Surgery in Hemophiliacs with Special Reference to the Central Nervous System *

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THE purposes of this paper are to: (1) State the difficulties encountered in operating on hemophiliacs, especially in regard to the central nervous system. (2) Briefly review the experiences of others in dealing with this problem. (3) Present our own experiences and suggestions for improving technic in operating on the central nervous system of hemophiliacs. It is beyond the scope of this paper to discuss the complex problems of the patho-physiology and medical therapy of hemophilia.

Surgery in the hemophiliac, until recently, was still accompanied by a high mortality and morbidity despite the advent of various clotting agents, antibiotics and improved technics that have brightened the outlook for the surgical patient in general. With the exception of Weil [15] (1931), most writers have taken a pessimistic attitude and state that the outlook for hemophiliacs requiring operation is very poor.

Friedrich [6] estimated the overall mortality of hemophiliac patients undergoing major surgical procedures as 35%. The largest single group of successful operations was reported by Craddock.[5] These ranged in magnitude from the correction of squint (Lane, 1840), the first reported operation on a hemophiliac, to a mastectomy for cancer of the male breast (Frior-Woodhall, 1939).

Hemophilia is characterized by a familial tendency to hemorrhage due to specific alterations in the blood coagulation mechanism. The essential coagulation defect is a delay in the conversion of prothrombin to thrombin (Addis, Eagle, Brinkhaus [1]). More specifically, Quick [10] believes that the essential defect is in the thromboplastinogen fraction of the clotting mechanism. The cause of this abnormality is not fully understood. It is apparently not due to the action of an anticoagulant, a qualitative or quantitative defect in prothrombin, or other recognizable deficiency.[2, 10] At times the bleeding continues even when the clotting time is normal, indicating the complexity of the clotting process.

The types of bleeding most frequently encountered in patients with hemophilia are hemarthrosis, epistaxis, hematuria, and prolonged hemorrhage into or from any lacerated or contused organ or tissue.

Bleeding into and about the central nervous system is a rare complication of hemophilia. Bulloch and Fildes [3] summarized the literature up to 1912 and found only 13 cases. By 1944 there had accumulated a total of 45 cases. It was assumed that there were actually fewer cases in which all of the modern criteria for the diagnosis of hemophilia were fulfilled and in which there was anatomic proof of a neurologic lesion.[2] Aggeler and Lucia [2] (1944) at the time of their review were able to note only 32 cases of hemorrhage into or about the central nervous system, but their criteria for a diagnosis of hemophilia were more strict. Five additional cases were added in 1945 by Skold [13] from his analysis of the Scandinavian literature.

Bleeding into and about the central nervous system is the most serious complication of hemophilia. Imhoff [7] states that the mor-

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tality is 86% at the time of the first hemorrhage if no treatment is undertaken.

Because of the rarity of involvement of the central nervous system in the hemophiliac, and the paucity of the hemophiliac cases in which there has been a primary disease of the central nervous system requiring operation, the recorded instances of neurosurgical intervention for the correction of a disease process are few. Furthermore, the cases reported with neurosurgical intervention in which the outcome was satisfactory, even for a short period of time, are even more scarce.

Detailed studies of autopsied cases of hemophilia with hemorrhage into the nervous system reveal that the most common site of bleeding is into the cranial subdural space. The total reported cases up to 1945, and including our own, and including peripheral nerve involvement, was 64. Of these, 16 bled into the cranial subdural space (see Table 1). In three cases there was subdural bleeding in association with the intracerebral portion of a hemorrhage.[9] Surgical intervention in two of these last three patients resulted in death from hemorrhage. The longest survivor died 48 hours postoperatively.

On analyzing other case reports, certain characteristics seem to apply to hemorrhage into or about the nervous system in hemophiliacs.

(a) Despite the presence of many superficial vessels along the spinal axis and on the surface of the cerebrum, subarachnoid hemorrhage does not seem to be a common complication. Only three cases of hemorrhage into the intracranial meninges have been reported. Hemorrhage into the ventricular system has never been reported.

