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Hemophilia In Man: The Need for Complete Familial Data

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that the size of the yellow perch is influenced very little, if any, by the number of *Clinostomum* metacercariae parasitizing its tissues.

HEMOPHILIA IN MAN; THE NEED FOR COMPLETE FAMILIAL DATA

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Hemophilia, though not too common in this country, has been brought to our attention through its high mortality and even higher morbidity. In this disease the clotting of the blood is much delayed, although the formed elements and the chemical constituents of the blood, and the vessel wall, all appear normal. Hemophilia, as differentiated from other bleeding diseases, is probably due to an alteration in the physical structure of the plasma (Blacker, 1934, p.236). Thus, from even a slight injury, the blood keeps flowing and the individual is in danger of bleeding to death.

Hemophilia has a definitely recognized mode of transmission which differs from the inheritance of other bleeding diseases. It is apparently due to a sex-linked recessive factor; that is, it is inherited with the X-chromosome. As we know, the human female has two X-chromosomes and the male has only one. A man will therefore show a recessive sex-linked trait if he has only one gene for the trait, but a woman can show the trait only if she has two genes for the trait. Since a man receives his single X-chromosome from his mother, he will inherit the trait only through his mother. A woman will receive an X-chromosome from her father and an X-chromosome from her mother. Therefore, if the father has a sex-linked trait, his daughters will receive the gene for that trait. According to the cases of hemophilia on record, this disease is transmitted with the X-chromosome and may be carried by a female, appropriately known as a "carrier," who does not show the disease herself since it is recessive to the normal. Theoretically the female carrier passes her hemophilic X to one-half of her sons and one-half of her daughters. If a son gets the defective X from his mother, he will have hemophilia because there is no normal X to dominate the hemophilic X, due to the fact that a man has only one X-chromosome. As to the daughters, there are two possibilities. If we can assume that the father is normal, and it is usually safe to assume this not only because hemophilia is rare but because most hemophilic males die before reaching the age of 22 (Snyder, 1932), we find that (1) a daughter may receive a normal X from her mother, in which case she is not a carrier and, of course, does not show the trait; or (2) a daughter may receive the hemophilic X from her mother, with the result that she does not show the trait,

but is, like her mother, a carrier. There is also a possibility that a hemophilic male married to a carrier woman might produce a hemophilic daughter. However, such a possibility would occur extremely rarely (Snyder, 1932).

FAMILY HISTORIES

The two family histories which we are reporting present two very different pictures. One (fig. 1), collected by Dr. W. W. Canfield and sent to the Dight Institute, is rather typical in that the trait appears in some of the males of several generations; the other (fig. 2), collected through the cooperation of Dr. John Adams and D. Simon, is definitely atypical, at least at first glance. In the figures, Roman numerals represent the generations; an Arabic number placed above the person represents the number of that individual; an Arabic number below the individual represents the age at the time of the study or, if dead, the age at death.

In case K6 (fig. 1), which actually shows only a part of this extensive family but does show all members related to the hemophilics,

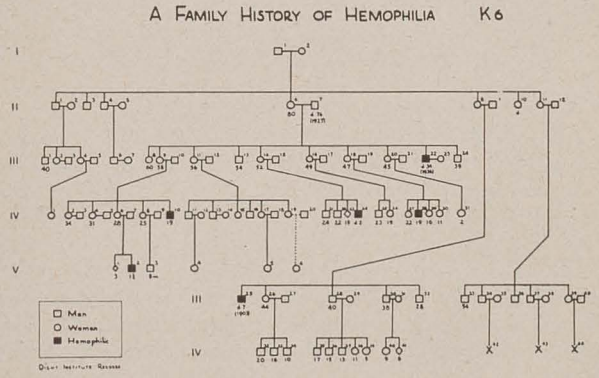

Fig. 1

we find several female carriers as evidenced by the six hemophilic sons. Known hemophilia cases occur in generations III, IV, and V, as might be expected. Here we must assume that the mothers of the hemophilic males are carriers, since none of the males showing the disease produced children, and no male can be simply a carrier. In generation II, two (Nos. 6 and 8) of the four sisters produced hemophilic sons. Each of these sisters produced a hemophilic son (Nos. 22 and 25 in generation III), one of whom died at 34 years, the other at 7 years. Thus we find that in generation III one of three sons in one family and one of four sons in the other showed the trait. Judging from the offspring, it might be said that *at least* three (No. 9,

No. 14 and No. 18) of the eight sisters in the sibship of the hemophilic males in generation III were carriers. These three female carriers each produced one hemophilic son (No. 10, No. 24 and No. 28 in generation IV), the total incidence in the affected sibships being three of nine sons. Only one sister, No. 6, of the hemophilic individuals of this generation is known to be a carrier, as may be seen by her one hemophilic son, No. 2, in generation V. In general, it might be said that this family is rather typical in that hemophilia does show up in several male relatives through sisters and aunts.

