STUDIES IN HUMAN INHERITANCE VII HEMOPHILIA.

LAURENCE H. SNYDER,
Department of Zoology, Ohio State University.

Recently Birch (1931) has reported the use of the female sex hormone in the control of hemophilia. While we can not question the results of this treatment as recorded, its use is based on a fundamental misconception, to which attention should be directed. The author says "Taking into consideration that only males have the disease, while it is transmitted through the unaffected female, one is forced to the conclusion that if the female can transmit the disease, she must potentially have the disease. Then there must be something in the female mechanism which holds the disease in abeyance." Based on this assumption, ovarian extract and ovarian transplants were used as a means of control for hemophilia in man, with apparently good results.

It must first be pointed out that it is not in the least necessary to assume that because unaffected females can transmit the disease they must potentially have the disease. Such a conclusion is contrary to all genetic principles. Hemophilia is known to be a sex-linked character. Males show it with a definite frequency because only one of the pair of sex chromosomes in the male carries the factor, thus making a single dose of the factor *h* for hemophilia effective. In women, a single dose of the factor will be recessive to the normal dominant allelomorph on the other member of this pair of chromosomes. Unaffected males also have this normal dominant factor *H*. Of the women who transmit the disease, practically all, if not absolutely all, will be heterozygous, free from the symptoms because of the presence of the normal dominant allelomorph.

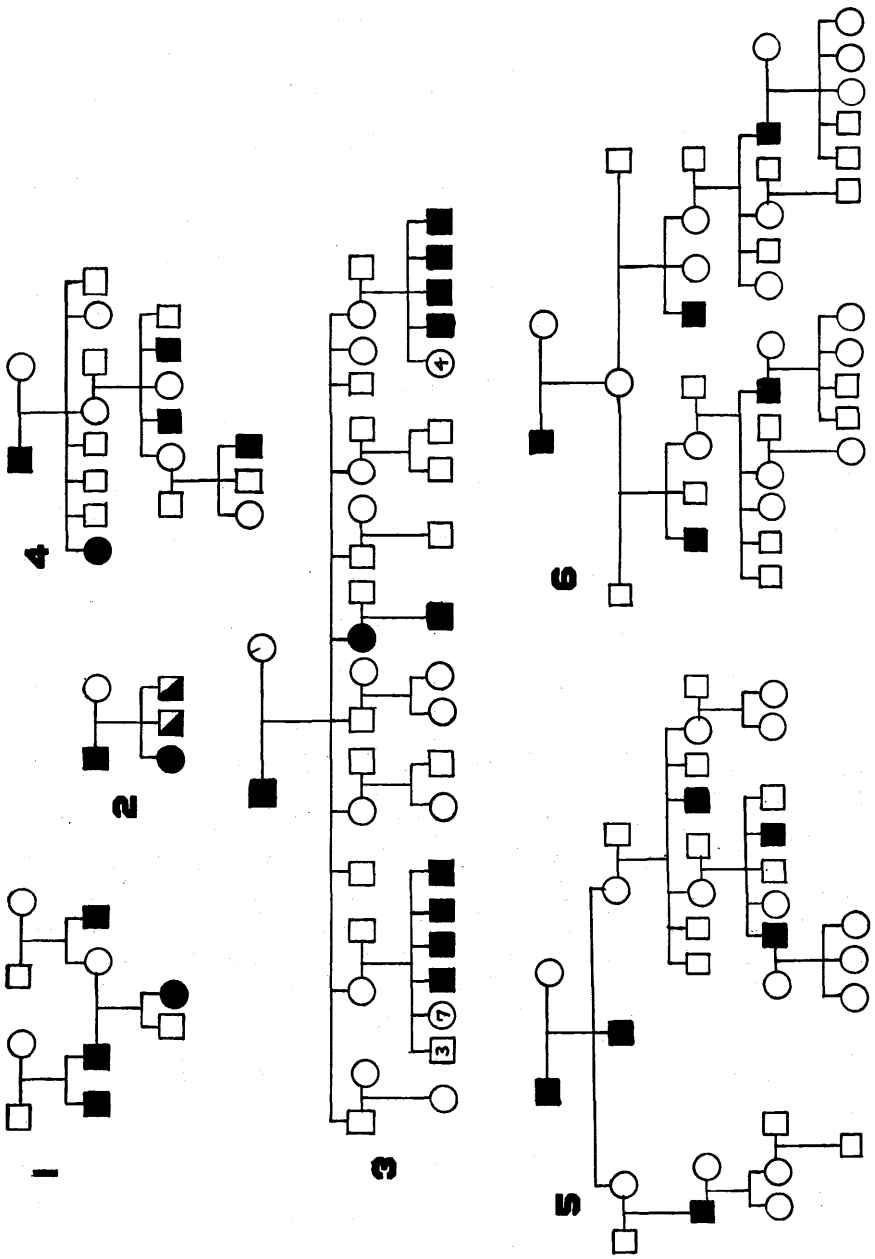
There is thus no *a priori* reason for supposing that the female sex hormone should be a specific for the control of hemophilia. It is known that injection of a foreign protein is efficacious as a control for this disease (Minot and Buckman 1927), and it would seem safer to assume that the results recorded by Birch are manifestations of a more general phenomenon, rather than to invoke a more specialized and definitely questionable hypothesis as an explanation.

