HEMOPHILIA. A CLINICAL STUDY OF FORTY PATIENTS

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Introduction

Since 1803 when hemophilia was first accurately described by Dr. John C. Otto, investigators of this disease have centered their efforts chiefly in the elucidation of its hereditary nature and in the study of the constant defect in blood coagulation. In the study presented here we wish to emphasize certain clinical manifestations of the disease and methods of practical therapeutic management which have been learned in this laboratory during the last ten years in the course of a study of the defect in coagulation of the blood in individuals with the disease.

The deep interest of Dr. George R. Minot in hemophilia began in 1918 when he and Dr. Roger I. Lee first demonstrated in this country that whole blood transfusions were effective in shortening the blood coagulation time. He has been the guiding spirit of the investigative work in hemophilia in this laboratory, and this presentation is dedicated to him. His guidance in this problem has given experience to many young men in the methods of clinical investigation.

Hemophilia is an hereditary disease limited to males, those afflicted exhibiting both impaired coagulability of the blood and a strong tendency to bleed especially following trauma. Although there may be variations in the frequency and severity of hemorrhagic episodes, the disease is always present for life. Transmission of the disease is always through the female to the second generation, the genes being sex-linked and recessive. Although the possibilities exist of both a first generation male with hemophilia as well as a female with the disease, authenticated cases are not known.

Although Otto was the first to bring the true nature of the disease into clear focus, there is evidence that certain aspects had been known in ancient times by the Arabs and the Jews. Bullock and Fildes in their classical monograph on the disease report descriptions of a condition resembling hemophilia by Albucasis in the tenth century. Among the recent general articles or monographs on hemophilia are those of Birch, Howell, Stetson and Lozner, Quick, Davidson and McQuarrie, Ely, Mills, MacFarlane, and Kark.

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HEMOPHILIA

The coagulation defect in hemophilia is observed in vitro as a prolongation of the whole blood clotting time. Normal blood clots in from 6 to 12 minutes as measured by a modification of the method of Lee and White. The blood of a patient with hemophilia under the same circumstances may not clot for many hours. However, most of the patients in our series have clotting times of from 1 to 2 hours, but in a few the clotting time is in the range of 20 to 40 minutes. Although it has been reported that patients with hemophilia will occasionally exhibit a normal coagulation time, this phenomenon has never been observed in this laboratory.

The coagulation defect in hemophilia has been ascribed by some to an abnormality of the platelets and by others to the presence of an antithrombin. Tocantins has described the presence of an antithromboplastin in hemophilic blood, while workers in this laboratory believe that there is a deficiency of some factor associated with plasma globulins. Nevertheless, it is generally agreed that fibrinogen, prothrombin, calcium, and the number of platelets are all normal in hemophilic blood. Thus, whatever the abnormality, for practical purposes transfusion of whole blood or plasma and certain plasma derivatives will usually bring the blood coagulation time to or near to normal. Hemophiliacs have been observed whose coagulation time does not respond as is customary to the administration of blood, plasma or its derivatives. The basis for this failure to react has not been fully elucidated.

Fractionation of blood plasma has led to the identification of the antihemophilic activity with the euglobulins and particularly with fraction I according to the nomenclature used by Cohn et al., Fraction III-1 also contains considerable antihemophilic activity. Because of the impracticability at present of the administration of fraction III-1, the fibrinogen fraction I has been chiefly studied in vivo and contains antihemophilic activity which has been clearly shown not to be fibrinogen itself.

Occasionally patients are seen who have suffered hemorrhagic episodes but whose coagulation time is only slightly prolonged. It is very difficult either to establish or exclude the diagnosis of hemophilia in these patients, particularly if a family history of the disease is not obtained, as is frequently the case. Certain laboratory procedures may be helpful in this regard. Among these is the well-established reduction in the clotting time of hemophilic blood by the addition of small amounts of normal plasma or its derivatives. The measurement of the recalcification time of plasma centrifuged at different speeds may prove to be a valuable diagnostic test, if substantiated.

CLINICAL MANIFESTATIONS OF HEMOPHILIA

It is our purpose to report observations on the clinical manifestations and practical management of forty patients with hemophilia, all of 12 years of age or over, who have been followed in the Thorndike Memorial Laboratory during the last ten years. All were males; the youngest 12, the oldest 58. Eight were in the second
decade of life, 19 in the third, 7 in the fourth, 5 in the fifth, and one in the sixth.

Twenty-eight of the 40 (70 per cent of the series) had a family history of hemophilia. Twenty-five had a known member of the family in the same generation with the disease, 14 one generation back, 4 two generations, while none was able to trace the disease further. The lack of a positive family history is in part due to inadequate knowledge on the part of the patients about their families.

There were three patients in whom the family history was known and in whose family no hemophilia had appeared during three previous generations. Whether these instances represent sporadic hemophilia or whether the disease was carried by the female through successive generations without manifestation in a male offspring is not known, but the latter possibility would appear to have more support from the literature.

"Spontaneous" hemophilia has been reported, the most recent article by Boggs reviews the reported cases and presents six brothers with the disease whose family history gave no evidence of bleeders, although it was known for four generations on the mother’s side. Boggs admits that the legitimacy of the mother could be questioned. The statistical likelihood of the occurrence of hemophilia and of carriers in families has been studied by Haldane and Philip who have said "the daughters of hemophilic men bear equal numbers of normal and hemophilic sons, whilst half the sisters of hemophilic men are heterozygous for hemophilia." The number of individuals in the two sexes in hemophilia was shown to be normal by Macklin.

