HEMOPHILIA*

PROBLEM OF SURGICAL INTERVENTION FOR ACCOMPANYING DISEASES REVIEW OF THE LITERATURE AND REPORT OF A CASE

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THE NUMBER OF CASES OF HEMOPHILIA who have undergone minor surgical procedures is very great and will not be a subject of review in this report. However, Birch[1] in a monograph on hemophilia in 1937 reported the following in regard to surgery in 113 cases of hemophilia studied. Analysis of the cause of death showed that the greatest number were due to hemorrhage following surgical procedures, all but one of which were operations of a minor nature. There can be no doubt that the great majority of hemophiliacs who undergo minor surgical procedures at the present time probably are brought through safely to recovery. Nevertheless, even the simplest operation still presents a serious problem calling for intensive treatment with prophylactic transfusions or injections of fresh plasma or Fraction I of Cohn before operation, with repeated use of these procedures postoperatively. In addition, local hemostatic measures should be used.

It is obvious that if minor surgical procedures are accompanied by such risk of fatal hemorrhage, major operations must be proportionately more hazardous. The site of trauma is probably the most important criterion of operability. If the operative site is exposed so that local hemostasis, pressure, and application of hemostatic substances can be employed, the chances of staunching the flow of blood are vastly increased. Thus Firor and Woodhall[2] successfully carried out the amputation of the thumb in a hemophiliac; Davidson and Levenson[3] have succeeded in skin grafting a hemophiliac with the help of thrombin; and Blalock[4] in 1932 amputated the arm of a proven hemophiliac. The occurrence of hemorrhage internally, either spontaneously or secondary to trauma, where local controlling measures cannot be continually applied presents a much more serious and difficult problem of management. A review of the literature in an attempt to collect opinions and results of major surgery in cases of hemophilia yields conflicting data. It is apparent that a wide discrepancy exists in the minds of the various authors as to the efficacy of surgery in acute emergencies, varying from almost complete lack of restraint

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in regard to operability to a feeling that no operation should be considered under any circumstances. Because of lack of unanimity of opinion as to the best course to follow in hemophiliacs who develop acute surgical conditions, a thorough search of the literature has been made with the hope that definite conclusions might be reached.

It is unfortunate that in many instances sufficient evidence is not presented by the particular author to allow an unequivocal diagnosis of hemophilia to be made. In view of the necessity of accurate diagnosis in attempting to formulate an opinion as to the advisability of surgery in hemophilia, we have eliminated from the analysis those reports in which there is any doubt of the specific nature of the hemorrhagic diathesis. The criteria established for the diagnosis of hemophilia are clear cut. These will be discussed further together with the reasons for exclusion of questionable cases. Those reports in which the diagnosis of hemophilia was unquestionable and those cases in which operative intervention for some associated disease was carried out will be reviewed in some detail.

In 1931 Emile-Weil[5] presented the results of surgical treatment of various disorders in an extensive article. The most outstanding case was one in which a gastro-enterostomy was performed because of a bleeding prepyloric ulcer. The operation was successful, hemorrhage being controlled by transfusions. In this case the coagulation time was two hours; clot retraction was good; bleeding time was three to seven minutes. Family history and past history were dubious. It seems probable that this was a case of true hemophilia. Another case reported by the same author involved the operative removal of a gangrenous appendix with recovery of the patient. This patient was five years of age; the family history, past history, and the sex of the patient are not given. The clotting time was 45 minutes; the bleeding time, nine minutes. Insufficient data are given to establish the diagnosis beyond doubt in this instance, although the prolonged coagulation time is highly suggestive.

The case of Blalock[4] reported in 1931, and already mentioned, was undoubtedly one of true hemophilia. However, here the application of local measures was possible; and although the procedure was major, it is not comparable to one accompanied by internal hemorrhage.

Cioran[6] in 1935 reported a case of acute appendicitis in a soldier shown to have hemophilia after operation. Bleeding of more than the usual amount was noted during operation, and later it was found that the coagulation time was four hours. Platelet counts were normal. It was determined that a maternal grandfather had a questionable hemorrhagic history and had died at an early age. The patient's past history revealed that he had had repeated nose bleeds and bruised easily during childhood. The patient was given two transfusions postoperatively without effect on the hemorrhage. However, intramuscular and intravenous injections of a substance called "Clauden" controlled the bleeding. This substance, "Clauden," was said by the author to be thrombokinase (thromboplastin) and was an aqueous extract of lung tissue. The patient gradually convalesced over a 35-day period. There is little doubt that this case was one of true hemophilia. It is rather startling

that hemorrhage should have been controlled by intravenous injections of thromboplastin, a procedure which has been shown in animals to be accompanied by intravascular thrombosis and death if given in large amounts.

Friedrich[7] in 1935 published an extensive article on the risk of operation in hemophilia. He cited several cases of his own and reviewed the literature, and arrived at some very definite conclusions. However, he made no attempt to present data supporting the diagnosis of hemophilia in these cases. He estimated the overall mortality of all major surgical procedures in hemophiliacs at 35 per cent. He felt operation in cases of appendicitis contraindicated except in the event of peritonitis, and cited two appendectomies which terminated fatally. He felt that the risk of hemorrhage following surgical intervention in appendicitis was greater than the risk of infection with conservative treatment (and this at a time before antibiotics and sulfonamides were available for clinical use.) He also found reports of six cases of retroperitoneal hematomata which were incorrectly diagnosed as acute abdominal emergencies, and were operated upon with uniformly fatal results. His opinion was that abdominal surgery should not be undertaken unless it was evident that death would ensue if surgical measures were not taken to alter the course. He pointed out that only in those cases where local measures could be applied was the prognosis favorable following surgery.

