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Hemophilia and Hemophiliacs

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FEW diseases have been dramatized as much as hemophilia. It has been called the royal disease and also the "curse of the Hapsburg," although it is doubtful whether any member of that family ever had the disease. To present a true picture of hemophilia, it is necessary to divorce facts from fancy and to consider this disease as any other clinical deviation from the normal.

Hemophilia is an inherited disease characterized by defective coagulation of the blood which results in excessive and sometimes uncontrolled hemorrhage after injury. To understand the cause of the disease, it should be stated that for blood to clot at least eight separate constituents of the blood are required. The lack of any one of them results in faulty clotting. In hemophilia, the substance called thromboplastinogen is deficient. The amount of this agent even in normal blood is very small. It is probable that if one could isolate all the thromboplastinogen that is in the total volume of circulating blood, the quantity would probably not exceed in weight that of one or two tablets of aspirin. Yet, this small quantity is far in excess of the minimal requirement for normal clotting. In moderately-mild hemophilia, a small but measurable amount of thromboplastinogen is present in the blood, but this is only about one-half or one per cent of the concentration in normal blood. In severe hemophilia, only a trace of the clotting factor can be detected.

The hemophiliac is entirely normal except for his proneness to bleeding. Contrary to popular opinion, external bleeding is much less common than internal, but the former attracts more attention. Any hemophiliac who bleeds several weeks following the extraction of a tooth is sure to come to the attention of a newspaper reporter. It is the internal type which is the more dangerous and insidious. One could cite as illustrations many examples such as the following. One hemophiliac recently fell on ice and ruptured presumably a small blood vessel. In the course of a day or two, he poured about one-half of all his blood into his upper thigh. He could have bled to death, paradoxically, without spilling a drop of blood.

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The loss of blood externally is rarely as serious as the swelling produced by internal bleeding. Such a swelling may compress a nerve, thereby causing excruciating pain and sometimes even paralysis. A blood vessel may be similarly compressed and this may have serious consequences, such as blocking the circulation which sometimes terminates in gangrene and the loss of a limb. Brain hemorrhages, which usually occur after head injury, are often rapidly fatal. Abdominal bleeding may pose a serious problem especially since it may simulate an inflammatory process such as appendicitis.

The most troublesome and the most serious in its consequences are hemorrhages into joints. Few severe hemophiliacs escape them and many sustain permanent joint deformities. This crippling effect constitutes one of the most important considerations of hemophilia. Since nearly all bleeding in hemophilia is caused by injury and since the knee and the elbow are the most vulnerable to trauma, it is not surprising that these joints are most commonly involved.

Although no cure for hemophilia has been found nor probably ever will be achieved (since a disease which has its roots in the very germ plasma is not correctable by the machinations of man), it is remarkable how great the advances have been in the management of this disease. Part of this success has come about by the education of parents on how to handle the hemophilic child. By impressing the mother with the dangers of injury and stimulating her ingenuity, for instance in the use of sponge rubber, many a fall results in merely a bounce and not a bump.

It is remarkable how much has been accomplished by the simple application of cold and pressure to a fresh injury and how much more could be achieved if that gospel could be spread to reach everyone entrusted with the care of a hemophilic child. In the past, many well-intentioned mothers applied heat sometimes (unfortunately, at the advice of a physician) and thereby accentuated the hemorrhage. Many times a child may be spared a prolonged stay in the hospital by aborting a hemorrhage with these simple means.

Only one specific means is available to treat hemophilic bleeding and that is a transfusion of fresh human plasma or blood. By this means, thromboplastinogen, which normal plasma contains in relative abundance, can be elevated sufficiently in the hemophiliac to produce temporarily-sufficient normal clotting to control bleeding. The active principle, thromboplastinogen, is not stable and disappears on storage. Therefore, banked blood is of very little value, but fortunately by freezing plasma its full potency can be preserved for a longer period.

