Hemophilia in Jewish Traditions and Genomes

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About the Author

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Abstract

Over the past century, the congruency between the modern description of hemophilia and a hereditary coagulation disorder described in the Talmud has been widely noted. Examination of the Talmudic text suggests that:

1. The disease described there closely resembles the modern characterization of classic hemophilia.
2. The hereditary pattern described is consistent with the distinctive inheritance pattern of chromosome-X lined recessive genetic disorders. An empirical basis for the observation of this disorder, as well as its inheritance patterns, was plausibly supplied by the Jewish practice of ritual circumcision, which facilitated a universal hematological evaluation of all males.
A corresponding pre-modern report of hemophilia from a Muslim surgeon is harmonious with this description.

The Talmudic description of hemophilia in subsequent rabbinic writings, notably the description of hemophilia as possibly paternally inherited, are coherent in light of the etiology and progression of factor XI deficiency, which is uniquely prevalent among Jewish populations and is associated with chromosome 4, an autosome. Hemorrhage following circumcision can also result from non-genetic diseases caused by spontaneous mutations arising during gametogenesis. These scenarios help to clarify the rationale behind the Talmudic requirement of multiple presentations to affirm a hereditary danger.

INTRODUCTION

“Had the advisers to the Russian Royal House, descendants of Queen Victoria, been equally well informed [as was the Talmud], the course of European modern history might have been quite different!” (Joseph 2010). This statement from The British Journal of General Practice refers to hemophilia, a bleeding disease that devastated European royalty in the nineteenth and twentieth centuries.1 Hemophilia is a blood-clotting disorder associated with gene mutations resulting in the deficiency of proteins synthesized in the liver that are essential to normal blood-clotting function. This disorder is of unique significance to Jewish traditions in a variety of ways. Many hematology and medical textbooks acknowledge that the first recorded description of hemophilia and genetically transmitted disease is found in the Talmud (Arceci et al. 2008; Emery 1968; Kelly 2012; Kumar and Weatherall 2008; Snustad and Simmons 2003; Sturgis 1955). Halakhah (Jewish law) broadly deliberates upon how the Jewish obligation to circumcise an eight-day-old male infant is affected by hemophilia. Genetically, Jewish populations possess unique hemophilia-causing mutations that provide an interesting window into their early history and literature. A survey of this pathology will provide insight into the Talmudic discussions of hemorrhagic disorder and facilitate a broader understanding of the interface between Jewish traditions and modern medicine.
BLOOD CLOTTING

When the walls of blood vessels are breached, the body uses a number of mechanisms to restore hemostasis. Upon blood vessel rupture, smooth muscle cells that form the vascular walls contract and reduce blood loss for a short period of time, thereby giving the body precious time to initiate more effective methods of hemostasis. Platelets, which are anucleate cell fragments derived from megakaryocytes formed in the bone marrow, plug the rupture by aggregating and adhering to the broken blood vessel. A platelet plug is temporary, as it is too weak and unsystematic to function as a permanent hemorrhagic barrier. The next stage of the clotting response involves the activation of a complex chain of enzymatic reactions known as the blood clotting cascade; these reactions involve over twenty different proteins (Carson-DeWitt 2004) and culminate in the formation of a tougher, insoluble, well-organized plug made of a thread-like protein called fibrin. This clot remains in place until the body repairs the underlying tissues (Tortora and Derrickson 2009), and is subsequently dissolved by plasmin and the blood-lysing system.

HEMOPHILIA

Hemophilia is a genetic disease characterized by the deficiency of protein crucial to blood clotting. There are many forms of hemophilia, each type affecting specific clotting factors. Hemophilia A results from mutations of a gene associated with producing factor VIII, a protein of the blood clotting cascade. Hemophilia B is associated with mutations of a gene associated with factor IX. Hemophilia A and B result from over a thousand different mutations, including insertions, deletions, and missense and nonsense mutations, and their severities vary greatly among these mutations (Kaushansky and Williams 2010). Hemophilia A and B are the most prevalent forms of hemophilia, representing 80 and 20 percent of hemophilia cases, respectively (Knobe and Berntorp 2011). There are also many acquired coagulation disorders, which are more frequent and complex than genetic variation (Handin 1998). Hemophilia is diagnosed by examining familial history or, in
modern times, through laboratory plasma evaluation of the levels of clotting factors vii, ix, and xi.