Mertz and Meiks[8] in 1938 reported a hemophiliac in whom nephrectomy was necessary because of a severe left hydronephrosis with infection. The diagnosis in this case was adequately established, and treatment was thorough and according to the accepted principles. This report will be quoted in some detail because of the striking similarity between the course of their patient and that of the case included in this paper. The patient was carefully studied and prepared preoperatively by means of sensitization to sheep serum and transfusion. The clotting time was brought down from 120 minutes to five and a half minutes prior to operation. Especial care was taken by the surgeons to obtain complete hemostasis, and no unusual bleeding was apparent at operation. Postoperatively, the patient's clotting time was six minutes and was kept down to low levels by repeated transfusions. There were no signs of bleeding for three days, and the patient appeared to be recovering. The drain which had been placed at operation was removed. However, the patient began to run a fever as high as 104.4.° On the fourth postoperative day, it was thought that free abdominal fluid had collected. The signs of this became more definite later; the intra-abdominal hemorrhage progressed in spite of repeated transfusions, and the patient died on the twelfth postoperative day due to hemorrhage and streptococcal septicemia. Autopsy showed a large hematoma at the site of the removed kidney with no evidence of bleeding from a major vessel but merely a slow ooze from the renal bed. The authors emphasized the fact that bleeding continued despite repeated transfusions and a clotting time at the lower limits of normal.

Vance[9] in 1939 reported four cases of surgical conditions in male patients with abnormal bleeding. One underwent a radical mastectomy because of carcinoma. He experienced some bleeding postoperatively which gradually

stopped without the necessity of transfusion. The clotting time in this patient was 16 minutes; family history and past history negative. The second patient had acute appendicitis. The clotting time in this case was only six minutes (method not given) and yet the diagnosis of hemophilia was made. Postoperatively the patient did well for five days but then bled continuously into the abdomen, in spite of blood transfusions, and died on the ninth postoperative day. The third case was one of acute appendicitis with a history very suggestive of hemophilia and a coagulation time of 18 minutes. Family history showed that a brother also had a hemorrhagic tendency. He was treated conservatively, with appendiceal rupture and subsequent localized peritonitis. The patient apparently bled considerably per rectum in spite of repeated transfusions and continued to do so for two weeks. Following this he rapidly improved. The fourth case was a brother of the above patient who also developed appendicitis. He was treated in the same manner as the previous case and died at the end of eight days. It is probable that these last two patients with appendicitis were true hemophiliacs. In respect to the first two patients, however, the diagnosis, if made on the basis of the data presented, is less certain.

Birch[1] in her monograph mentions one case of acute appendicitis in a true hemophiliac. Although the details of this case and the operation are not given, apparently the patient recovered from the operation but died one week later from postoperative pneumonia with hemorrhage from the lungs. It is doubtful that this case can be justly classified as an operative success.

A German military surgeon, Karitzky,[10] reported the treatment and course of a hemophiliac who had received severe combat wounds in October, 1939. There could be no doubt of the accuracy of the diagnosis in this case, the past history, family history and laboratory findings being classical of hemophilia. This marine had been injured by the explosion of a mine under his ship, steel splinters entering the left neck and hip regions. The steel fragment entering the hip region had penetrated, leaving a large wound of exit in the gluteal region near the anus. Hemorrhage was intense, and the patient lapsed into shock. Débridement was carried out, the fragment removed from the neck with closure; and the gluteal wound was packed with iodoform gauze. The cervical wound healed normally. On the fifth day after injury, the patient began to lose large amounts of blood from the gluteal wound. He continued to bleed for 24 days and became dangerously anemic in spite of repeated transfusions and injections intramuscularly of substances such as Redoxon, Koagulen, Gelatine, Clauden, etc. A putrid wound infection developed. Massive transfusions and pressure dressings finally controlled the bleeding to a large degree, but oozing from stitch wounds and needle punctures continued for some time. The patient finally recovered. This example of protracted uncontrollable hemorrhage from a wound which was amenable to local measures in a hemophiliac treated intensively with blood transfusions again demonstrates the serious difficulties which may be encountered in bringing about hemostasis. However, the fact that no internal operative procedures were performed in this case removes it from that type of operative intervention with which we are concerned.

In addition to those reports reviewed, there have been numerous others of major surgery performed in patients suffering from some hemorrhagic diathesis. The nature of the surgical condition, the results of surgery, and the data upon which the diagnosis of hemophilia was made are presented in Tables 2 and 3. It was our opinion that insufficient information was presented by the authors for the diagnosis of true hemophilia in these instances. The criteria necessary for the diagnosis of this particular hemorrhagic diathesis and the reasons for excluding these cases will be discussed in more detail later.

PRESENTATION OF A CASE

E. W., a 27-year-old single white male, was admitted to Strong Memorial Hospital October 4, 1947. He had been awakened the previous morning by a crampy epigastric pain which was followed by nausea and vomiting. The pain persisted after he had vomited, was generalized throughout the abdomen but was slightly more pronounced in the right lower quadrant. He had taken a dose of cascara which he had promptly vomited. In spite of a small but normal bowel movement that day, his pain became steadily worse. On the morning of admission the pain was localized in the right lower quadrant, was constant and rather dull and aching in character. He had felt feverish but had no other complaints.