(b) Hemorrhage into the brain has only been reported supratentorially. There was no recorded instance of hemorrhage into the cerebellum. Cerebral hemorrhage has further shown a predisposition to occur in the frontal lopes of the brain. In three autopsied cases, the hematoma was "walnut" sized and had indirectly pressed on the brain stem or caused a herniation of the cerebellar tonsils by increased intracranial pressure even though they were situated in the posterior portion of the frontal lobe. There is only one recorded instance or mid-brain hemorrhage.

TABLE 1. *Reported Instances from the Literature of Bleeding into or about the Central Nervous System in Hemophiliacs*

	Number	Surgical Intervention	Recovered	Recovered Spontaneously
Cerebral subdural	16	5	3	1
Spinal subdural	3	1	1	0
Subarachnoid (cerebral & spinal)	9	0	0	4
Intracerebral	12	1	1	1
With subdural extension	3	2	1	1
Intraspinal (hematomyelia)	6	0	0	4
Midbrain	1	0	0	0
Spinal epidural	3	1	1	0
Peripheral nerves	11	0	0	11
Facial 1				
Sciatic 1				
Femoral 2				
Peroneal 3				
Median 1				
Ulnar 3				
	64	10	7	22

(c) The majority of the hemorrhages into the spinal cord have been post-traumatic though there have been a few reported "primary" episodes of bleeding. The prognosis in hematomyelia is purportedly good without any treatment, but only six cases have been documented.[7]

(d) Including our own case, there are three reported instances each, of spinal subdural, and of spinal epidural hemorrhage. Three cases of spinal subarachnoid bleeding showed spontaneous improvement after a number of months. Of all reported spinal cases in which bleeding occurred either sub- or epidurally, only two were operated on: one by Schiller [11] and one of our own (RSK).

(e) The isolated reports of hemorrhage into the peripheral nerves are chiefly of academic interest since they usually resolve spontaneously, and are included here for the sake of completeness.

Of the cases in which surgical intervention was undertaken for treatment of hemorrhage into the central nervous system, the most successful and detailed report is that of Schiller, *et al.*[11] In this case a spinal subdural hematoma occurred that produced paraplegia. The onset of the bleeding was apparently spontaneous. An extensive dorsal laminectomy and aspiration of the hematoma was undertaken. Postoperatively there were two sizeable hemorrhages from the operative site. In each instance it was treated with fibrin foam and packing. Eventually, the bleeding stopped and the patient was discharged from the hospital. His condition was markedly improved but some evidences of paraplegia remained.

The following are cases of our own in which there was bleeding into or about the central nervous system and in which surgical intervention was undertaken. Lengthy discussion of the hematologic problems encountered and the exact therapy along these lines (hematologic) is omitted since this paper deals primarily with the surgical approach. Each case, however, was a proven hemophiliac of the AGH type.

CASE PRESENTATIONS

G. S., a 12-year-old boy, had had 26 previous admissions to the hospital for episodes of bleeding (epistaxis, hemarthrosis, abrasions, lacerations). During these instances he received a total of 32 transfusions (50 to 250 ml. each). On the occasion of his bleeding into the central nervous system, the patient experienced the apparently spontaneous onset of pain in the back of his neck and paresthesias in his hands. A playmate at school had struck his back with a book 10 hours previously. Within 2 hours of the onset of pain the patient developed a paraparesis which rapidly developed into a paraplegia with a sensory level at C_{7-8}. Lumbar puncture revealed a complete "block" and myelography showed an obstruction at T_2. A laminectomy of C_6, $_7T_1$ was done and a large epidural clot was exposed and removed. A small opening was made in the dura and the cord inspected; it appeared to be normal. The bleeding was controlled with bone wax, Gelfoam® and electrocautery. The entire wound was irrigated with antihemophiliac serum globulin. Two drains were left in situ.

Postoperatively the patient had a mild paresis of both arms and a spastic paraplegia. During the course of the hospitalization the child received 78 transfusions (250 ml. each). The patient received physiotherapy and other ancillary treatment but at the time of discharge continued to manifest a spastic paraplegia, paresis of both arms and a sensory level at T_1.

The child returned six months later with bleeding from the urinary and gastro-intestinal tracts and died. No autopsy was performed. His neurologic status had remained unchanged.