The possibility exists that females receiving the double dose of the gene for hemophilia may live without manifesting symptoms of the disease. This is unlikely from a genetic standpoint, but if it were the case, Birch's hypothesis might still be tenable. This brings up again the old question as to the fate of homozygous hemophilic females. Do they exist with the symptoms of the disease? Do they exist as apparently normal individuals because of some protective mechanism? Has such a zygote ever been formed and the result recorded? Or is a double dose of the gene lethal, so that they never exist at all? Geneticists have favored the last hypothesis.

A female of the formula *hh* would only be expected to occur when a hemophilic man married a woman who was a carrier, or who was herself hemophilic. How often have matings of this sort actually occured in the pedigrees which have been recorded? In looking for such matings, it is necessary to search for instances where a hemophilic man has a hemophilic son or a hemophilic father-in-law. In such cases he might theoretically have a hemophilic daughter, since the wife would certainly be a carrier. A hemophilic brother or grandfather of the wife, even though her father were normal, would indicate that she might be a carrier.

Color-blindness, which is also a sex-linked character, presents the same requirements. To illustrate how this character can appear very occasionally in women, Fig. 1 is presented from our records.

Upon examination of 250 published pedigrees of hemophilia, the conditions under which a hemophilic woman would be expected to arise are found to be extremely rare. This is to be expected, as only 11% of hemophilic males live to be 22, and the chances of these marrying carrier females are extremely small. Only nine times in these 250 pedigrees, involving many hundreds of hemophilia males, did an alleged hemophilic man marry a known carrier. Seven of these cases are authoritatively considered by Bulloch and Fildes, who reviewed them, to be not true hemophilia at all. These are the Fischer, Weitz, Heath, Dunn III, Vanderveer, Treves and Masters families. In another instance (the Mampel family, reported in 1908 by Morawitz and Lossen), Klug (1926) has shown that several of the alleged hemophilic males did not have hemophilia, but merely said they did in order to escape military service. These included one who married a carrier. Thus this case must also


1
2
3
4
5
6
4
7
3

be left out of consideration. This leaves but a single published instance (the Hauser-Keller family, from Stahel, 1880) in which a known hemophilic male married a known carrier female. One hemophilic son and one normal daughter were produced, thus giving no evidence as to the possibility of hemophilic daughters.

In the 75 families recorded by Bulloch and Fildes as instances of true hemophilia, involving several hundred hemophilic men, there are found nineteen cases of alleged hemophilia in women. Of these, 15 had normal fathers, and therefore from a genetic standpoint could not have had hemophilia. The other four had hemophilic fathers, but each had at least one normal son, which could not happen if they were homozygous *hh* females. We can thus agree from a genetic viewpoint that these were not cases of hemophilia in women.

Three interesting recent pedigrees are on record in which hemophilic females are reported. In each of these cases the father is hemophilic, but there is no proof that the mother is a carrier, although she may very well be.

In the Nar family (Figure 2, after Davenport, 1930) a hemophilic man had a daughter who was diagnosed as hemophilic. She had a coagulation time of 15 minutes. She has two brothers, aged 2 and 4, who although too young to be definitely diagnosed, bleed very easily and for a long time after minor cuts, and are probably hemophilic, indicating that the mother is a true carrier.

Warde (1923) gives a pedigree involving a hemophilic woman. Her father was hemophilic, as was her only son. She suffered extremely from hemorrhage at the birth of her son,

---

EXPLANATION OF FIGURES

FIGURE 1. The occurrence of color-blindness, a sex-linked character, in women. The H. family, Ohio. Similar conditions would be necessary for the appearance of hemophilia in women.

FIGURE 2. The Nar family, after Davenport. The daughter, aged 8, has been diagnosed as hemophilic. The two sons are too young to be definitely diagnosed, but bleed very easily and for a long time after cuts.

FIGURE 3. Warde's pedigree involving a hemophilic woman.

FIGURE 4. The Dorr family, after Madlener, showing alleged hemophilia in a woman.