Past History: The patient had been seen in this hospital in 1927 at the age of seven with a history of having bled profusely and bruised easily since early childhood. The coagulation time of whole blood was found to be 4 hours, and a diagnosis of hemophilia was made at that time. He had had numerous hospital admissions and clinic visits from that time forth because of hemoarthrosis, hematuria, and hemorrhage from the gums. He was intensively studied in 1940 and again in 1945, and had received extensive orthopedic care. As a result of the use of fresh plasma and whole blood and of careful orthopedic management, he had been able to work fairly regularly and to walk during much of this time. He had been free of bleeding during these periods of therapy for as long as one year. Fresh whole blood or plasma always lowered the coagulation time. In spite of 6 whole blood transfusions and 100 plasma transfusions from 1927 to the present time, no refractory state ever developed. A detailed summary of the laboratory findings is found in Table I.

TABLE I

	1927	1939	1940	1941	1945
Coagulation time	40′	30′	70′	85′	36′–72′
Clot retraction	good	good	good	good	good
Bleeding time	3.25′	1.5′	....	....	....
Prothrombin concentration (% normal)	....	normal	....	....	80 per cent
Calcium	....	10 mg. per cent	....	....	10.4 mg. per cent
Fibrinogen	....	....	....	....	0.2 Gm. per cent
Vitamin C	....	....	....	....	.76 mg. per cent
Platelets	250,000	normal no.	normal no.	normal no.	normal no.

Family History: revealed that a maternal great-uncle had "bled to death," but no other important family history could be obtained. This is shown in Figure I.

Physical Examination: revealed a moderately well developed, somewhat dehydrated 27-year-old white male in moderate distress. There was a fine macular rash over the anterior chest, and there were ecchymotic areas over the left hand. His temperature was 101.3° F. The blood pressure and pulse were normal. The pertinent physical findings were limited to the abdomen and the extremities.

The abdomen was slightly distended, tender in the epigastrium and more so in the right lower quadrant where there was also spasm and rebound tenderness. There was bilateral rectal tenderness, more marked on the right. Both ankles and both knees showed old joint deformities.

The white blood count was 14,200 per mm.^{3} at the time of admission. The urine was negative except for a strong acetone reaction. In view of this patient's known hemophilia, it was decided to employ conservative measures even though it was felt that he had acute appendicitis. Accordingly he was given penicillin 100,000 units intramuscularly every three hours, was hydrated, and given 5 grams of sodium sulfadiazine in 1000 cc. of saline intravenously. It was decided to reduce the coagulation time, which was found to be 60 minutes. Four-tenths Gm. of Fraction I of Cohn ("Antihemophilic globulin") and 100 cc. of freshly prepared plasma were administered intravenously. The coagulation time was 11 minutes when observed 20 minutes after this treatment and was 15 minutes 4 hours later.

After a period of observation of 10 hours, during which the leukocytosis, the fever and the symptoms increased, it was decided to operate. This decision was reached after much deliberation and in view of the normal coagulation time, although it was felt that there was considerable risk involved in the procedure.

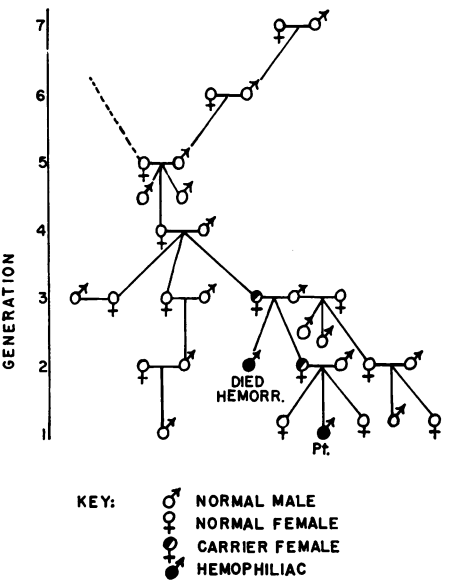

FIG. 1.—Graphic representation of patient's family history.

Operative Note. Under ether anesthesia, the abdomen was opened through a small McBurney incision. No unusual bleeding was encountered. The peritoneal cavity contained a small quantity of cloudy fluid which on culture was found to contain *E. Coli.* The cecum was delivered into the wound without difficulty. The appendix lay in a retrocecal position with its tip beneath the ileocecal valve and surrounded by fairly dense adhesions. These adhesions were broken up by blunt dissection, but the tip of the appendix could not be mobilized. A small Weir extension was made for better exposure, in spite of which the appendix could not be delivered. It was thought unwise to mobilize the cecum by incising its lateral attachments because of the danger of hemorrhage. For this reason the appendix was removed in a retrograde fashion partly by blunt dissection. Its wall was necrotic at the site of two fecoliths near its mid-portion. The stump was ligated with a surgeon's knot of 000 silk and inverted beneath two purse string sutures. There was a moderate ooze from the appendiceal bed which could not be visualized. It did not appear to be dangerous in quantity and was not felt to be arising from any sizable vessel. It was satisfactorily controlled with a pack of gelfoam. Drainage was discussed but not carried out. The abdominal wall was closed in layers with silk, taking great pains to ligate or cauterize the smallest bleeding points. In spite of this care, there was minimal ooze from the subcutaneous tissue.

The patient's condition was good at the close of the procedure. Pathologic examination of the specimen confirmed the clinical diagnosis of acute appendicitis.