Most of our cases were of recent European extraction. The family extractions (known in 38 of the families) were "New England" 6; Nova Scotia 7; Irish 8; Italian 7; Jewish 3; English 2; Eastern European 5. There were no Orientals or Negroes in the present series, although hemophilia has been reported in both mixed and presumably full-blooded Negroes and six probably authentic cases have been described in native Japanese. Ten of the patients in this series are married with a total of 13 children, 3 males and 10 females. There are no grandchildren.

There were five deaths in the series of forty patients in ten years. Three of these were from conditions quite unrelated to hemophilia; one, age 16, from fractured skull and broken leg following an automobile accident, the second, age 32, from cerebral hemorrhage in terminal malignant hypertension; and the third, age 34, from pulmonary tuberculosis. The fourth, age 21, developed an apparently spontaneous massive hematoma in the left gluteal and thigh muscles with secondary necrosis, slough and sepsis. The fifth death was from rapid submucosal pharyngeal and laryngeal hematoma formation which blocked the airway before help was available.

There were no deaths in this series from acute blood loss, the popularly supposed cause of death in hemophilia. This was in spite of frequent tooth extractions and five relatively serious operative procedures (cf. section on Treatment, "Surgery in Hemophilia"). Moreover, most of the patients at some time have been admitted to the hospital with a severe hemorrhagic episode.
First Hemorrhagic Episode

In 36 of the patients the first hemorrhagic episode was known and varied in time of onset from the age of one week to 13 years. Three were following circumcision in the first two months (two at the age of one week). Eight others had their first bleeding during the first year of life; two developed an hematoma of the head from known trauma, two bled from cut lips, one had an hemarthrosis of the knee, one hematoma around the knees from crawling, one multiple hematomata, and for one the precise nature of the bleeding had been forgotten. The remaining 25 patients experienced their first hemorrhagic episode during childhood, 19 before five years of age having a variety of hemorrhagic lesions not differing essentially from those to be described for adult life and in most following known trauma.

Excessive bleeding from primary dentition occurred in only one instance of the 2.2. in whom the history was available, while 13 of 2.2. had excessive bleeding from secondary dentition. Hemorrhage following the extraction of permanent teeth is much more frequent and will be discussed in a separate section.

Hemarthrosis

Bleeding into joints is the most frequent hemorrhagic episode in adult hemophiliacs. It is usually repeated often so that eventually many joints acquire some degree of permanent damage. Thirty-six of the patients in this series had chronic hemophilic joint disease and almost all of these gave a history of one or more acute hemarthroses. Of the four who exhibited no chronic joint disease and had no history of acute hemarthroses, two had suffered relatively few hemorrhagic episodes of any kind.

Acute hemarthroses and chronic hemophilic joint disease affected the joints in about the same incidence, the knees and elbows being by far the most frequently involved. The ankles, hips and shoulders were affected much less frequently, and the wrists, fingers and toes only occasionally.

Acute hemarthroses frequently occur without known external trauma, although joints, especially those bearing weight, are subject to the continual trauma of movement. The hemarthrosis is heralded by stiffness that soon becomes painful on movement of the joint. It is followed within a few hours by swelling which gradually distends the joint capsule causing severe pain even at rest, being greatly aggravated by motion. Tenderness is exquisite and limited, at least at first, as is the swelling, to the areas where the joint surface is relatively superficial. For example, in the elbows, the areas lateral to the olecranon are swollen, tense and exquisitely tender. The blood may break through the tense capsule and be released into the neighboring tissues, temporarily relieving somewhat the pain and tenderness of the hemarthrosis. When this occurs the blood may dissect superficially giving the typical discoloration of an ecchymosis. However, usually the blood remains confined to the joint and discoloration is then not observed. It is because of this lack of discoloration around a joint that an acute hemarthrosis is sometimes mistaken for other forms of acute arthritis. During the acute phase the joint is usually held in the position of greatest relaxation, the knees and elbows, for
example, in partial flexion, and any attempt to change the position is attended by severe pain.

Usually in from four to six days recovery from the acute phase begins. Pain and tenderness subside a little and the previously tense stretched skin over the joint shows a fine wrinkling. Recovery usually then proceeds rapidly but may require two or three weeks before it is maximal. Residual limitation of motion is common and may become permanent, particularly if the joint has been the object of frequent previous attacks.

Acute hemarthrosis has been mistaken for acute rheumatic fever, rheumatoid, gonococcal and other types of arthritis, but may be readily differentiated if hemophilia is considered.

**Chronic Hemophilic Joint Disease**

Following repeated acute hemarthroses a chronic and often deforming joint disturbance occurs. This is not to be thought of as a chronic hemarthrosis, but rather as the result of frequent irritation to the joint leading to roughening of the joint surfaces and fibrosis together with both areas of bone reabsorption and new bone formation. The description of both acute and chronic hemophilic joint disease by König is the classical one, but a considerable body of literature has been published on the subject. Caffey and Schlesinger point out that coxa plana resembling Perthe’s disease may be the result of joint hemorrhage and further that epiphysseal overgrowth and precocious ossification may be demonstrated by x-ray. Fonio, Newcomer, Lamy, Keifer and Myers, and MacDonald and Lozner, have discussed the clinical and x-ray findings. The latter two papers are based on patients included in the series reported here.