E. B., a 7-year-old boy, had had 8 previous admissions for bleeding, chiefly from the nose and into the joints. Prior to his admission for central nervous system bleeding, he sustained a minimal head injury while climbing out of a high-chair. At the time of admission 8 hours later he complained of headache and had a paresis of his left leg. On the second hospital day he became very stuporous and began to have generalized convulsions. The right pupil was larger than the left and there was engorgement of the retinal veins.

A posterior frontal trephination was carried out on the right side and a brain cannula inserted into the underlying tense cerebral cortex. A hematoma was encountered and aspirated (40 ml.). A fibrinogen solution was reinjected. The child rallied temporarily but expired on the following day. Postmortem examination revealed a cerebellar pressure cone and a hematoma in the right posterior frontal region of the brain, superiorly placed, which measured 4.5×4 cm. The needle tract had passed into this area. Apparently there had been recurrent bleeding into the area of the initially aspirated hematoma.

T. B., an 11-weeks-old male infant, had an essentially normal delivery and his immediate postnatal course was uneventful. At 11 weeks he was readmitted to the hospital showing pallor, lethargy and fever. Examination revealed a tense anterior fontanelle and a left hemiparesis. A subdural tap was done. It revealed a subdural hematoma on the right side. Daily aspirations of 10 ml. each were carried out until the hematoma had been completely emptied. During this time the child received 16 transfusions of 50 ml. each. At the termination of this course of treatment the hemiparesis had completely regressed. He was

discharged with plans for possible future admission for definitive treatment.

Two months later he re-entered the hospital. There had been an apparently spontaneous episode of subdural bleeding. The anterior fontanelle was full but there was no paralysis. Two subdural taps were done but the fontanelle remained tense and the child became progressively more stuporous. The anterior fontanelle was opened and the subdural space packed with aureomycin gauze. The wound was left open. Postoperatively the pack was slowly removed. On the seventh postoperative day hemorrhage from the operative site occurred as the pack was being removed. The entire pack had to be re-inserted. Again, it was slowly removed. After two weeks only an external dressing was needed. It was hoped that this area would granulate in, but plans for skin grafting had been made before the child was discharged. During this hospitalization the child received 14 transfusions (250 ml. each).

The patient was brought back to the hospital 3 weeks later with evidences of increased intracranial pressure (papilledema, left 6th nerve paralysis). The previous operative site was filled with a cerebral herniation. There was no evidence of a hematoma beneath the anterior fontanelle. Operative repair of the previous surgical defect was undertaken and internal decompressive procedures carried out for relief of increased intracranial pressure. The child died 24 hours postoperatively.

Postmortem examination revealed 2 fresh subdural hematomas situated anteriorly to the anterior fontanelle and each measuring 3 × 4.5 cm. There was also intracerebral hemorrhage on the left side and a marked cerebellar pressure cone.

The surgical principles of operating on a hemophiliac with bleeding into the central nervous system, or with a primary disease of the central nervous system, are essentially the same as in any general surgical problem. The various antihemophiliac agents and surgical technics used in hemophiliacs are helpful, but certain factors remain basic.

Aside from exsanguination, the greatest danger in hemophiliacs is pressure by a hematoma on some vital organ. If the operative site is exposed so that local hemostasis, pressure, and application of hemostatic substances can be employed, the chance of stopping the bleeding is good. When this is not the case, a much more difficult problem presents itself. When local pressure can be applied, the mortality can be reduced more than one-half of that expected when this is not possible. Thus, in cases of hemorrhage from the nose, hemorrhage into joints, and bleeding from superficial abrasions or cuts, the treatment is relatively satisfactory.

Where organs are deeply situated in a cavity, or are themselves hollow, the problem becomes difficult. In this respect, the central nervous system is relatively superficial and, with the exception of the ventricular system, is relatively solid. The chief problem to be considered is the prevention of pressure on a vital part of the nervous system.

At the present time, probably the best treatment of a hemophiliac patient who is to undergo operation is the use of fresh blood or fresh whole plasma. The effect of blood transfusions, however, only lasts 4 to 6 hours and therefore multiple transfusions are necessary.