During the operation the patient received 500 cc. of fresh compatible whole blood, and one hour later he was given 0.2 Gm. of Cohn Fraction I and another 500 cc. of fresh compatible whole blood. He was placed on Wangensteen suction. Careful check was kept of the coagulation time (the Lee-White method, performed at 37.5° C, and by the same person as often as possible) and the plasma and whole blood specific gravity. These, in addition to the antihemophilic therapy, are summarized in Figure 2. At no time could a circulating anticoagulant be demonstrated similar to that described by Craddock and Lawrence.[19]

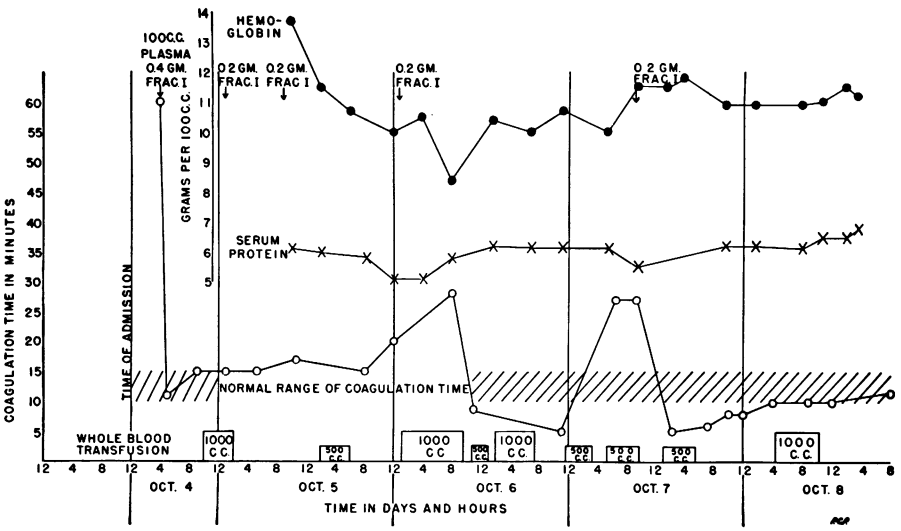

FIG. 2.—Course of patient in hospital showing amounts of antihemorrhagic treatment, response of coagulation time, and degree of serum protein, and hemoglobin deficiency.

Penicillin was continued, but because of the presence of albuminuria and microscopic hematuria, sulfadiazine was discontinued. A conscientious attempt was made to maintain a normal fluid and electrolyte balance.

In spite of the fact that the coagulation time was kept almost entirely within normal limits, the patient continued to lose blood into his peritoneal cavity and into his abdominal incision. His abdomen became distended to the point where he had severe respiratory embarrassment, and on the fourth postoperative day it became necessary to perform an abdominal paracentesis, 600 cc. of bloody, incoagulable fluid being removed. The patient experienced some relief, but later in the day he was again severely dyspneic; and there were signs of atelectasis. The abdominal wound was partially opened under sterile precautions and 600 cc. of fluid, defibrinated blood removed, this later proving to have been extraperitoneal.

On the evening of the fourth postoperative day, the patient's respiratory embarrassment became extreme; there were signs of bilateral pleural effusion, and thoracentesis was performed. After 150 cc. of bloody fluid had been withdrawn, the patient's respirations ceased. Artificial respiration and intravenous coramine were of no avail, and the patient expired.

Post mortem Examination: revealed pulmonary edema, bilateral hemothorax, a large blood clot in the appendiceal bed extending along the right peritoneal gutter from the pelvis to the liver. There was no evidence that the bleeding had come from any large bleeding point. There was also a tremendous hematoma at the site of the abdominal wound, not communicating with the peritoneal cavity.

DISCUSSION

In reviewing the literature on this subject, we have attempted to analyze critically each report in order to determine which cases represented operation in true hemophilia. The criteria selected by us for the establishment of the diagnosis of hemophilia in the individual cases reviewed are the following (see Table II.) (1) Laboratory findings showing definite prolongation of the clotting time as the only abnormal test of those routinely performed pertaining to the hemostatic mechanism. (2) Positive family history (although occurrence of sporadic spontaneous cases is occasionally found.) (3) A past history typical of that exhibited by the majority of hemophiliacs. (4) Occurrence in a male. These criteria are taken because the majority of the reports do not include detailed clinical and laboratory data in regard to the question of hemophilia. Attempt has been made to weigh the facts given in each instance and determine whether or not they permit the diagnosis of hemophilia.

It is recognized that there is great variation in the technic and results obtained in tests performed in regard to the clotting mechanism. Nevertheless, the one laboratory abnormality necessary for the diagnosis of hemophilia (in the untreated case) is a prolonged clotting time of the blood. In most instances the technic used for this test was not stated, but unless a definite prolongation over the stated limits considered normal by the author is recorded, the laboratory data cannot be regarded as diagnostic unless accompanied by other tests supporting the contention. In true hemophilia all the other tests routinely performed pertaining to coagulation time are normal (*i.e.,* prothrombin time, bleeding time, tourniquet test, platelet count, and clot retraction, and determinations of calcium and fibrinogen concentrations.)

In those cases reported, if the laboratory data are of questionable significance, the other criteria are studied. If there is a definite positive family history, that is, reliable evidence of hemorrhagic disease in male members of previous generations on the maternal side, then this is considered to support the diagnosis of hemophilia in the face of positive or suggestive laboratory data. Here again in many reports, the family history was either not mentioned or else was not elucidated in questionable instances. It is recognized that sporadic cases occur in whom no family history is detectable no matter how far back it is investigated. For this reason a negative family history does not exclude the diagnosis, but a positive one is good supportive evidence. In regard to the criterion of past history in the particular cases reviewed, it is felt that most hemophiliacs present stories of previous hemorrhagic phenomena which are fairly typical of the disease. Such occurrences in the past history as repeated hemarthrosis, subcutaneous bleeding after slight trauma, spontaneous bleeding per rectum or hematuria without the

presence of pathologic lesions, and prolonged bleeding from minor cuts are usually cited by the hemophiliac. The absence of such a past history by no means excludes the diagnosis, but its presence lends support in questionable cases. However, such symptoms can occur in other hemorrhagic diseases. and for this reason a positive past history alone cannot be used as the sole criterion for the diagnosis. The sex of the patient was not given in all reports. As far as is known at present, hemophilia occurs only in males. This has not always been accepted as true in the past. Therefore, in the older reports unless the sex is definitely stated or inferred, doubt is cast on the validity of the diagnosis of hemophilia.