In spite of active preventive measures, such chronically affected joints usually show some limitation of motion and may eventually become ankylosed. The joints are enlarged, the characteristic fusiform appearance being accentuated by atrophy of muscles on either side of the joint. Tenderness and pain on movement are not characteristic of chronic hemophilic arthritis; in fact, if either is present, recent active bleeding has probably occurred.

In only two of this series of forty hemophiliacs was there no evidence of chronic hemophilic arthritis. One would, in fact, hesitate to make the diagnosis of hemophilia without the presence of joint deformity unless the diagnosis could be otherwise conclusively established.

Arising usually after extensive bleeding into and around a joint, Volkmann’s contracture sometimes becomes a serious deformity, greatly limiting usefulness of the extremity. Hemorrhage into the Skin, Subcutaneous Tissue and Muscles

Purpura is not the characteristic phenomenon in hemophilia that it is in purpura hemorrhagica. Ecchymosis and hematomata when they occur usually follow known trauma rather than appear spontaneously as they do in purpura hemorrhagica. Ecchymoses seldom spread extensively but hematomata into subcutaneous tissue often spread until they are limited by fascial attachments.
Bleeding into muscle almost always follows severe trauma and may spread rapidly, usually into the subcutaneous tissue and along fascial planes. Subcutaneous and intramuscular hematomata are usually much larger than superficial examination would suggest. Shock from blood loss is not uncommon, and anemia, icterus (with an increased indirect serum van den Bergh reaction), reticulocytosis and urobilinogenuria follow. Hemorrhage into the gluteal region with spread into the thigh is one of the most common and because of the amount of available space may be extensive and lead to early shock.

**Hemophilic Pseudo Tumor**

Occasionally, bleeding into or around bone tissue may be extensive and persistent enough to interfere with the blood supply and cause reabsorption of bone. This is observed chiefly in the hands or feet and the part may be converted in the course of weeks or months into a swollen, tense sac of old blood and destroyed tissue. X-ray examination is usually misinterpreted as sarcoma because of the soft tissue swelling and bone absorption. Firor and Woodhall reviewed the literature on this subject and reported a case of their own, a 15-year old boy who developed a gradually progressive swelling of the right thumb over 18 months following injury. X-ray revealed absorption of bone and a diagnosis of bone sarcoma was made. Successful amputation was done with the aid of an electric cautery. A 16-year old boy in our series had a similar occurrence which developed over the course of almost a year and involved the left foot from the mid-tarsus distally. The metatarsal bones were almost completely resorbed and an x-ray diagnosis of sarcoma was made. Surgical amputation was done with great care and with a good result.

In addition to the pseudo tumor of the distal end of the extremities, other changes such as calcification in a subperiosteal hematoma have been described as sarcoma. In these instances there may be reabsorption of bone also, making the resemblance to sarcoma of bone the more real. Starker discussed subperiosteal hematoma in hemophilia and Echtermacht described a 13-year old boy with a huge hematoma associated with the left tibia that was mistaken at first for tumor. The patient died three days after amputation.

**Hematuria**

Attacks of hematuria are one of the most frequent hemorrhagic episodes in hemophilia; in fact almost 90 per cent of the patients in our series have had one or more episodes. Recurrent attacks are very common. The attacks are usually spontaneous but occasionally follow direct trauma to the kidney region. In one instance an attack was apparently induced by a prolonged train ride, the patient being frequently jarred while sitting up in the coach.

The onset of hematuria is usually symptomless except for the appearance of red urine. Occasionally pain may herald the beginning of the attack or may occur at any time during the course, but it is most common toward the end. The pain is due to the passage of clots, and its location and character depend upon the site of
clot formation. Generally the pain is typical renal colic indicating that the bleeding is from the kidney or pelvis. Following a bout of pain a clot is sometimes passed during micturition and is usually accompanied by severe dysuria.

An attack of hematuria may last a day or so, or may be prolonged for several weeks, no known factor or form of treatment apparently affecting the duration.

Initial or terminal hematuria are seen occasionally as a complication of disease in the anterior or posterior urethra. The spontaneous hematuria of hemophilia may be confused with any one of the other causes of the symptom for which investigation should be made, particularly if the hematuria frequently recurs. Weil\(^5^4\) believes that hematuria in hemophilia is in most instances caused by the presence of stone. The frequent occurrence of hematuria in the disease makes this appear unlikely.

Although the urine may become quite dark, the actual loss of blood during an attack of hematuria is usually not enough to alter significantly the blood hemoglobin content.

**Pharyngeal and Laryngeal Hematomata**

Hematoma formation beneath the mucosa of the pharynx and larynx is one of the few emergencies in hemophilia because of the rapid occurrence in some of airway obstruction. Fortunately this does not occur very often, although one of the five deaths in this series was from this cause. Baird and Fox\(^5^5\) found seven instances of this complication reported, in four of whom tracheotomy was not performed and who recovered, while three died following this operation. In their own case tracheotomy was done with recovery.

The patient usually complains first of sore throat, loss of voice, or both. With either of these symptoms careful examination of the larynx and pharynx must be made at once. Sometimes the bleeding begins as an obvious swelling on the posterior pharyngeal wall, but more commonly it cannot be seen except by indirect laryngoscopy. In the latter case the hemorrhage frequently discolors the mucous membrane over the arytenoids and spreads down the laryngeal wall to the false and true cords. Fortunately, obstructive symptoms have not occurred in most of our patients, but when they do they may either appear within a few hours or be delayed for a day or so.