An essential, too often overlooked, is the preservation of injectable veins. In Schiller's experience,[11] venipuncture is preferable to a "cut-down" because of the need of a long series of daily transfusions. In his patient, who required 62 separate transfusions, the right external jugular vein was selected. Up to eight daily consecutive transfusions would be given before the vein was thrombosed. It then took seven to ten days for the vein to regain patency. The above mentioned vein was used 21 times. Eventually a "cut-down" was resorted to and the same hole in the vein was used each time.

Many agents have been suggested to control bleeding in hemophiliacs[9, 14] but experience has proved most of them valueless. Recently, the use of various antihemophiliac globulin fractions has been somewhat efficacious in controlling local oozing when applied to the open wound at the time of operation.

The value of these serum fractions given

systemically is still moot. Lately it has been suggested that cortisone tends to inhibit the anticoagulation fractions that are prone to develop after repeated transfusions. This point is still in question and readers are referred to papers dealing specifically with this problem in hemophiliacs.[7, 10]

From a mechanical point of view, use of the electrocautery is valuable. However, its efficacy has been over emphasized. Coagulation stops the immediate bleeding but actually causes local necrosis which eventually enlarges the wound. An even more serious disadvantage is that in the process of coagulation, the adjacent healthy tissue becomes engorged with dilated blood vessels and when the necrotic tissue sloughs off, an abnormally vascular bed presents itself. This probably explains the usual post-operative hemorrhages that are so disastrous in these cases.

Cooling is one of the better methods, along with pressure, for local control of bleeding.[10] Cold causes a contraction of the blood vessels in the injured area and this may often be sufficient to bring about permanent closure of the traumatized vessel. It is of the utmost importance to avoid the application of heat to a newly traumatized area in hemophiliacs. Dilatation of the vessels may cause a hemorrhage, that would otherwise remain minor, to become massive.

More recently, dermal homografts [4] have been applied locally with success. The effectiveness of skin grafts is explained by the fact that the "borrowed" skin usually fails to "take"; the failure of growth being explained by the formation of clots in the blood vessels in the region of the recipient site under the graft. These clots, therefore, stop any bleeding. Later an autograft can be used to replace the sloughed off skin from the homograft.

The most rational approach to the surgical treatment of hemophiliacs seems to consist of primary excision and/or repair of the pathologic site, with conversion of the operative site into an open wound. The wound may then be firmly packed to control hemorrhage and allowed to heal by secondary intention as the packing is slowly removed.

This approach appears to be feasible in the nervous system. It was with this in mind that our third case was treated by open drainage and packing of the subdural space. When this approach is used in the cranial cavity and depending on the presence or absence of increased intracranial pressure, an additional complication may arise, namely the development of a cerebral herniation through the operative site prior to healing. This occurred in our third case and necessitated a second operation.

Actually, the method of exteriorization of a cerebral lesion is not new. Prior to the advent of antibiotics, external drainage was the treatment of choice for brain abscess.

We also believe that it should be possible safely to convert laminectomy incisions into open wounds in which the loss of blood from the wound edges could be controlled by external pressure. Obviously, exteriorization of a large part of the spinal cord or brain would be fraught with danger, but possibly some artificial covering could be interposed should it become necessary to sacrifice the dura.

In the spinal cord, unless the bleeding is intra-myelic, the dura can be reapproximated, if the bleeding beneath is controlled, with little probability of bleeding from the dural edges themselves. This would be preferable in the spinal cord in order to permit the re-establishment of the cerebrospinal fluid circulation, and the return of part of the cord inferior to the operative site to a more physiologic surrounding. This need not obtain in localized areas of exteriorized brain.

Multiple, fresh, whole blood and plasma transfusions, before and after operation, still appear to be the most important ancillary treatment in these cases. We feel that a vein cannulated with a polyethylene

catheter is preferable to repeated venipunctures.

All of the technics outlined in this paper are merely steps in the progress of treatment of the hemophiliac requiring operation. The goal is correction of the primary blood clotting mechanism.

SUMMARY

A review of the literature concerning hemophiliacs, with lesions of the central nervous system requiring surgical intervention, together with three cases of our own, is presented. A surgical technic for reducing operative and postoperative hemorrhage in hemophiliacs is suggested in which operative sites are exteriorized so that local measures to control hemorrhage can be applied.

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