SURGERY IN HEMOPHILIA

REPORT OF FOUR CASES

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IN 1803, John Otto[1] published "An Account of an Hemorrhagic Disposition Existing in Certain Families," and, thereby, introduced hemophilia to the medical profession. We have, indeed, much earlier references to constitutional hemorrhagic tendencies which we would be justified in assuming to have been hemophilia. The most noteworthy is an account given by an Arabian author,[2] concerning a village of which the male inhabitants were liable to fatal hemorrhages from skin abrasions and other slight traumata. This report dates from the eleventh or twelfth century. Otto was, however, the first to call attention to what we now know as Nasse's law, that the disease manifests itself only in males and is transmitted by the females of the affected family as a sex-linked character. Nasse's[3] promulgation of this law did not appear until 17 years after publication of Otto's observations on the subject. What this law means is that the children of a sufferer from hemophilia will not show the disease, but his daughters and the female descendants of his children of either sex may transmit the disease to their sons. Apparently sporadic cases of hemophilia have been reported, and it is, of course, unsafe to rule out the condition because of the absence of a family history of the disease.

The exact nature of the hemophilic diathesis is still uncertain. The sole primary clinical symptom is hemorrhage. The major, if not the sole, demonstrated pathologic phenomenon is an abnormally slow coagulation of the blood. The bleeding time is generally normal. The blood cells are normal. The blood platelets are normal in number and size. The platelets show delayed clumping and disintegration; authorities are not agreed as to whether this is or is not important for the clotting time abnormality. Prothrombin and antiprothrombin, thrombin and antithrombin, blood fibrinogen and calcium in hemophilic blood have been assiduously investigated, and reinvestigated, sometimes with conflicting results. There is wide agreement that the blame for the protracted clotting does not lie in the blood fibrinogen or calcium, or in the anticoagulants present in the blood. Quantitative deficiency of prothrombin in the blood is the responsible factor in the view of Howell.[4] Addis'[5] experiments showed thrombin production to be normal in amount but delayed in time, and Mills[6] came to a similar conclusion, *i.e.*, "that the fault lay not in the amount of prothrombin or thrombin, but in the delayed activation of the latter by the former." He found the prothrombin in hemophilic blood much more resistant to activation with cephalin than that in normal blood. On the other hand, prothrombin once formed in hemophilic blood is the same both in amount and in action as that found in normal blood. Lenggenhager[7]

describes an experiment *in vitro*, which demonstrates the delayed formation of thrombin in hemophilic blood, the delay varying directly with the severity of the hemophilia; and he also found the final amount of thrombin formed to be the same in hemophilic as in normal blood.

According to Lenggenhager, this is not the solution of the hemorrhagic anomaly in hemophilia. He calls attention to the normal bleeding time, *i.e.*, the fact that the bleeding from small wounds, as from pricking of the ear lobe or finger tip, ceases as promptly in the hemophiliac as in the normal person, whereas, the bleeding from larger wounds is frequently so prolonged in the hemophiliac as to cause exsanguination. He is unwilling to accept the usual explanation, that small wounds close through the elasticity of the tissues, without the help of a blood clot. He states that the last blood to flow from a small wound always clots with great rapidity because thrombin is already present in large amounts, evidence that the bleeding is in process of being stopped by blood coagulation. Now this is the same in the hemophiliac as in the normal person. But if, after the spontaneous cessation of the bleeding, the small wound is pressed open, the bleeding which now begins does not cease promptly, but, under pressure, may continue for hours, in the case of the hemophiliac, whereas, it cannot be made to continue for longer than five to ten minutes in the normal person. In connection with this clinical experiment, Lenggenhager made the observation that, in the case of the normal person, clotting time decreased progressively with the duration of the bleeding, whereas, in the hemophiliac the contrary held: The first drops of blood to escape clotted in normal time, the later drops progressively slower; at the end of 45 minutes the blood which continued to flow from the ear lobe under the influence of pressure clotted almost as slowly as hemophilic blood from a vein. His explanation is that the thrombin first formed acts as catalyzer for the more rapid formation of more thrombin in the case of normal blood, but that this catalytic action is lacking or deficient in the case of the hemophiliac. Lenggenhager suggests that the use of the spring-lancet phlebotome, in obtaining blood for testing for coagulation time, may have been the cause of the paradoxical findings reported in the literature of almost normal coagulation time in hemophiliacs who, nevertheless, bled to death when operated upon.