It has been our custom to hospitalize each of these patients at once and to keep a tracheotomy kit readily available (see section on Treatment).

Although most instances of pharyngeal and laryngeal hematoma formation appear to be spontaneous, it may follow overvigorous use of the voice, against which hemophiliacs should be cautioned.

**Pulmonary and Pleural Complications**

Pulmonary and pleural bleeding are uncommon complications in hemophilia, although mediastinal and pleural shadows appearing in roentgenograms, presumably from fresh or old hematoma, have been reported.\(^5^6\) Massive hemothorax and hemoptyisis are rare.\(^5^7\) These complications were not observed in our patients.
The Acute Abdomen in Hemophilia

Not only are the usual acute abdominal conditions a problem in hemophilia because of the high operative mortality, but in addition, certain forms of intra-abdominal and retroperitoneal hemorrhage so resemble acute surgical emergencies that the greatest diagnostic acumen and surgical caution must be exercised to avoid a fatal result.

All the common acute abdominal conditions such as acute appendicitis, acute cholecystitis, perforated peptic ulcer, acute pancreatitis, etc., may, of course, appear in hemophiliacs. Although it is difficult to ascertain the degree, bleeding from or into the damaged tissue may complicate these acute abdominal conditions by increasing the symptoms and delaying healing. Where infection is present it may travel with the bleeding, and in this way spread much farther than it otherwise would. Therapeutic procedures will be discussed in the section on treatment.

Hemophiliacs, in addition, suffer a variety of purely hemorrhagic intra-abdominal episodes which both closely mimic and are more frequent than the usual acute abdominal emergencies. In many instances such hemorrhagic episodes are difficult, if not impossible, to differentiate from the common forms of the acute abdomen. Sometimes the course of the illness establishes whether it is purely hemorrhagic or not, but all too frequently the differentiation is obscure and it is extremely difficult to decide not to perform a highly dangerous operation.

Severe upper abdominal pain, usually cramp-like, but sometimes steady and resembling a penetrating or even perforated ulcer, is occasionally seen. The onset is usually progressive over several hours with pain reaching great severity and usually associated with nausea and vomiting. The abdomen may become distended, with upper abdominal tenderness or even generalized tenderness and a board-like rigidity. Moderate leukocytosis is usual. The acute condition usually lasts from one to two days and then gradually subsides over a period of several days or occasionally recurs. To place the bleeding accurately in these episodes is usually difficult. In some instances, intraperitoneal bleeding becomes evident by the appearance of free fluid in the peritoneal cavity, together with signs of acute blood loss. A positive benzidine or guaiac reaction in the stool a day or so after the beginning of the episode indicates bleeding into the gastro-intestinal tract, which may be due only to mucous membrane bleeding from persistent retching and vomiting. Massive melena may sometimes complicate this upper abdominal bleeding syndrome, but hematemesis is rare.

Pain in the midabdomen, usually cramp-like, and resembling small bowel obstruction is a distressing although uncommon complication in hemophilia and is probably due in most instances to bleeding into the bowel wall, the mesentery, or both, and sometimes associated with intra-abdominal bleeding. Moderate distention and vomiting are the rule and are due to paralytic ileus.

Low abdominal pain is the commonest of the abdominal emergencies in hemophilia. Two apparently unrelated forms of bleeding may occur: into the colon wall or the mesocolon, or into or around the iliopsoas muscle. In the first instance, bleeding into the colonic wall or mesentery, the signs are usually those of partial
bowel obstruction: vomiting, cramplike abdominal pain, and abdominal distention. A tender, low intra-abdominal hematoma usually forms after a day or so, and finally after several days it may discharge its contents into the bowel with the sudden appearance of melena. Patients exhibiting this condition have been described by Vance and Platou and Platou.6

Retroperitoneal bleeding is more common in the low abdominal syndrome than that associated with the colon, and is usually due in these instances to bleeding into or around the iliopectos muscle. The fact that 15 of our 40 patients had at least one episode of iliopectos hemorrhage illustrates its frequency and importance as a complication of hemophilia. The syndrome has been described by Birch, Günther, and Fallroth.6 When on the right side, the iliopectos hemorrhage resembles acute appendicitis, although the pain seldom begins in the epigastrium. At first the pain is mild but usually in the course of hours becomes severe. Tenderness to palpation and percussion are often exquisite over McBurney’s point and rebound tenderness is the rule. There may also be tenderness on rectal examination on the affected side. Leukocytosis is almost always present but usually is moderate. The blood loss is seldom sufficient to produce anemia or signs of acute blood loss. A mass due to a retroperitoneal hematoma often appears within 24 to 48 hours and may be mistaken for an appendiceal abscess, even though the latter seldom appears this early after the onset of the symptoms. Occasionally the hematoma spreads distally down the iliopectos muscle and may become palpable at Poupart’s ligament or even in the femoral canal. When this occurs, differentiation from acute appendicitis becomes easier.

Further aid in differentiating iliopectos hemorrhage from other intra-abdominal conditions is the distressing complication of partial or complete involvement of the femoral nerve. This usually begins with pain on the anterior surface of the thigh and may be observed soon after the onset of the bleeding. A positive “psosas sign” may be seen at this time and the hip is usually held in partial flexion. Paresthesiae and usually partial or complete anesthesia often follows within two or three days and weakness or paralysis of the thigh extensors with subsequent muscular atrophy follows. As mentioned above, the acute episode lasts as a rule for but a few days, but the mass when present may disappear slowly or even may remain permanently. Likewise, the femoral nerve damage is slow to heal and hypesthesia, muscular weakness and atrophy may be permanent.