FIGURE 5. Mc C. family, Ohio, showing conditions (second generation) under which a hemophilic female might be expected to arise. This pedigree is the second one to be published in which such conditions occur. In this case both daughters were free from the disease, but carriers.

FIGURE 6. Co. family, Ohio, showing the identical transmission of hemophilia through both lines of descent from a carrier who married twice.

as well as from other operations and minor cuts. This family is shown in Figure 3.

An interesting pedigree is given by Madlener (1928). The girl involved had subcutaneous hemorrhage from an early age, and frequently bled all day from a scratch. It has been suggested by Lenz that perhaps she was an intersex. This family is shown in Figure 4.

It is of course possible that even the cases just cited are examples of purpura or some other hemorrhagic defect, and not true hemophilia. They may be due to imperfect dominance of the normal allelomorph of the hemophilia gene. Laboratory diagnoses are unfortunately all too rare in reported cases. It is of interest to note, however, that in these three cases the father was hemophilic, and in one case the son as well, thus fulfilling the genetic requirements. It is to be hoped that adequate laboratory diagnoses may be made in these cases.

There still remains the bare possibility that potentially hemophilic females (*hh*) live as normal individuals, protected by some mechanism peculiar to the female sex. Such women, if they exist, should have all hemophilic sons, no normal ones. The fact that only one published family is found where a female of the formula *hh* would be likely to arise, makes conclusive data on this point impossible to obtain. There is no logical basis, however, for supporting such a supposition.

Among our records at the genetics laboratory of the Ohio State University are several cases worthy of note. First is a case where a hemophilic male married a carrier female, as evidenced by a hemophilic son. This is apparently only the second authentic case to be recorded. The diagnosis in this family was supported by complete laboratory examination. In the second generation of this pedigree half of the daughters might be expected to have hemophilia. The two daughters occurring here were normal, however, although both were carriers. Here again is no definite evidence for or against the possibility of the realization of a hemophilic female. This family is shown in Figure 5.

Three families in Ohio have been referred to us as containing hemophilic females. Upon laboratory diagnosis, no evidence of true hemophilia was found.

Another new pedigree of hemophilia is offered here, chosen from many in our records as showing the practically identical course of heredity through both lines of descent from a known carrier who married twice. (Figure 6).

CONCLUSIONS.

Upon the examination of 250 published pedigrees of hemophilia, only one authentic instance could be found where a known hemophilic male had married a known carrier female, and where a hemophilic daughter might therefore be expected. A second pedigree involving a mating of this sort is presented in this paper. A total of three daughters, all normal, and two hemophilic sons, result from these two matings. Examination of 22 pedigrees where hemophilic women are recorded indicates that from a genetic standpoint nineteen of them could not have had hemophilia. The other three cases, more recently described, may possibly be true hemophilia. There is therefore at hand insufficient data with which to definitely settle the question as to the fate of homozygous females. There is not the slightest evidence, however, that such women can live as normal individuals because of some protective mechanism.

Women who transmit the disease are undoubtedly all heterozygous, free from the symptoms of the disease not because of any inherent protective mechanism peculiar to their sex, but because of the presence of the dominant allelomorph of the hereditary gene for hemophilia, which is also present in non-hemophilic males. There is thus no basis for Birch's assumption that women who transmit the disease must potentially have the disease. The suggestion made at the beginning of this paper is therefore offered again, that the results achieved by Birch are manifestations of the broader phenomenon that injection of a foreign protein is efficacious as a control for hemophilia. Experiments are now in progress in our laboratory in connection with the University Hospital, to test the value of this suggestion. This paper is merely to call attention to the genetic aspects of the problem.

BIBLIOGRAPHY.

Birch, C. L. 1931. Sci. 74: 16.
Bulloch, W., and **Fildes, F.** 1911. Treasury of Human Inheritance, Parts V and VI, London, Dulan & Co.
Davenport, C. B. 1930. Genetics 15: 401.
Klug, W. J. 1926. Deutsche Zeitschr. f. Chir. 199: 145.
Madlener, M. 1928. Arch. Rass. u. Gesellsch. Biol. 20: 390.
Minot, G. R. and **Buckman, T. E.** 1927. "Hemophilia," in Cecil, "Textbook of Medicine," p. 961, Phila., W. B. Saunders Co.
Morawitz, P. and **Lossen, J.** 1908. Deutsche Arch. f. klin. Med. 94: 110. (Pedigree 389 in Bulloch and Fildes.)
Stahel, H. 1880. Inaug. Diss., Zurich. (Pedigree 407 in Bulloch and Fildes.)
Warde, M. 1923. Brit. Med. J., 1923: 599.