I have taken for the title of my paper, "Surgery in Hemophilia," because I have four cases of serious surgical illnesses in hemophilic patients to report. I have observed a number of other hemophiliacs who had various hemorrhages into joints and muscles and from gums, kidneys and rectum. Operations should, it is admitted by all, be avoided in hemophiliacs. The lesser indications for surgical intervention are suspended and even in what we usually consider surgical emergencies, every effort is made to carry the patient safely through without resort to operation. Nevertheless, operation must sometimes be chosen as the lesser of two risks to life. In two of the four cases which I am reporting, operation was performed, and in two it was denied. In each of these groups, one patient survived and one succumbed.

CASE REPORTS

Case 1.—In August, 1921, W. R., age 19, consulted me for a tumor of the right breast, of six to eight months' standing. As given by the patient, the family history was negative; especially he gave no history of any member of the family having been a "bleeder." But the mentality of the family seemed low and I was unable to get any clear history from them after the operation. I made a diagnosis of carcinoma of the breast and proceeded to perform a radical breast amputation, removing both pectoral muscles and dissecting the axilla and closing the wound with a drain inserted through a stab wound in the side. During the operation I noticed that the bleeding was greater than usual.

About six hours after the operation, the skin flaps were markedly distended and a dirty looking, bloody fluid was oozing from the wound. I opened the wound a little so that the blood could be evacuated and gave the patient large doses of calcium lactate and several doses of horse serum. Before this medication his bleeding time was ten minutes and clotting time 16 minutes. The bleeding finally ceased and the wound healed rather slowly. The pathologic diagnosis of the specimen showed adenocarcinoma, without any metastases in the axilla.

Later this patient admitted that he had had hemorrhages before and had always had considerable trouble in stopping the bleeding whenever he cut himself or received any injury.

He continued to take calcium lactate for some time after leaving the hospital. I saw him at intervals for 10 years following the operation, and have seen him in the last month. He had been entirely normal and had had no trouble except small hemorrhages into several of the joints.

Case 2.—In January, 1931, Robert S., age 25, was admitted to the hospital, with indications of an abdominal emergency. His mother died in his childhood and an adequate family history was not obtained. He stated that he had been found to be a bleeder when he was two years old and that he had been sick all his life. He had had hemorrhages from the bladder and kidneys and bleedings into several joints. Six years before he had an attack of appendicitis, from which he recovered without operation. On the day before admission, he had an attack of abdominal pain, followed by nausea and vomiting. On examination, the abdomen was markedly tender and rigid. The urine contained red blood cells. The leukocyte count was 18,600 with 90 per cent polymorphonuclears. The bleeding time was three minutes, the coagulation time six minutes. He appeared acutely ill, and I believed there was perforation of the appendix with spreading peritonitis.

Appendicectomy was performed under a general anesthetic. A gangrenous, perforated appendix was found, with free pus in the peritoneal cavity. Particular care was taken to clamp and ligate all vessels and the patient was given 500 cc. of citrated blood by transfusion after the operation. His coagulation time was the same as before the operation.

For five days his condition remained very good. He was given quantities of dextrose solution intravenously, and a second transfusion of 500 cc. of citrated blood. He also received fibrinogen. There was no bleeding from the wound, nor was the wound swollen. On the sixth day, the patient did not look so well. He complained of abdominal pain and had considerable bleeding from the wound. The wound edges were distended. The coagulation time was now increased to ten minutes. He was nauseated and vomited. He was given a third 500 cc. of citrated blood and more dextrose solution intravenously. The wound became distended with blood clots and opened up throughout. The whole abdomen was markedly distended and rigid. The patient died on the ninth day after the operation.

The patients in Cases 3 and 4 were brothers. It was stated that the maternal grandfather may have been a hemophiliac, but the mother was not certain of this. I did not see the patient in Case 4 during his fatal illness, as he was at that time living in another city. But his physicians consulted with me and were kind enough to supply me with the data.

Case 3.—In October, 1935, M. H., age 19, was admitted to the hospital because of

abdominal pain. Since the age of eight months, he had been known to have hemophilia. He had had numerous hemorrhages into the joints and into the tissues of the neck, and at one time hemorrhage had followed suppuration of the sublingual glands. For the past few years, he had been under the care of Dr. C. A. Mills, of Cincinnati, and I had seen him many times with hemorrhages and injuries. On the night of October 26, 1935, he was seized with sudden severe abdominal pain, which localized in the right lower quadrant. He was nauseated, but did not vomit. There was much tenderness in the appendiceal region and rigidity of the right abdomen. No mass was made out. The leukocyte count was 22,300, with 90 per cent polymorphonuclears, 17 per cent nonsegmented cells. Coagulation time, Biffi Brooks, ten minutes; test tube, 18 minutes.