ANALYSIS OF REPORTED CASES OF MAJOR SURGERY IN HEMOPHILIA

As shown in Table II extensive surgical procedures have been successful in areas where local measures could be applied to control blood loss. However, in regard to abdominal surgery, the chances for a satisfactory outcome are much less. If one accepts all cases reported as being true hemophiliacs, it would appear that the risks of major operation are not more extreme than would be indicated in the past.

Thus, of 15 major operations performed in areas of the anatomy where the application of pressure and local hemostatic agents was not possible, there were 11 recoveries and four deaths, or a mortality of 26.7 per cent. This mortality is close to that estimated by Friedrich for operations of this type in hemophilia. The percentage of recoveries is higher than might be anticipated. Indeed, from analysis of the cases, excluding those not proven to be true hemophilia, it is evident that the percentage is less optimistic. Of the 15 cases reported, there are only four which, on the basis of the facts presented, fulfill the criteria needed for the unequivocal diagnosis of hemophilia. Of these four, there were two fatalities which gives a mortality of 50 per cent. If our case is included, the mortality is raised to 60 per cent. All of these fatal cases received adequate treatment with transfusions. It would seem, therefore, that major surgery in cases of hemophilia of the type where local hemostatic measures cannot be utilized is accompanied by an expected mortality rate which is much greater than that which is usually indicated by the literature on this subject.

In regard to treatment of acute appendicitis *per se* in cases of hemophilia, the literature reviewed by us discloses 11 reports. Eight of these were operated upon and three treated conservatively. Of the eight receiving operative treatment, there were six recoveries and two deaths, or a mortality of 15 per cent. However, among the eight undergoing appendectomy, there were only two who fulfilled the criteria needed for the unequivocal diagnosis of hemophilia. Of these two, one died, and one recovered, thus giving a mortality of 50 per cent following operation. Our case would raise the mortality to 66.6 per cent.

On the other hand, there were three cases of true hemophilia with appendicitis treated conservatively. Two of these were definite instances of acute

TABLE II.—*Reported Cases of Major Surgery in Hemophilia.*

Associated Disease	Authors	Operation	Outcome	Criteria of Diagnosis of Hemophilia: Laboratory Data	Family History	Past History	Sex	Positive Diagnosis Hemophilia	
Gangrene, arm	Blalock[4]	Amputation	Recovery	+	+	+	♂	Yes	
Trochanteric hematoma	Emile-Weil,[11] Scemama	Incision and drainage	Recovery	+	+	+	♂	Yes	External operative site; local hemostatic measures applicable
Carcinoma of breast	Vance[9]	Radical resection	Recovery	±	O	±	♂		
War wounds	Karitzky[10]	Debridement	Recovery	+	+	+	♂	Yes	
Tuberculous knee	Friedrich[7]	Removal of foreign body Exploration of knee	Recovery	O	+	O	♂		
Bladder polypi, prostatic median bar	Mathe and Mitchell[12]	Polypectomy Fulguration of median bar	Recovery	−	−	±	♂		
Prostatic hypertrophy	Hinman[13]	Perineal prostatectomy	Recovery	−	±	+	♂		
Hydronephrosis with infection	Mertz, Meiks[8]	Nephrectomy	Death	+	+	+	♂	Yes	
Peptic ulcer with hemorrhage	Emile-Weil[5]	Gastro-enterostomy	Recovery	+	±	+	♂	Yes	
Pre-pyloric ulcer with hemorrhage	Wosnessensky[14]	Gastric resection	Death	O	O	O	♂		Internal operative site; local hemostatic measures not applicable
Appendicitis	Emile-Weil[5]	Appendectomy	Recovery	+	O	O	O		
Tonsilitis and appendicitis	Hays[15]	Tonsillectomy Adenoidectomy Appendectomy	Recovery	−	O	O	♂		
Appendicitis	Vance[9]	Appendectomy	Death	±	O	O	♂		
Appendicitis	Birch[1]	Appendectomy	Death*	+	+	+	♂	Yes	
Appendicitis	Prima[16]	Appendectomy	Recovery	O	O	O	♂		
Appendicitis	Cioran[6]	Appendectomy	Recovery	+	+	−	♂	Yes	
Appendicitis	Hipsley[17]	Appendectomy	Recovery	O	±	+	♂		
Appendicitis	Paz[18]	Appendectomy	Recovery	O	−	+	♂		
Ruptured spleen	Friedrich[7]	Splenectomy	Recovery	O	+	O	♂		
Gastro-intestinal bleeding	Friedrich[7]	Gastric resection	Recovery	O	+	+	♂		
Appendicitis	This report	Appendectomy	Death	+	+	+	♂	Yes	

* Patient survived operation one week, but died with postoperative hemorrhagic pneumonia.