SEX-LINKED RECESSIVE GENES

Hemophilia A and B are genetic diseases that have a unique inheritance pattern due to their localization on the X chromosome. Whereas all female ova contain one X chromosome, a male produces both X-carrying sperm and Y-carrying sperm, in equal numbers (Figure 1).

A son who inherited an X chromosome with a defective gene necessary for blood clotting will suffer from hemophilia. However, a daughter who inherited only one defective X chromosome still has a corresponding, normally functioning X chromosome and will be either asymptomatic or slightly symptomatic (BABUL-HIRJI et al. 2007). Because of a shorter expected lifespan for a fully hemophilic male, especially in pre-modern times, the disease is typically transmitted through an asymptomatic female carrier.

THE TALMUD AND HEMOPHILIA

A Talmudic passage regarding the laws of ħazakah (recurring events that establish the presumption of future occurrence) seems to describe hemophilia and its unique inheritance pattern:

...for it was taught: if she circumcised her first child and he died, and then a second one who also died, she must not circumcise her third
child; so ruled Rabbi Yehudah Ha’Nasi. Rabbi Shimon ben Gamliel said: She circumcises the third, but must not circumcise the fourth…

Come and hear: Rabbi Hiyya ben Abba said in the name of Rabbi Yohanan: Once it took place with four sisters at Sepphoris that when the first [sister] circumcised her child, he died; when the second [circumcised her child], he also died; and when the third [circumcised her child], he also died. The fourth came to Rabbi Shimon ben Gamliel, who said to her, “You must not circumcise”…regarding circumcision, one can understand [why the operation endangers some children and not others] since one family may bleed profusely while another family may bleed slightly (Talmud Yevamot 64b).

The bleeding disorder described in this passage correlates with the modern description of hemophilia, and is widely cited in textbooks and research articles as the first recorded description of hemophilia (Cahill and Colvin 1997; Franchini and Mannucci 2012; Kaushansky and Williams 2010; Ponder 2011; Rosner 1998). In addition, the maternal inheritance of the disease implicit in the Talmudic discussion is confirmed by modern genetics (Massry et al. 1997; Raabe 2008) — although some later halakhic authorities, notably the Shulhan Arukh, applied or extended this principle to paternal siblings.

The Talmudic description of hemophilia was two millennia ahead of its time, as the first modern description was recorded in 1803 (Ingram 1976). Perhaps the Talmudic scholars were in a good position to notice this disorder and its hereditary patterns empirically because the universal Jewish practice of circumcision on the eighth day after birth facilitated the prompt diagnosis of bleeding disorders. Over a few generations the maternal hereditary pattern may have been noticed if after an affected couple divorced, the disorder continued in the maternal line but not in the paternal line. Circumcision may also have been the reason for the widespread impression that classic hemophilia is more frequent among Jews — a notion lacking scientific basis (Krikler 1970). Ingram notes that another pre-modern observation of a hemophilia-like condition was made by the Muslim surgeon Abu al-Qasim Khalaf ibn al-Abbas Al-Zahrawi (936–1013), known in Western literature as Albucasis. Islam also requires universal circumcision, and this might have facilitated Albucasis’ observation of excessive bleeding among males of a village. These reports stand in stark contrast to the
Western world, where even Renaissance-era European physicians failed to catalogue hemophilia (Kerr 1963).

There is another possible origin to the description in the Talmud of hemorrhage disorders as maternally inherited. The Talmud describes the origin of embryonic development in the following manner:

The rabbis taught: There are three partners in the creation of a person: the Holy One, Blessed be He, the father, and the mother. The father supplies the white seed from which the bones, sinews, fingernails, brain matter, and white of the eyes [are formed]; the mother supplies the red from which the skin, flesh [blood], hair, and black of the eye [are formed]; and the Holy One, Blessed be He, contributes the spirit, soul, countenance, vision, audition, speech, mobility, intellect, and discernment (Talmud Niddah 31a).