Neurologic Complications in Hemophilia

Spontaneous intracranial hemorrhage is rare in hemophilia in contradistinction to purpura hemorrhagica in which it is the most common cause of death. Bleeding into or around the spinal cord is likewise seldom seen in hemophilia, although retroperitoneal hemorrhage sometimes impinges upon a nerve root as it emerges from the spine producing typical unilateral radicular pain.

Peripheral nerve lesions of varying severity and location are very common and usually complicate hemorrhage into a joint or muscle which is in close proximity to the nerve. Thus, the ulnar and superficial peroneal nerves are frequently damaged
in this way. Retroperitoneal ilio-pectineal hemorrhage affecting the femoral nerve is discussed above in the section on the acute abdomen. A very complete review of the neurologic complications of hemophilia is to be found in an article by Aggeler and Lucia.

**Therapy in Hemophilia**

In addition to the many manifestations of hemorrhage itself, bleeding in hemophilia may complicate other coexistent diseases. The treatment of these primarily nonhemorrhagic conditions may be further complicated by secondary hemorrhage. Treatment is directed both to rectifying the diminished blood coagulability locally and systemically, as well as to whatever nonhemorrhagic condition may be present.

1. **Blood coagulants.** For generations man has been searching for methods to stop bleeding and the number of remedies, both household and medical, attest both to the frequency of the problem and the general inefficacy of the methods of hemostasis. In an effort to halt the excessive bleeding in hemophilia, a great many remedies have been described, most being for parenteral administration. We have had little or no experience with most of these therapeutic agents, many of which have been proven ineffective. Since Weil in 1905, found that the therapeutic effect of blood transfusions in hemophilia was due to bringing the coagulation time to or near normal, this form of therapy has not only passed the test of time, but also is the most physiologic of all the parenteral remedies tried. However, even when the coagulation time is brought to normal with blood transfusions the bleeding may continue.

Since the antihemophilic activity of both blood and plasma gradually disappears when preserved even at refrigerator temperatures it has been our policy to use human whole blood or plasma not over 24 hours old unless, in the case of plasma, it has been separated soon after phlebotomy and preserved in the frozen state. Lyophylized plasma has been shown to be active, but for optimum effectiveness it can not always be depended upon, as several days often elapse between the drawing of the blood and its processing.

In the case of acute blood loss of significant proportions either externally or into the tissues, fresh whole blood is the choice, for it not only provides antihemophilic activity but replaces the loss in both red cell and plasma volume. Plasma, fresh or frozen, is simpler because cross-matching is not required and it is as rich as whole blood in antihemophilic activity. It has been our custom to administer whole blood in the amounts dictated by the severity of the blood loss. If whole blood is not necessary, plasma is given in 100 cc. to 250 cc. quantities for its antihemophilic properties. The reduction in coagulation time is usually to or near to normal. This effect persists for 6 to 12 hours at the minimum and then the clotting time gradually rises to its preinjection level in the course of another 6 to 12 hours (fig. 1). Thus, for continued effect on the coagulation time of the hemophilic patient, blood or its products should be given once or perhaps twice daily during the period of active bleeding.

A hemophilic may vary considerably from time to time in his response to antihemophilic material of known potency. It is important to determine the coagula-
Since this paper has been submitted for publication, two cases of hepatitis probably transmitted with the administration of Fraction I have been observed.

As described above in the section on the coagulation defect in hemophilia, blood plasma fractionation has led to the production of a preparation of human fibrinogen which contains antihemophilic activity and which can be given intravenously to patients with hemophilia. In the dosage recommended there have been no significant reactions observed, and no reported cases of serum jaundice have occurred. In addition to absence of icterogenic properties, the material has the advantages over whole blood and blood plasma that very small amounts need be administered for maximum effect and that it can be easily and quickly given. There is a great deal of variability in the antihemophilic activity of Fraction I as now available, and there are, in fact, instances when fresh whole blood is more effective in reducing the coagulation time. Thus, the material is in no sense a “cure” for hemophilia, but its production is a step toward finding a potent therapeutic substance and hopefully a prophylactic material which could be given in hemophilia much as insulin is to a diabetic. For many years such a preparation has been the dream of both hemophiliacs and investigators. In his lectures to students, Dr. Minot has often referred to this goal. At present the limitations in the avail-

* Since this paper has been submitted for publication, two cases of hepatitis probably transmitted with the administration of Fraction I have been observed.
able quantity of Fraction I and problems of stability and route of injection have prevented its use as a prophylactic. Nevertheless, attempts at maintenance of a reduced blood coagulation time have been made by injecting fresh or lyophylized plasma once a week or more often. Significant prolongation of the interval between hemorrhage has been obtained in this way.

The refractory state to blood and its derivatives referred to in the introduction follows, in some instances, the repeated administration of blood, plasma, or the antihemophilic globulin fraction, and arises during or promptly after an hemorrhagic episode, although occasionally it is spontaneous. The exact nature of this refractory state is still obscure, but recent work has suggested that there may be a production of antibodies to the antihemophilic substance. This observation has yet to be confirmed.