It has long been the dream to prepare the active antihemophilic principle in concentrated form and to administer it in a manner similar to that of insulin for diabetes. Unfortunately, a number of serious difficulties are encountered. The material must be given directly into the blood stream, whereas insulin is injected under the skin. Furthermore, no satisfactory source outside of human

blood has as yet been established. As long as it can only be obtained from human plasma, it is more economical to give plasma or whole blood directly rather than to attempt isolating and concentrating the active substance, thromboplastinogen. If one gives a hemophiliac a transfusion of one pint of plasma, he obtains all the thromboplastinogen it contains, whereas if one attempts to concentrate it, one must consider the cost both for the labor to produce it and the loss of material in the process. Another consideration enters the picture, namely, the diabetic needs insulin daily, whereas even a severe hemophiliac may not require a transfusion for periods of months or even years. A daily injection could, therefore, be justified only as a prophylactic measure with only partial assurance of effectiveness. It must be remembered, furthermore, that such injections may cause the development of a resistance to the active principle, which is exceedingly serious since in such a condition the patient will no longer respond to transfusions.

It seems clear that for the present the management of hemophilia should remain essentially as it is now. The local treatment of fresh injuries as stated, with recourse to transfusion when the need arises, is making it possible for most hemophiliacs to lead a surprisingly normal life.

When one studies a large number of hemophiliac families and obtains their pedigree, one is struck by the immutability of the hereditary pattern. Without going into genetic technicalities, it may be stated that hemophilia is transmitted as a sex-linked recessive trait. That means that if a hemophiliac marries a normal woman, all of his sons will be entirely normal, whereas all his daughters will inherit the defect but will not be bleeders. They are called "carriers" or conductors, for they in turn transmit the defect to half their sons and daughters. The sons will be bleeders and the daughters again will be carriers. Statistically, a carrier will have only one active bleeder to three non-bleeder children. As her offspring marry, the ratio of bleeders to normals in her descendants progressively

TABLE I

Dilution of the Hereditary Defect in Hemophilia

Generation	If the hemophiliacs					
	Do not marry			Do marry		
	Bleeders	Carriers	Normal	Bleeders	Carriers	Normal
I*	1	1	2	1	1	2
II	1	1	10	1	3	12
III	1	1	42	3	5	56
IV	1	1	171	5	11	240
V	1	1	690	11	21	992

* These figures are calculated on the theoretical supposition that every individual marries, has 4 children, and that every carrier has one bleeder son and one carrier daughter.

decreases as is shown by Table I. Such a process is called elimination of an inherited defect by dilution. This explains why hemophilia is relatively uncommon and yet often appears without any obtainable positive family history.

It is both significant and interesting that the severity of hemophilia is the same in all the affected members of any one family. The defect is quantitatively transmitted from one generation to another. If the disease is mild, it will be so in all the bleeders who have a common progenitor. So consistent is this finding that it can be designated as a law.

Any hereditary disease has social implications, and hemophilia perhaps more than any other disease demonstrates the impact of that statement. As is well-known, Queen Victoria was a hemophilic carrier. Of her nine children, two daughters were proven carriers and one son a bleeder. One granddaughter brought the disease into the Bourbon family of Spain, another granddaughter to the Romanoff family of Russia. The consequence of this is recorded in history. A people will overlook tyranny, corruption, and stupidity in a royal family, but a physical defect in the anointed is not tolerated. Curiously, the *Encyclopaedia Britannica* fails even to mention that Queen Victoria was a carrier, but it is certain that because of this inborn defect, she contributed greatly, although entirely innocently, to the downfall of two dynasties and brought about or at least hastened two revolutions that have changed the course of history.

Hemophilia spares neither royalty nor commoner and since the disease is widely spread, especially in the white race, our population has many carriers, many of whom are totally unaware of having this defect and to whom the birth of a hemophilic child is completely unexpected. Fortunately, due to the genetic dilution process already mentioned, the number of carriers has remained relatively small, particularly because few of the bleeders in the past married. Since nearly all the affected males in a primitive society die early, the disease appears to be much more rare than in more civilized people. Hemophilia in the Negro until recently was found so rarely that when a case was discovered, it was considered worthy to be reported. As medical care of infants has improved, the incidence of hemophilia has sharply increased. Interestingly, the incidence of hemophilia in Jews is apparently lower than in Gentiles, even though there is evidence that the disease was in Jewish families at the time when the Talmud was written. It seems likely that the rite of circumcision may have been responsible. The medical literature records a number of fatal bleedings following circumcision and it is certain that the number of unrecorded cases of bleeding is much larger.

Modern medicine has made it possible for the hemophiliac to live and to lead a fairly normal life. It is natural that many desire to marry and many do and have children. Since all of their daughters are carriers, the incidence of the disease is greatly increased as shown in Table I. Thus, medicine by its success in controlling hemophilic bleeding more effectively has created another social problem—the increase of hemophilia in society.