This attribution of “the red from which the flesh [blood]” and therefore the plasma proteins made in the liver as maternally inherited may have been the origin of the Talmudic ruling that coagulation disorders were maternally inherited, and is cited as such by several halakhic commentators (Taz; Gra, Yoreh Deah 263). Yet, there is a significant difficulty in accepting this proposed derivation. The Talmud is comprised of two distinct subject matters: halakhah, judicial discussions and decisions, and aggadah, homiletic discourses and interpretation. The aggadic portions of the Talmud normally are not utilized in deciding halakhah (Noda B’Yehudah, Yoreh Deah 2:161). There are two reasons for this distinction. First, aggadah is not generated by the rigorous debate, deliberation, and analysis that define the halakhic process. Second, often it is unclear whether aggadah is referring to physical reality, describing metaphysical ideas, or teaching through analogy (Maharal, Be’er Ha’Golah 6). Rabbi Shlomo Zalman Auerbach, the twentieth-century authority on medical halakhah in Israel, applies this distinction to the statement in the above Talmudic citation that the woman supplies the blood. Rabbi Auerbach explains that because in this case the Talmud Sages are describing metaphysical concepts, not natural and biological properties, this statement cannot be used to decide halakhic questions (Steinberg 1994).
The Talmud rules that after two separate occurrences in which brothers hemorrhaged and died at circumcision, the third son should not be circumcised. This exemption applies only to maternally related siblings, and also to maternally related cousins. The Talmud does not consider paternal inheritance a significant factor in the transmission of coagulation disorders, and the majority of subsequent halakhic authorities, including Maimonides, Agudah, and Tor (Bah 263), rule accordingly. The Shulḥan Arukh, the Code of Jewish Law compiled by Rabbi Yosef Karo in the sixteenth century, however, rules that paternally related children also can establish a hereditary pattern of hemorrhage, even though such a genetic transmission is implicitly rejected by the Talmud. A chronology of the realities observable to these halakhic authorities in their lifetimes will illuminate the underlying reasons for their differences of opinion.

Although the overwhelming majority of hemophiliacs suffer from either hemophilia A or B, there is another form of clotting protein deficiency called factor XI deficiency (also known as hemophilia C) caused by mutations of an autosomal gene (i.e., not a gene located on the sex-determining chromosome) that encodes for factor XI. Factor XI deficiency seldom affects non-Jewish populations but is relatively common among Ashkenazi Jews, with a heterozygote frequency of 9 percent (Castaman 2008), and it is present, albeit to a lesser extent, in other Jewish populations. A common mutation associated with factor XI deficiency identified among Ashkenazi and Iraqi Jews is estimated to have occurred more than one hundred generations ago, suggesting that it emerged prior to the date traditionally ascribed to the Babylonian dispersion. This finding provides evidence for the common ancestry of these distinct Jewish populations (Goldstein et al 1999). Subsequent mutations have accounted for the increased rate of factor XI deficiency in Ashkenazi Jews (Asakai et al. 1991).

Interestingly, in contrast to hemophilia A and B, which are associated with mutations on the X chromosome, factor XI deficiency is linked to gene mutations on chromosome 4, an autosome. Autosomal traits

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1. Editor's note: Factor XI deficiency was discovered by Dr. Nathan Rosenthal, the first hematologist in New York City.
are inherited from both sexes equally and do not follow the distinctive inheritance pattern of genes on the X chromosome. Thus, it seems difficult to understand why the Talmud described hemophilia as inherited from the mother only when, according to Goldstein’s research, the mutation causing factor XI deficiency had already occurred while the Talmud was being compiled. This is especially challenging considering the high incidence of factor XI deficiency among Jewish populations. For example, the rate for homozygotic factor XI in Israel is one in 190, making it one of the most common genetic disorders among that population (Asakai et al. 1991). There are no statistics to show the prevalence of factor XI deficiency among Talmudic-era populations, yet the fact that one of the most prevalent mutations associated with factor XI deficiency among Jews likely occurred prior to the Babylonian exile (Goldstein et al. 1999) suggests that factor XI deficiency was already present many centuries before the final editing of the Talmud. This suggests that, although not recorded in the Talmud, the non-maternal hereditary pattern of factor XI deficiency could have been observed by Talmudic era decisors.

There are many enigmas regarding the etiology and treatment of factor XI deficiency. One mystery is that some patients will suffer mild post-traumatic hemorrhage, while others will not, and these variations do not correlate with the plasma level of factor XI (Bolton-Maggs 2009). Many patients with factor XI deficiency only suffer severe bleeding following surgery or trauma involving mucosal surfaces due to local fibrinolytic activity involving tissue plasminogen activator in saliva (Asakai et al. 1991). Surgical complications to anatomical areas not characterized by high fibrinolytic activity, such as with circumcision, are rare, with a bleeding rate of 6.5 percent (Castaman 2008), although severe bleeding can occur following circumcision of severely deficient infants (Bolton-Maggs 2008). This low rate of incidence may have been unperceived by the Talmud Sages, or it may have been recognized as an anomaly, causing the Sages to disregard biparental inheritance of genetic coagulation disorders as a significant halakhic factor. The subsequent recognition of such patterns of inheritance, or the subsequent amplification of factor XI deficiency among the Jewish population due to additional mutations, as documented by Goldstein and colleagues in 1999, may have prompted the Shulḥan Ārukh to suspend circumcision.
for paternal relatives of chronic hemorrhagic families. Although hemorrhagic death from factor xi deficiency is uncommon, halakhah is extra-vigilant in protecting life, as Rabbi Moses Isserles confirms in regards to the ruling in the *Shulḥan Ārukh*: “In matters of life and death, we are lenient” (*Yoreh Deḥ* 263). It should be noted that this ruling in the *Shulḥan Ārukh* is derived from the late thirteenth-century Rabbeinu Manoḥa, one of the Rishonim who lived in Provence, France. This may be significant in identifying the original Jewish population among whom this ruling originated, and in ascertaining the existence of additional mutations causing factor xi deficiency among this population.