2. Rest and exercise. Although strict precautions must be taken by the hemophilic against trauma, this does not mean that he should live a sheltered, inactive life. Heavy manual labor, prolonged fatiguing exercise, the more vigorous sports, and other activities that require severe physical exertion should not be attempted; however, moderate activity should be encouraged depending upon the physical capabilities of the individual, for it not only gives the individual a sense of equality with his associates, but also helps to maintain muscle tone and joint mobility. It is our impression that the decrease in muscle size and tone which occurs with immobilization and disuse may be an important factor in initiating hemorrhage into the muscles and neighboring tissues. Although it is difficult to evaluate because of the possible cyclic frequency of hemorrhages, bed rest with its attendant inactivity appears to us to be an important predisposing factor to hemorrhage. Thus, a hemophiliac confined to bed for an acute hemarthrosis, for example, not uncommonly develops hemorrhage in other parts of the body. Convalescent patients are therefore encouraged to take moderate exercise. The aid of an expert physical therapist should be available for directing exercise, both while the patient is in bed and during ambulatory convalescence.

3. Use of sedatives and analgesics. The fact that internal hemorrhage in hemophilia is regularly accompanied by severe pain which may last for several days or more, and that repeated episodes may be expected throughout the patient's life makes the choice and use of analgesics difficult and of prime importance. The use of morphine is sometimes necessary, but should be avoided if possible. If it is required, the drug should be administered for as short a period as possible because of the danger of dependence and habituation. Meperidine hydrochloride ("demerol hydrochloride"), also contributing to addiction, has been useful in our hands, but occasions arise in which only morphine is effective. When it is decided to administer these or similar analgesics, maximum effective doses should be used to control the pain.

Aspirin, often fortified with codeine, is often effective for less severe pain, but in the case of codeine too, care against habituation must be taken since moderate pain may be prolonged for weeks, as for example, following an hemarthrosis. Hypnosis with barbiturates may make pain bearable, especially at night.

* Presently available evidence suggests that this refractory state may occur more frequently following the administration of the antihemophilic globulin fraction than following the administration of blood or blood plasma. The therapeutic use of the antihemophilic globulin fraction cannot be advised, therefore, until further studies have eliminated this hazard.
4. Local treatment of external bleeding. Aside from the parenteral administration of blood and its derivatives to reduce the blood coagulation time, many substances have been produced for use locally at the site of bleeding. Some of these preparations are very poor coagulants, and most of those that are effective at all exert their effect as a thromboplastin. That is, they hasten the coagulation of the blood by action with prothrombin and calcium, resulting in the production of thrombin which converts fibrinogen to fibrin. We prefer thrombin as a coagulant because it directly converts the fibrinogen to form a fibrin clot. We have had excellent results with a thrombin prepared from animal blood.*
Thrombin may also be prepared from human blood† and has recently been produced on a large scale as a by-product of the preparation of human serum albumin from plasma.‡

No matter what local coagulant is chosen, adherence should be made to certain general principles. The wound should be cleaned with as little trauma as possible, debris and clots of blood being gently removed. Approximation of the edges may be desired but should not be made with sutures unless absolutely necessary, as each needle hole is another source of bleeding. Thrombin is applied directly to the site of bleeding and is held there by appropriate pressure dressings. It is important to emphasize that the thrombin must be applied directly to the source of bleeding; if not, it will merely form a blood clot in the wound, keeping it open and preventing approximation of the edges, effective hemostasis, and healing. The two principles of treating superficial wounds in hemophilia, then, are first that a known active coagulant be applied to the bleeding surface, and second, that it be maintained there with some form of pressure dressing.

Some of the earliest surgical experiences with hemophiliacs were with the use of cautery, both chemical and thermal. Poland§ in 1850 described a patient in whom pure nitric acid stopped bleeding from a traumatic lip lesion on two occasions. Ericksen‖ in 1856 tells of a 34-year old male who developed an hematoma extending from the ankle to the popliteal space. Following incision, bleeding areas were touched with cautery with cessation of bleeding. Gangrene developed, however, and following amputation by ligature and cautery, the patient died.

Although cautery may temporarily stop bleeding, its use is not advised since surrounding tissues are usually destroyed or damaged, leading to a secondary area of slough and an enlarged area of bleeding. Thus, a ten year old boy seen by one of us had been treated by cautery with dichromate for a clean tongue cut. The bleeding stopped, only to recur two days later with renewed vigor from a larger wound, this time being stopped only by the application of thrombin on a gauze pack held in place by sponge forceps.

5. Surgery in Hemophilia. Operative surgery in patients with hemophilia is hazardous and attended by a high mortality.‖ Friedrich** estimated a 35 per cent mortality following major operations, and his estimate is probably a conservative one. The operative treatment of specific conditions will be discussed in subsequent sections.

Medical literature concerning hemophilia is replete with reports of various surgical procedures which have been attempted. In most instances some form of local or parenteral coagulation therapy was used, often in addition to blood trans-

* "Hemostatic Globulin" (Dried), furnished by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.
fusions. Many of these were listed above (Section 1. "Blood Coagulants") but are not discussed because of their large number and variety and the lack of precise observations of their effectiveness. Some have been shown to be ineffective.

In spite of the high mortality rate, operations, sometimes of considerable magnitude, have been done. Among those reported, some of which were successful but many not, are: appendectomy, gastro-enterostomy, partial gastrectomy, arthroplasty, eye enucleation, prostatectomy, nephrectomy, mastectomy, and various amputations.

If an operation is decided upon, the free use of preoperative and postoperative blood transfusions and, when possible, the local application of thrombin (Section 4) are the only important additions to careful surgical technics. Specific surgical problems will be discussed as they occur in the following sections.