The family history K50 (fig. 2) represents quite a different picture. Here we find the hemophilia limited to one family of one generation; it does not occur in any male cousins or uncles of the

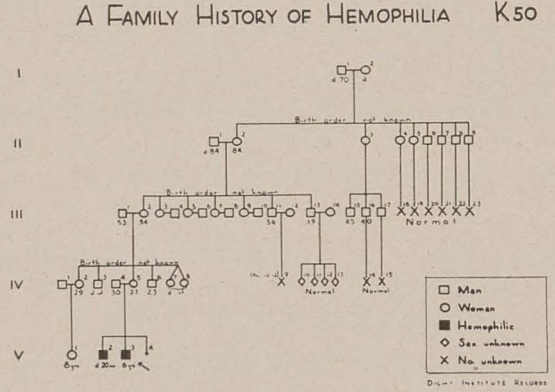

Fig. 2

affected individuals. However, it does occur in more than one of the affected sibship, so cannot be considered sporadic. A closer examination of the pedigree explains the lack of manifestation among relatives.

In generation IV, No. 5 is apparently a carrier, since her sons are hemophilic. The only other female in that generation who married is No. 2 and she produced only one daughter, No. 1 in generation V, who could not show the trait unless she received a hemophilia gene not only from her mother but also from her father, and in this case the father was not hemophilic so could not pass on a hemophilia gene.

It should be noticed that no cousins of the parents (Nos. 4 and 5 in generation IV) show hemophilia. This may be explained by the fact that of the four maternal aunts and two maternal uncles (generation III), only the uncles (Nos. 11 and 13) have children. These uncles, who do not have hemophilia themselves, cannot transmit the disease. The aunts (No. 3, No. 5, No. 7 and No. 9 in generation

III), who in this case *might* have been carriers, had no children, thus making it impossible to ascertain whether they were actually carriers or not. As to more distant relatives, no known cases of hemophilia are reported. This might be due to lack of information concerning them or to sheer chance. There is a possibility, also that a mutation occurred in a recent generation, thus not affecting the more distant relatives. Haldane (1935) estimated that mutations in this disease occur once in about 50,000 life cycles. If the disease is due, in our second history, to a mutation, it might have occurred in a gamete leading to the mother or the grandmother of the affected individuals — or even earlier.

As to the affected sibship (generation V), the mother is apparently a carrier, since it is not likely that the same mutation occurred on two occasions to produce two hemophilic sons, and each male child born to her has a 1:1 chance of showing the disease. Contrary to popular belief, the next son born to her would also have a 1:1 chance of being hemophliic. Many people erroneously believe that since two sons already show hemophilia, the chance of another son showing the disease would be less than 1:1. A daughter of this mother would have a 1:1 chance of being a carrier, but would not show the disease herself. Only through the daughter's sons could it be determined whether she carried the hemophilia gene or not.

CONCLUSIONS

Thus we see, from this second case history, the importance of obtaining as complete a family history as possible, even when a member of the family reports that the family history is negative. Although it should not be necessary to have a positive family history for the diagnosis of hemophilia, it must be recognized that a positive history might help to differentiate between hemophilia and other hemorrhagic disease. The fact that a family states that the history is negative should not prevent the genetic study of that family. In this case the negative history is easily understood: the cousins of the parents of the hemophilic sons all came from the uncles, not from the aunts who could have been carriers. Understanding the genetics of sex-linkage, we should therefore expect a negative history.

Particularly important in the study of a known or suspected sex-linked trait is accurate information on the sexes of children and relatives of the immediate family. It is also important in any genetic study that all possible factors be considered, particularly if a history appears negative. For example, mutation might be an important possibility, since there is always a first time for a trait, and mutations may occur more than once. Another factor is sheer chance. Because human families are as a rule small, we cannot expect to find "perfect" theoretical genetic ratios. Just as we can not expect the boy-girl ratio to hold true in every family, we cannot expect the hemophilia-non-hemophilia ratio to hold true in every case, even

if the mother is a carrier. These possible factors can be considered only if the data collected are complete.

SUMMARY

1. Two family histories of hemophilia are presented, one of which is typical, the other atypical.
2. The typical history shows hemophilia in some of the males of several generations.
3. The atypical history shows hemophilia limited to two male members of the same sibship.
4. The atypical distribution of hemophilic males in this second history can be explained by the fact that the maternal aunts of the mother, whom we assume to be a carrier, did not produce children; only the non-hemophilic uncles produced children, and these children would not be expected to receive a hemophilia gene.
5. The second history shows the importance of obtaining as complete data as possible in a genetic study, particularly if the history is reported as negative.

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THE RELATIVE DEGREE OF EXPRESSION OF THE GENE DWARF-2 IN MESOCOTYL AND COLEOPTILE OF MAIZE

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ABSTRACT

While the action of the gene d_2 in the homozygous recessive state in maize may be readily recognized because of the extreme dwarfing of the plants, it has not been known whether it has the same quantitative effect on the various organs of the plant. Two seedling organs were chosen as the basis for an investigation of this problem. One organ is the mesocotyl or underground stem of the seedling; the other is the coleoptile or sheathing above-ground leaf.

Maize seedlings segregating for d_2d_2 were grown at a constant temperature and humidity in the dark. Measurements were made of the length of the mesocotyls and coleoptiles at three stages of development (59, 135, and 329 hours). The normal mesocotyls averaged 5.3 times the length of the dwarf-2 mesocotyls, while the normal coleoptiles averaged 2.2 times the length of the dwarf-2 coleoptiles.