma. This heralded the era of HIV transmission. AIDS was first described in two patients with hemophilia in 1982. From the late 1970s to the mid-1980s, approximately half of the hemophilia population contracted HIV through blood products. In the ensuing years, heat treating which destroyed the HIV virus, became standard for production. It would still be many years until highly active retroviral therapy would be developed. Thousands of persons with hemophilia died of AIDS in the 1980s and 1990s. Further progress continued in the development of ways to inactivate blood-borne pathogens, such as implementation of the use of solvent detergent. These improvements in viral inactivation and viral screening have dramatically improved the safety of plasma derived products. There has been no transmission of HIV or hepatitis from plasma concentrates since 1987. Transmission of prions and subsequent variant Creutzfeldt–Jakob disease has been a concern since the discovery it could occur due to blood transfusion. However there has not been a case of transmission via plasma-derived products.

In 1984, the gene for factor VIII was located and cloned from human cells. This allowed for the development and production of recombinant factor VIII and eventually factor IX as well. Recombinant factor VIII was licensed by the US Food and Drug

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Administration (FDA) in 1992. Since that time the use of recombinant factor has become the mainstay in North America and Western Europe. However in the last few years new data have challenged the trend towards use of recombinant factors. Two studies of previously untreated patients with hemophilia A suggest that the incidence of inhibitors is higher with recombinant factor VII than with plasma derived products. It is postulated that this may be due to the presence of other proteins in plasma derived products, such as von Willebrand factor. Further study is ongoing to address this important issue.

The development of inhibitors in the patient with hemophilia is a much dreaded, devastating consequence. Two bypassing agents are available for this patient population, one recombinant. Activated prothrombin complex concentrates (aPCC) have been used since the 1980s. The risk of thrombosis in association with their use is well-documented. The FDA licensed recombinant human coagulation factor VIIa (rFVIIa) on 25 March 1999, for bleeding in patients with hemophilia A or B and inhibitors to factors VIII or IX. In addition to great strides in treating bleeding patients with inhibitors, major research has occurred in the area of inhibitor eradication through immune tolerance induction. Two large international registries have documented that immune tolerance induction with large and frequent doses of factor VIII was effective in approximately 70% of patients [7,8]. More study regarding dosing and timing of factor VIII infusions are ongoing. However neither of these issues addresses the prevention of inhibitors through the maintenance of tolerance, which is the ultimate goal.

Primary prophylaxis is an ongoing area of research. Studies have demonstrated that while this method may be expensive, it is more efficacious than on demand treatment [9]. Various options currently exist for the dose and dose interval. While primary prophylaxis may be an option in wealthier countries, in many areas of the world it is financially impossible.

Conclusions

To have to now address the issues of the aging hemophiliac demonstrates the advances that have been made in the treatment of this disease [10]. The field of biologics is constantly evolving, and the goal is to continue to produce more effective and less immunogenic therapies. Strides must be made to address the need of the underserved international patient and access to care. The ultimate goal in coming years will be the cure of hemophilia through gene therapy. Promising studies in animal models continue to fuel scientific drive to apply such technology in patients. Through continued international collaboration in clinical research, through the drive and passion of physicians and patients, we hope these goals will be reached.

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