6. Treatment of acute hemarthrosis. When an acute hemarthrosis occurs in the lower extremity, bed rest is necessary; otherwise, the patient may be ambulatory, with a sling or other support if the pain permits. Ice bags to the part give some symptomatic relief. Pain is usually extreme and analgesia is indicated. Compression bandages applied before much swelling has occurred have been found useful by some. Aspiration of the fluid blood in the joint is not recommended because of the danger of infection and, moreover, in our hands has failed to shorten convalescence significantly. Following aspiration of blood the joint pain is usually greatly relieved but returns again in a very few hours. Thrombin preparations (sterile, human) may be injected into an acute hemarthrosis, but this therapy has not yet proven to be of value.

It is usually not possible to place the affected joint in optimum functional position during the acute phase nor do we consider it necessary since as soon as signs of reabsorption of blood appear, cautious active movement up to the point of pain may be begun and gradually increased, usually until the former range of movement is attained. As convalescence progresses and danger from renewed bleeding diminishes, physical therapy is in the form of radiant heat, and whirlpool baths hasten recovery of function. Early active movement and physical therapy are the best preventatives of ankylosis.

7. Treatment of Chronic Hemophilic Arthritis. Treatment of arthrosed or otherwise deformed joints is largely orthopedic and must be undertaken with great care so that hemorrhage is not induced either into the affected joint or at points of pressure. The use of plaster casts which are gradually wedged to the desired position has often been successful. The amount and frequency of the wedging is distinctly less than in nonhemophilic patients, each spreading of the cast being up to the point of first pain. Simple Buck’s extension is also frequently useful but the same precautions must be observed.

Arthroplasty, like other operative procedures in hemophilia, must be seldom undertaken and then only with full knowledge of the mortality as well as the likelihood of a poor result from bleeding into and around the operative site. If operation is decided upon, the suggestions listed under "Surgical Treatment" may be helpful in avoiding complications.

However, in spite of these measures, the joints of patients with hemophilia may
become partially or completely ankylosed with deforming muscle contractures and atrophy. When this happens in the legs, symptomatic calluses usually develop on the feet. Softening and removing these calluses provides only temporary relief, but more prolonged help can be obtained with corrective shoes. Patients with hemophilia can use aids to walking without difficulty, such as canes and crutches, and we have one individual in our series who is successfully wearing a prosthetic for a surgically amputated foot.

8. Treatment of subcutaneous and intramuscular bleeding, and of pseudo tumor. Bed rest with immobilization of the part is usually automatically resorted to by a patient with a large hematoma of the soft tissues. Ice bags, as in acute hemarthrosis, provide some relief, and analgesia is often required. Firm pressure from an elastic bandage over the entire area and especially over the bleeding point, if known, may reduce the bleeding. It cannot be overemphasized that a large amount of blood may be lost into the soft tissues without producing what would seem to be commensurate swelling. A continual watch of pulse, blood pressure, and hematocrit must be made so that shock does not occur. Blood transfusions not only supply the antihemophilic factor but also replace blood lost.

Great care must be taken to prevent ulceration of the skin over the hematoma as infection and renewed bleeding may become major therapeutic problems.

Hemophilic pseudo tumor, with necrosis and readsoption of bone, as well as soft tissues, is a potential hazard when fully developed because of its awkwardness and susceptibility to infection. Amputations have been done for this condition. If undertaken, extreme care must be exerted to see that the blood coagulation time is as close to normal as may be obtained and that the surgery induces the least possible trauma. Thrombin should be placed between the stump and its covering.

9. Treatment of peripheral nerve lesions. Little further than the treatment outlined in section 7 and 8 can be done to treat the neuritis that not uncommonly develops during the active phase of intramuscular or subcutaneous hemorrhage. Complete regeneration of nerves may be expected in the course of time in many instances while some will be left with residual nerve damage. Physical therapy to maintain muscle tone and prevent contracture and bony ankylosis of joints is indicated. When splints are applied to avoid contracture, they should be bivalved so that physical therapy may be instituted.

10. Treatment of hematuria and certain urologic complications. Bleeding from the genito-urinary tract is usually renal in origin and is frequently resistant to treatment, continuing in spite of the repeated administration of fresh blood or its derivatives and satisfactory reduction of the blood coagulation time. Absolute bed rest in the supine position may be tried but in our hands has been largely ineffectual. In occasional patients there may be prompt cessation of bleeding following some form of therapy, but generally after a variable period it ceases spontaneously. Except for the occasional development of a mild blood loss anemia there have been no ill effects from continued hematuria. The ureteral passage of blood clots, particularly frequent when bleeding is decreasing, usually causes severe renal colic and may require the administration of morphine or demerol for relief.

As mentioned above, search should be made, if suspected, for stone, tuberculosis,
malignancy, or other causes of hematuria, particularly if repeated episodes of bleeding occur. Cystoscopy may be performed in hemophilia if necessary and if carefully done, but ureteral catheterization or retrograde pyelography may induce submucosal ureteral bleeding and probably should not be performed.

Operative intervention in urologic problems in hemophilia is extremely serious. Barney in 1933 described a case in which following a necessary suprapubic cystotomy, failure to control the bleeding resulted in death. Mertz and Meiksi reported a patient who died eight days after a nephrectomy for hydronephrosis in spite of repeated transfusions. Hinman, however, successfully removed a prostate in a 66-year old hemophiliac.