Symbols: + = Positive findings. − = Negative Findings. ± = Questionable or inadequate findings. O = Data not given.

appendicitis. The other patient, that of Platou[20] was felt at first to have appendicitis with intestinal obstruction. The latter disappeared after Wangensteen suction was instituted, and the patient recovered. The authors later felt that this patient probably did not have acute appendicitis but rather a hemorrhage into the submucosal area of the small intestine. Therefore, the total number of cases of appendicitis in hemophiliacs reviewed by us who received nonoperative treatment is two, with one death.

TABLE III.—*Results of Treatment of Appendicitis in Hemophilia.*

Author	Type of Treatment	Outcome	Criteria of Diagnosis of Hemophilia: Laboratory Data	Family History	Past History	Sex	Positive Diagnosis Hemophilia
Hipsley[17]	Appendectomy	Recovery	O	±	+	♂	
Emile-Weil[5]	Appendectomy	Recovery	+	O	O	O	
Hays[15]	Appendectomy	Recovery	−	O	O	♂	
Vance[9]	Appendectomy	Death	±	O	O	♂	
Cioran[6]	Appendectomy	Recovery	+	+	−	♂	Yes
Birch[1]	Appendectomy	Death*	+	+	+	♂	Yes
Prima[16]	Appendectomy	Recovery	O	O	O	♂	
Faz[18]	Appendectomy	Recovery	O	−	+	♂	
This report	Appendectomy	Death	+	+	+	♂	Yes
Vance[9]	Non-operative	Recovery	±	+	+	♂	Yes
Vance[9]	Non-operative	Death	±	+	O	♂	Yes
Platou[20]	Non-operative	Recovery**	+	+	+	♂	Yes

* Patient survived operation one week but died with postoperative hemorrhagic pneumonia.
** The diagnosis of appendicitis was not felt to be definitely established by the author.
Symbols: + = Positive findings.
− = Negative findings.
± = Questionable or inadequate findings.
O = Data not given.

The small number of reported cases of acute appendicitis in hemophiliacs treated by either operative or nonoperative means does not allow any valid comparison of expected results. Nevertheless, it is obvious that the dangers of uncontrollable fatal hemorrhage following internal operative intervention multiply many times the operative risk. Most statistics on the subject place the present mortality rate following acute appendicitis with rupture and peritonitis at 10–15 per cent in otherwise normal individuals.[21-24] It is not known how much the presence of hemophilia would increase the dangers of peritonitis of appendiceal origin. Certainly there is no good evidence to suggest that hemophiliacs cannot handle infectious processes as well as normal individuals. From our review of the literature, we believe the mortality rate following appendectomy in hemophiliacs is around 50 to 60 per cent. It is probable that the chances of death due to postoperative hemorrhage outweigh the expected mortality associated with the nonoperative treatment of appendiceal rupture and peritonitis.

The hemophiliac presented by us had been followed in this hospital since the onset of his hemorrhagic difficulties and had been the subject of extensive investigative and therapeutic procedures. It was well known that he obtained marked benefit from plasma injections, and he had been kept entirely free of

hemorrhagic phenomena for long periods of time without ever showing evidence of becoming refractory. As shown in the case report, when he was given blood, his clotting time fell rapidly to normal. He was of the optimal age group for surgery and possessed the physical stamina to withstand such a procedure. It was our hope that if operation were necessary, the coagulation mechanism could be augmented by transfusion or injections of fresh plasma or Fraction I of Cohn to such an extent that severe hemorrhage could be controlled.

The persistence of hemorrhage in this patient in spite of a normal coagulation time demands further comment and brings to mind several considerations in regard to the present concept of the fundamental defect in hemophilia. It is the belief of many investigators in this field at the present time that the underlying abnormality in hemophilic blood is a deficiency or lack of a plasma factor necessary for coagulation to take place in the normal span of time. This factor has been shown, by numerous workers,[25-27] to be present in normal blood but deficient in hemophilic blood. Howell[27] worked extensively with this factor which he called "plasma thromboplastin." Quick[28] feels, as did Howell, that this factor represents an inactive form of thromboplastin which is normally present in the blood and is activated by an enzyme released from platelets when coagulation begins. The factor has more recently become available in purer form and in greater amounts through the fractionation of plasma by Cohn and co-workers at Harvard. The active principle is contained in greatest concentration in Fraction I and Fraction III, subfraction 2 of Cohn's classification. It has been termed "antihemophilic globulin" by Lewis, Tagnon, *et al.*[29] and has been investigated extensively by these and other workers.

There is no question that "antihemophilic globulin" in very small amounts has a beneficial effect on the clotting mechanism of hemophiliacs. This effect is demonstrated by the sharp fall in coagulation time to normal values within a very short time after it has been injected intravenously. However, its effect is no greater and of no more permanency than the beneficial response elicited by whole blood or plasma. This is as might be anticipated since each type of treatment merely supplies a factor which is deficient in hemophilic blood. This factor, necessary for coagulation to occur in the normal span of time, is apparently used up over a period of 12 to 48 hours, so that at the end of this time, the deficiency again exists; and the coagulation time again becomes prolonged.

The fact that the deficiency of "antihemophilic globulin" was erased by the concerted treatment given this patient is borne out by the shortening of the coagulation times to normal levels. The continuation of hemorrhage, even in the face of the normal coagulation time of the blood, forces one to the conclusion that the mere deficiency of the substance "antihemophilic globulin" cannot be the sole abnormality of coagulation in hemophilia. There are other, perhaps more subtle changes from normal in the coagulation mechanism which cannot be measured by the tests of blood coagulability routinely used. It is well to remember, therefore, that the actual time consumed by clot formation in the test tube is by no means an accurate measure of the ability of the hemostatic mechanisms to control blood loss.