**HEMOPHILIA, CIRCUMCISION, AND TWINS**

When the Talmud ruled that if two siblings died of circumcision, the third should not be circumcised, the assumption was that a hereditary condition caused the circumcision to be dangerous. An interesting question was raised by the nineteenth-century adjudicator Rabbi J. S. Nathanson (*Sho’el U’Meishiv* 1:238): What is the status of a family in which a set of twins died following circumcision — are these deaths considered as two distinct occurrences, thus prohibiting the circumcision of a later son, or are they considered as a single unit? Without differentiating between monozygotic and dizygotic twins, Rabbi Nathanson ruled that the death of twins established a pattern of hereditary disease (*Rosner* 1998). A reevaluation of this question in light of current medical knowledge will help illuminate aspects of the underlying rationale of this ruling.

If one child died of blood loss following circumcision, a genetic disorder cannot, as yet, be assumed. Perhaps the bleeding disorder was not genetic. Acquired coagulation disorders are more frequent and complex than the genetic varieties, and some of these acquired disorders affect children (*Handin* 1998). One such disorder is vitamin k deficiency bleeding (*vkdb*). A proper concentration of vitamin k can prevent life-threatening hemorrhage. While extremely rare in adults, *vkdb* is more common in neonates (*Lippi* and *Franchini* 2011). To rule out *vkdb*, a second death must occur before a hereditary disease is assumed. Thus, the death of twins, whether identical or fraternal,
following circumcision may have resulted from dietary-related \textit{vkdb}. It would follow that the deaths of the twins should be considered jointly. Lippi and Franchini note that \textit{vkdb} normally presents either from days one to seven of a neonate’s life (classic \textit{vkdb}) or after two weeks (late \textit{vkdb}). In studies involving thirty-nine cases of \textit{vkdb}, the disease never presented between days eight to ten (McNinch, Busfield, and Tripp 2007). An infant circumcised on the Biblically commanded eighth day would therefore be unlikely to be susceptible to lethality due to \textit{vkdb}.

Giving birth to a child with hemophilia does not conclusively indicate that the parents carry the defective gene in their body, or somatic cells. Rather, the defective gene may have arisen during gametogenesis in either parent. At least 30 percent of hemophilia cases are due to spontaneous \textit{de novo} mutations occurring during the processes of spermatogenesis and oogenesis in the parents (Kaushansky and Williams 2010). Such spontaneous mutations are the suspected cause of hemophilia in individuals with no family history of the disease. Because neonates with a family history of hemophilia are not circumcised, \textit{de novo} mutations may often be the cause of hemophilia presenting upon circumcision. In a case of twin hemophiliacs, the feasibility of a spontaneous mutation resulting in their disease would depend on whether they are identical or fraternal twins. If the twins are identical, they may have acquired the same mutation from the single gamete from which they originated, and a familial disease would not be conclusively shown. In the case of fraternal twins, two simultaneous mutations would have to be assumed, making it more plausible to assume common inheritance.

Although knowledge of these possibilities is based on modern medical discoveries, the absence of a hereditary pattern of disease is empirically recognizable. The Talmudic requirement of multiple presentations to establish a hereditary disorder may have been based on the observation that often coagulation disorders are not present in siblings of sufferers.

\textbf{SUMMARY}

In summary, “...we are impressed by the seeming purposefulness of many of the inspired religio-medical laws which so nicely dovetail into
our present concepts of the prophylaxis of disease” (Miller 1937) and the eventual genetic therapy of disease by allelic replacement.

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Mohel and baby after brit milah (ritual circumcision).
Photo by Avi Ohayon, courtesy of the Israel Government Press Office.

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