It was decided that the patient had a better chance for recovery without operation, and Doctor Mills' advice was sought and treatment as recommended by him was carried out. The patient was given 1 cc. theelin and fibrinogen each day, nothing by mouth, and fluids parenterally. A blood count was made every day. On November 1, 1935, the blood count was down considerably and he was given liquids by mouth. A definite mass could be palpated in the right lower abdomen, which seemed to me to be a walled-off abscess.

November 8, 1935, about 11 days after the beginning of his attack, the patient had acute abdominal pain and a short time afterwards evacuated large tarry stools. His temperature and leukocyte count came down. During the following two weeks, he continued to pass large amounts of tarry stools, and his red cells went down to 1,610,000, hemoglobin 24.2 per cent, and there was considerable reduction of the leukocyte count. Of course, he received frequent and large blood transfusions during this time.

At the end of two weeks, he improved greatly and the bleeding from his intestine ceased. He was now able to take nourishment normally and, with the aid of more blood transfusions, his hemoglobin and red blood cells had returned to normal by December 8, 1935, and his leukocyte and polymorphonuclear count was also normal. He was eating well and his bowels moved well. His abdomen was soft except in the right lower quadrant where he had a large and tender mass.

I have observed him frequently since his discharge from the hospital. His bleeding time has ranged from two to ten minutes and his clotting time from six to eight minutes. The mass in the right lower quadrant persisted for nearly a year. Now it cannot be palpated at all. Since his attack of appendicitis, he has had hemorrhages into several joints and bleeding from the kidneys; however, he has carried on his school and other work, though with some difficulty, and this year graduated from the University. At times he has been given courses of theelin and fibrinogen and kept on a high protein diet.

Case 4.—H. T. H., Jr., age 25, older brother of M. H. (Case 3), had been known all his life to be a bleeder, but had had no serious hemorrhages except small ones into several joints and from the gums.

After his graduation from the University he moved to an Eastern city. He seemed to be in perfect health when he left Lexington, but a few days after his arrival there he had an acute attack of appendicitis. He understood all about himself, as he had seen his brother go through the attack which I have described. He was taken to an excellent hospital and cared for by excellent surgeons and medical men. He was treated by blood transfusions, theelin and fibrinogen, with fluids parenterally and nothing by mouth. He was not operated upon. His appendix ruptured and the infection did not wall-off. He died of generalized peritonitis at the end of eight days.

The situation of the hemophiliac has changed greatly for the better in the last few years, and this is particularly true of the hemophilic individual who must undergo a surgical operation. To-day it is possible to prevent and to control hemophilic hemorrhages, whether spontaneous, accidental or postoperative, to a degree that was wholly impossible previously.

Of the 1,000 cases (approximate) which Carrière[8] collected from the medical literature, in 1907, 89 per cent had terminated in fatal hemorrhage

before the subjects had reached the age of 21. But, in 1929, Weil[9] felt able to assert that one no longer had the right to let hemophiliacs die of hemorrhage. The most dangerous period in the life of the hemophiliac lies between the age of one year and adolescence. If he can be brought safely to manhood, there is a chance that the hemorrhagic tendency may lessen to a considerable degree.

It is important to note that the clotting time of the blood of the hemophiliac is liable to wide variations for no known reason. These swings are equally sudden in both directions, and it would, therefore, be highly unwise to assume safety in operating upon a known or suspected hemophiliac because his clotting time at some recent period had been relatively close to normal. While on the subject of cautions, a word might be said as to the danger of mistaking the symptoms of hemophiliac hemarthrosis for rheumatism and proceeding, thereupon, to tonsillectomy or tooth extraction. Another caution worth repeating is not to let slow bleeding or oozing of blood go on for a day or two with the expectation that, being slight, it must soon stop of itself. Conrad[10] tells of a hemophilic child who was allowed to ooze blood for six days after an operation before any energetic measures were taken. The child was then too far exsanguinated to respond to blood transfusions.

There is no known curative treatment for the hemophilic diathesis, but it has proved possible, in a few reported cases, to bring about a certain inactivity and maintain this improvement by repeated treatments. Weil[9] has been able to follow, over a period of years, 20 patients treated monthly or every two months by subcutaneous injections of serum (probably horse serum), none of whom has had serious hemorrhages during this time. The injections reduce coagulation time. One of his results was particularly brilliant: A member of a notable hemophilic family, which has produced more than 200 cases of hemophilia since the beginning of the eighteenth century (the Tenna family) was given preventive serum injections regularly for seven years; ten years after the last injection he had had no return of hemorrhages and his blood coagulation time was still normal.