Other recent investigations into the clotting mechanism have made it highly suggestive that the present concept is incomplete. Attempt will not be made to review these advances, but it is becoming apparent that there are factors concerned in the first stage of clotting that heretofore have not been appreciated. Thus Ware *et al.*[30] believe an activator globulin (AC globulin) is necessary for prothrombin activation; Milstone[31] postulates a prothrombokinase which is activated in the presence of calcium ions to thrombokinase (thromboplastin) and which in turn activates prothrombin; Owren[32] reports a principle designated as Factor V which is essential for rapid prothrombin conversion to thrombin, and Quick[33] has designated two components of prothrombin (A and B) as well as a "labile factor" which is also necessary for coagulation to occur in the normal time. It is probable that these various factors are closely related, if not the same. It is not known where these factors fit into the present formula of clotting; there is little doubt that the speed of prothrombin conversion and hence the speed of clotting is greatly influenced by their presence. These investigations as well as others such as those of Ferguson[34] indicate the existing confusion and inadequacy of knowledge concerning blood coagulation. The importance of these advances in regard to the treatment of hemophilia are unknown at present. Certainly this case would indicate that a mere deficiency of "antihemophilic globulin" does not explain the blood loss in all cases. It is likely that the normal fresh blood given to this patient in large quantities contained an adequate amount of all the factors described by various authors as necessary for coagulation. It is evident that whatever the defect may be which causes hemorrhage in hemophilia, it cannot always be corrected, even temporarily, by supplying the patient with those factors concerned with clotting as they exist in normal blood.

The main points to be emphasized with regard to this case are the following: First, and most important, the coagulation time of the blood cannot be taken as a measure of the adequacy of the hemostatic mechanism in the hemophilic patient. Howell[27] has stated, "at present the one pathologic condition in hemophilia that is definitely established and that is directly connected with the hemorrhage is the prolonged clotting time of blood. Those who have had the widest experience with hemophilic patients believe the severity of the disease is in general proportional to the delay in coagulation." This feeling has been almost generally accepted in regard to the disease. The main object of all therapy up to the present time has been to lower the coagulation time of the blood. This patient demonstrates clearly that coagulation time alone can be used neither as the sole measure of the severity of the hemorrhagic tendency nor as a test of the response of the hemophiliac to treatment. There can be no doubt that the coagulation time of this patient's blood was usually maintained within limits which are considered normal, and yet hemorrhage continued with loss of the blood as rapidly as it was replaced.

The second point to be emphasized is the difficulty in choosing a case for operation. By all the accepted standards this hemophiliac met most of the requirements for operability, as well as any patient suffering from this disease

could meet them. And yet death resulted in spite of most intensive antihemorrhagic treatment.

The third point to be stressed is the infinite difference between controlling postoperative hemorrhage from areas that are exposed and amenable to local measures and controlling hemorrhage from internal areas. It is our feeling that if the site of bleeding cannot be treated with pressure, application of hemostatic substances, and other local measures, then the chances of recovery from surgery are poor.

In view of the unfortunate results of surgery in this case and the unconvincing reports of the efficacy of major surgery in hemophiliacs as gathered from the literature, it is our belief that conservative medical treatment is the course of choice in these cases unless it becomes clearly evident that death will ensue if surgery is not undertaken. The dangers of uncontrollable hemorrhage following surgery outweigh the dangers of generalized peritonitis and subsequent fatal infection, especially with the modes of controlling infection now at hand. The only existing well established means of combating hemorrhage in these cases is to give the patient fresh whole blood transfusions, injections of fresh or lyophile plasma, or the substance known as "antihemophilic globulin" as contained in Fraction I of Cohn. Each of these three forms of therapy accomplishes the same end. Each supplies the hemophiliac with a deficient substance necessary for coagulation to take place in the normal span of time. When the hemophiliac is given this substance by any of the means described, the coagulation time of the blood is reduced to normal. And yet, as demonstrated by this case, correction of this deficiency with a concomitant reduction in the clotting time to normal does not always promote hemostasis. This lack of response on the part of the hemophiliac's clotting mechanism to present modes of therapy in all instances further increases the dangers associated with any type of major surgical procedure undertaken in patients with this disease.

SUMMARY AND CONCLUSIONS

1. A review of the available medical literature reveals that the reported instances of internal operative procedures in patients with hemophilia require careful analysis. Many of the cases are accompanied by data that are inadequate for the diagnosis of this hemorrhagic diathesis.

2. The mortality following internal surgery in established cases of hemophilia is relatively high. Of four previously reported cases in whom the diagnosis of hemophilia was unequivocal, two died from hemorrhage following operation while two recovered. The other eleven reports of internal surgical procedures in patients with bleeding tendencies were excluded from this analysis because of inadequate basis for the diagnosis of hemophilia. If these were included, the total number of recoveries following operation would be eleven with only four deaths, or a mortality rate of 26.7 per cent, a figure we believe to be erroneously low.

3. A case of unequivocal hemophilia is presented with the complication of acute appendicitis. The patient received intensive antihemorrhagic therapy,

but despite a normal clotting time he continued to bleed profusely and expired four days postoperatively.

4. A discussion of the significance of continued hemorrhage in the presence of a normal *in vitro* clotting time and of its relation to the fundamental defect in hemophilia is presented. Emphasis is placed on the failure of the coagulation time to indicate the severity of the hemorrhagic tendency or the degree of response to treatment, the difficulty in choosing a suitable case for operation, and the great difference in controlling internal hemorrhage as opposed to bleeding from an external site.