Ovarian extract therapy has also been used in the hope of benefiting the basic condition. Birch[11] reports favorable results in 19 cases followed for six months. The treatment must be continued indefinitely. Unfortunately, a number of other investigators report failure with the method. Ovarian implants have been used with partial success in a very few cases. Birch used a preparation of the follicular hormone, theelin, injected subcutaneously every second or third day. In two or three weeks the clotting time is reduced nearly to normal, where it can be kept by an injection twice weekly. Mills[6] points out that a field of usefulness for this form of treatment might be in the preparation of a patient for tooth extraction or minor surgical procedures.

Other measures have been recommended, particularly for the preparation of a hemophilic patient for a necessary operation, the object being to shorten the clotting time temporarily. Mills gives first place in prophylaxis to sensitization to a foreign protein. He states: "It is effective in such a large percentage of hemophiliacs that no physician handling these patients is justified

in failure to make proper use of it." The idea is to sensitize the patient by intramuscular injection of a foreign protein, preferably sheep or hen serum, after which intradermal injection of a drop of the serum to produce local reaction (the usual urticarial wheal) will be followed by a marked improvement in the coagulability of the blood. The production of a generalized systemic protein reaction must be avoided, since this might increase the hemorrhagic tendency disastrously. Mills states: "By keeping all one's hemophilic patients sensitive to some foreign protein . . . one always has at hand an immediately effective method of treating hemorrhages as they occur. And if one desires to use the method for the prevention of bleeding, one needs only to induce the skin reactions as often as is indicated by observations of blood coagulability."

Mills also recommends a high protein diet in prophylaxis and in treatment of the hemorrhages. By a regimen containing some protein at each meal and milk, eggnog, *etc.,* between meals and once during the night, the protein effect on the blood coagulability, he states, is continuous and tends to be cumulative.

Vitamins, especially B, C and D, have been used with success in some cases and failure in others, in the effort to shorten the clotting time. Havet[12] states that the mechanism of vitamin effect in hemophilia is uncertain. There may be an action on the vessel walls; one of the theories of the etiology of hemophilia includes abnormal fragility of the vessel walls. Or it may be that an improvement is effected in the metabolism of calcium in the case of vitamin D. Vitamin C is given intravenously. The vitamin complex Nateina Llopis is given by mouth. Blood transfusion is generally recognized as the surest method of preventing, as well as of checking, hemorrhage in hemophilia. Transfusion fulfills a double function: it furnishes the principal coagulants in which the blood of the hemophiliac is deficient, and it supplies blood volume to replace blood loss. Both pure blood and citrated blood are used.

The reduction of the clotting time brought about by transfusion is of brief duration—about 24 hours, according to Feissly,[13] who was the first to publish success with the method—but the effect, when it wears off, may be renewed by a repetition of the transfusion. A transfusion may be given the evening before operation. Bertrand-Fontaine and l'Hirondel[14] feel that transfusions of 200 to 300 cc., carried out one hour before surgical intervention, will almost surely prevent postoperative hemorrhage if hemostasis is possible, especially if the patient has been given from 20 to 40 cc. of serum intramuscularly on each of the two days preceding the operation.

As to the technic of operation best suited to interventions on hemophiliacs, Firor and Woodhall[15] used an electrosurgical unit for the amputation of the thumb in a case of acute hemarthrosis simulating "bone sarcoma" in the roentgenogram. Blood loss was minimal and the healing process was essentially normal. These authors feel that the value of the electrosurgical technic "can scarcely be over estimated both for major surgical procedures on these (hemophilic) patients and for the control of hemorrhage from small lacera-

tions." Blalock[16] employed piecemeal tissue ligation with catgut ties in an amputation of the arm in a hemophiliac, the ligating process including "every bit of soft tissue except the skin." A slow but steady loss of blood continued for more than two weeks following the operation, in spite of direct transfusions given approximately every third day.

The attack on the hemorrhage itself should be by both general and local measures if the site of the bleeding can be reached. The usual measures of stopping bleeding, such as ligation of bleeders and compression, will, of course, be used, but measures directed to increasing the coagulability of the blood should also be applied at once, and in conjunction, not tried out one at a time. It cannot be too strongly emphasized that a "wait and see" policy has no place in treating hemophilic bleeding.

Unless the patient was under hospital care at the time the hemorrhage started, as in the case of bleeding following operation, much time is likely to have elapsed before the physician has the opportunity to start treatment. With great truth, Mills says: "The first two days offer the greatest chance of prompt stoppage of the bleeding. Beyond this period great difficulty may be encountered and repeated blood transfusions required."