BIBLIOGRAPHY

1 Birch, C.: *Hemophilia.* University Press, 1937.

2 Firor, W., and B. Woodhall: Amputation of Thumb in Hemophilia. Bull. Johns Hopkins Hosp., **59**: 237–250, 1936.

3 Davidson, C. S., and S. M. Levenson: Skin Grafting in Hemophilia with Preparation of Thrombin and Sulfonamide. J. A. M. A., **128**: 656–657, 1945.

4 Blalock, A.: Amputation of Arm in a Case of Hemophilia. J. A. M. A., **99**: 1777–1778, 1932.

5 Emile-Weil, P.: Les Interventions Chirurgicales Chez les Hemophiles. Presse Med., **39**: 1021–1024, 1931.

6 Cioran, S.: Chirurgischer Eingriff bei einem Bluter mit glucklichem Ausgang. Wien. Med. Wchnschr., **85**: 1937, 1935.

7 Friedrich, H.: Uber das Operations Risike bei Hamophilen. Chirurg., **7**: 73–78, 1935.

8 Mertz, H. O., and L. D. Meiks: Hemophilia as Surgical Risk; a Case of Nephrectomy with Death. Urol. and Cutan. Rev., **42**: 557–563, 1938.

9 Vance, C. A.: Surgery in Hemophilia. Ann. Surg., **109**: 872–880, 1939.

10 Karitzky, B.: Kriegsverlet zung bei Hamophilie Klinischer Beitrag sur Blut Transfusion Frage. Chirurg., **15**: 21–25, 1943.

11 Emile-Weil, P., and Scemama: Grande Hemorragie Post-Operatoire chez un Hemophile. Guerison apres 25 transfussions—12 litres de sang. Sang., **10**: 525–529, 1936.

12 Mathe, C., and V. Mitchell: Removal of Bladder Polypi and Prostatic Median Lobe in a Case of Hemophilia. J. Urol., **21**: 401–405, 1929.

13 Hinman, F.: Prostatectomy in Hemophilia. Surg. Clin. North Amer., **13**: 63–66, 1933.

14 Wosnessensky, W. P.: Eim Todesfall durch Verblutung Infolge von Hamophile mach einer Magenresektion. Zentralble. F. Chir., **57**: 1872–1874, 1930.

15 Hays, H.: Removal of Tonsils and Adenoids in a Case of Hemophilia. Laryngoscope, **44**: 312–317, 1934.

16 Prima, C.: Appendicitis Gangrenosa bei einem Hamophilen. Zentralbl. F. Chir., **58**: 2152–2153, 1931.

17 Hipsley, P. L.: Recovery from Hemophilia After Operation for Ruptured Appendix. M. J. Australia, **1**: 548–550, 1923.

18 Paz. B.: Complicaciones de Origen Apendicular en un Hemofilico. Prenza Medica Argentine, **20**: 349–352, 1933.

19 Craddock, C. G., and J. S. Lawrence: Hemophilia: A Report of the Mechanism of the Development and Action of an Anticoagulant in Two Cases. Blood, J. Hematol., **2**: 505–518, 1947.

20 Platou, E. S., and R. V. Platou: Hemophilia with Intestinal Obstruction. Minnesota Med., **23**: 857–858, 1940.

21 Crile, G., Jr.: Peritonitis of Appendiceal Origin Treated with Massive Doses of Penicillin: Report of 50 Cases. Surg., Gynec. & Obst., **83**: 150–162, 1946.

22 Ochsner, A., and J. H. Johnston: Appendiceal Peritonitis. Surgery, **17**: 873–892, 1945.

[23] Green, H. W., and R. M. Watkins: Appendicitis in Cleveland, Final Report. Surg., Gynec. & Obst., **83**: 613–624, 1946.

[24] Tashiro, S., and M. M. Zinninger: Appendicitis, Review of 936 Cases at Cincinnati General Hospital. Arch Surg., **53**: 545–563, 1946.

[25] Bendien, W. M., and S. Van Crevald: Investigations on Hemophilia, Acta brev. Neerland, **5**: 135–138, 1935.

[26] Patek, A. J., Jr., and F. H. L. Taylor: Hemophilia, Some Properties of Substances Obtained from Normal Human Plasma Effective in Accelerating Coagulation of Hemophilic Blood. J. Clin. Investigation, **16**: 113–124, 1937.

[27] Howell, W. H.: Hemophilia. Bull. New York Acad. Med., **15**: 3–26, 1939.

[28] Quick, A. J.: Hemophilia, Studies on the Enigma of the Hemostatic Dysfunction of Hemophilia. Am. J. M. Sc., **214**: 272–276, 1947.

[29] Lewis, J. H., H. J. Tagnon, C. S. Davidson, G. R. Minot and F. H. L. Taylor: The Relation of Certain Fractions of the Plasma Globulin to the Coagulation Defect in Hemophilia. Blood, J. Hematol, **1**: 166–172, 1946.

[30] Ware, A. G., M. M. Guest and W. H. Seegers: Plasma Accelerator Factor and Purified Prothrombin Activation. Science, **106**: 41–42, 1947.

[31] Milstone, J. H.: Prothrombokinase and the Three Stages of Blood Coagulation. Science, **106**: 546–547, 1947.

[32] Owren, P. A.: The Coagulation of Blood: Investigations on a New Clotting Factor. Acta. Med. Scandinavica. (Supplement to Vol. 194) 1947.

[33] Quick, A. J.: Components of the Prothrombin Complex. Am. J. Physiol., **151**: 63–65, 1947.

[34] Ferguson, J. H.: Mechanism of Blood Coagulation. Am. J. Med., **3**: 67–77, 1947.