For reasons of cost and because of the fact that the patient sometimes takes the preparation for blood transfusion as a signal for alarm, Mills does not advise transfusion during the first two days of bleeding, when other forms of treatment are usually effective. But by many, transfusion is regarded as the first line of defense in any serious hemophilic bleeding. It is recognized by all as the method of choice in prolonged hemorrhages. Transfusion usually checks the bleeding rapidly, but may have to be repeated. Intramuscular serotherapy, 20 cc. of some human or animal serum, such as antidiphtheritic serum, as fresh as possible, may be expected to act in from 12 to 24 hours. Kimm and Van Allen[17] recommend intramuscular injection of extract of the whole ovary, 4 gr. every six hours until the hemorrhage is controlled. Ovarian therapy in hemophilia is based on the assumption, not yet wholly confirmed, that the female hormone is totally lacking in the blood of hemophilic males.

Mills favors, among biologic coagulants, purified tissue fibrinogen, administered orally in 3 to 5 cc. doses (of a 1.5 per cent solution) in cold water, on an empty stomach, preferably one-half hour before meals and at midnight, or injected subcutaneously in doses of 1 to 2 cc. every two hours, changing to every eight hours after four doses. In treating hemorrhage by any biologic agent, it is important to continue the treatment for at least 24 hours after bleeding has ceased. Mills offers a special caution as regards the use of transfusion in connection with tissue fibrinogen treatment: Transfusion must not be carried out within eight hours of a previous dose of fibrinogen. However, it may be administered one hour after a transfusion. In the case of a patient previously sensitized to a foreign protein, one has at hand an excellent means of checking hemorrhage in the induction of the skin reaction, as already mentioned. Adrenalin by subcutaneous injection is useful if the hemorrhage is not arterial. Witte's peptone given subcutaneously, extract of platelets, calcium chloride given intravenously, and sodium citrate administered by the

same route, all find sponsors in the literature. Injection of blood into the buttocks has been followed by good results. Lucas[18] injected 10 cc. of the mother's blood subcutaneously in a newborn infant seen with a severe hemorrhage from the intestines. The bleeding diminished markedly and was later controlled by hemoplastic serum.

Eley[19] calls attention to the hemostatic value of human placental extract. He states that experiments *in vitro* suggest some degree of specificity for human as against bovine tissue extracts. He treated 20 hemophilic patients with human placental extract at the Children's and Infants' Hospital, Boston. In 13 cases, the coagulating time of the venous blood was reduced to ten minutes, and some reduction was obtained in three other cases. In four cases, the treatment failed to influence the clotting time. He found the oral preferable to the intramuscular route, since the extract was effective in from 20 to 30 minutes when given orally and required several hours to show an effect when injected into the muscle.

For topical application, Eley[19] used a sponge soaked in sterile placental extract applied over the lesion after the edges of the wound had been brought together with adhesive tape. Bleeding ceased and a firm clot developed.

Lenggenhager reports constant success from bringing into the wound a concentrated thrombokinin (or thrombokinase), prepared by boiling for three minutes finely chopped fresh human or animal struma in three to five parts of physiologic solution, and filtering. A pledget is dipped in this solution and applied firmly to the wound for several minutes or the wound is tapped lightly with the saturated pledget several times, so that the solution is pressed into all parts of the wound. He recommends injecting this solution into the operative field along with the anesthetic solution previous to operation. To stop bleeding from the gums he injects the thrombokinin solution together with adrenalin into the bleeding area. He has seen this solution stop bleeding after tooth extraction when all other methods failed.

A compressive dressing moistened with human or animal serum and applied to the wound after proper cleansing is often effective in the prompt control of hemophilic hemorrhage.

The treatment of an infected wound in a hemophilic patient is a tedious process, the continual danger of hemorrhage making great caution necessary. The successful use of maggots in the treatment of a large infected wound, in a case of severe hemophilia, was recently reported by Pohle and Maddock.[20] Their experience seems to indicate that when active bleeding has ceased, maggots can be applied without danger of exciting fresh hemorrhage.

SUMMARY AND CONCLUSION

Four cases of serious surgical illnesses occurring in hemophilic individuals are reported. Two were treated by operation, with one recovery and one death. Two were treated without operation, likewise with one recovery and one death.

The hemophilic individual should not be subjected to operation unless refusal of operation would place him in still greater danger to life.

Safeguards should be thrown about the hemophilic patient who must

undergo a surgical operation, by having recourse to the modern biologic methods of decreasing temporarily the clotting time of the hemophilic blood, such as blood transfusion, serum therapy, ovarian therapy, intradermal injection of a drop of serum to which the patient has been sensitized, administration of tissue fibrinogen, *etc.*

While these methods may not succeed in every case, nevertheless, applied in time and in proper combination, they have frequently proved life-saving.

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