Care of the teeth; dental extraction. Dental prophylaxis is of paramount importance in the care of the hemophiliac. It is to the advantage of the patient that he be seen regularly and often by his dentist and that prophylaxis and necessary repair be performed at an early date. Cavities can be filled without fear of hemorrhage although care should be taken to avoid undue trauma to the gums.

However, frequently, due to the failure of the patient to seek dental care or reluctance of the dentist to perform the indicated procedures, extraction is necessary. In conjunction with the Department of Oral Surgery, Boston City Hospital, the method described below has been successfully employed many times in the last five years.

The plan involves reduction in blood coagulation time by parenteral fresh blood or suitable derivates, and the application of thrombin with pressure to the socket provided by a partial or complete denture. By combining these two technics we have been able to perform dental extractions in hemophiliacs with a progressive reduction in the postoperative bleeding so that at present it is minimal.

Before the extraction is performed an impression is taken of the jaw from which the tooth is to be extracted. From this a well-fitting partial or complete denture is made. Its essential features are a labial flange extending from the main body of the denture across the socket from which the tooth is to be removed, and two wire clasps, one on either side of the denture, that serve to secure it firmly in position. Approximately a week prior to the operation, a thin, tightly fitting band of rubber (orthodontia band) is placed about the neck of the tooth to be extracted. During the succeeding several days this band progresses along the tooth root, partially separating it from the adjacent tissues. At times the band will progress rapidly along the root so that it may be necessary to use two or three such bands in order to keep the soft tissues from reapproximating to the tooth after the band has passed.

An hour or so before the actual extraction the patient is given an amount of antihemophilic globulin sufficient to reduce his coagulation time to 15 minutes, or lower if possible. In the event that this material is not available, fresh whole blood, frozen plasma, or its equivalents in antihemophilic activity, may be used. Similar amounts of antihemophilic globulin are routinely administered on the first, second and third postoperative days.

* The principles and technic employed are largely the result of the enthusiastic work of Dr. Stephen P. Malliet, Oral Surgeon-in-Chief, and his staff, particularly Dr. Phillip H. White. We are indebted to them for the details of this presentation which will subsequently be reported in full.
In the majority of our cases, novocaine has been used as an anesthetic although nitrous oxide-oxygen inhalation anesthesia may be safely employed. In extractions of the maxillary teeth it has been the practice of the operator to infiltrate with a fine gage needle the tissues at the free cuff margin of the gingivae rather than using the more conventional type of infiltration. By so doing, the tissues traumatized are localized in one area, over which the mechanical pressure of the denture will be applied. Mandibular block injections are usually necessary for the removal of teeth from the lower jaw, although in this procedure there is danger of causing pharyngeal hematomata.

An attempt should be made to extract the tooth with as little trauma as possible. On occasions, however, small lacerations of the gums have occurred and the socket septa have been removed without increased bleeding.

After the tooth has been removed the socket may be gently sponged and cleaned. Using dried thrombin, an empty novocaine capsule is then firmly packed into the defect and buttressed with a more solid mechanical filler. An oxidized cellulose preparation* has proven to be very satisfactory for this purpose. No attempt is made to suture the gum margins. The denture is then inserted into position, care being taken to see that the flange fits firmly over the socket.

In the majority of instances, there will be insignificant postoperative bleeding. If such is the case the denture is not removed for approximately a week. At the end of this time it may be taken out for a short trial period. If oozing still continues, a small amount of dried thrombin is applied to the bleeding surface and the denture reinserted. This is repeated at one- or two-day intervals until complete hemostasis has been obtained. If more vigorous bleeding occurs, the denture may be easily removed at any time, the socket cleaned of old clots and repacked, and the denture reinserted.

It is of utmost importance to have a well-fitting denture. It is uncomfortable to the patient if it fits too tightly and local pressure necrosis may occur. On the other hand, if it fits too loosely sufficient mechanical pressure will not be applied in the appropriate area or the movements of the denture may dislodge the clot and hemostasis will not be obtained. By adding flanges as needed to the original denture it may be used for more than one extraction. However, a new denture has to be made from time to time to compensate for the shrinkage of the soft tissues and reabsorption of the underlying bone. The unpleasant taste that usually occurs after two or three days' wearing of the denture may be partially alleviated with simple mouth washes.

During the period that the denture is being worn, the patients are permitted to be up and about the ward and to engage in their usual activities. They are able to eat and sleep regularly. Conventional partial or complete dentures can be worn by the hemophiliac without difficulty.

12. Treatment of pharyngeal and laryngeal hematomata. The potential seriousness of pharyngeal or laryngeal hematoma lies in its occasional propensity rapidly to occlude the airway. For this reason, if suspected, the diagnosis must be confirmed by a competent laryngoscopist and, if confirmed, the patient should be hospitalized.

* "Oxy-cel," provided by Parke Davis & Company, Detroit, Michigan.
so that proper supervision is available. A tracheotomy kit is kept near at hand. The diet should be soft or liquid and absolute voice rest enforced. Administration of fresh blood or its derivatives to reduce the blood coagulation time is essential. Generally within 24 hours the swelling begins to recede and convalescence is then rapid and uneventful. If obstruction of the airway becomes imminent, tracheotomy should be done, with the most careful surgical hemostasis and with the liberal use of blood or its derivatives.

13. Abdominal surgery. In the discussion above concerning "The Acute Abdomen in Hemophilia" the difficulty was emphasized of differentiating either intra-abdominal or retroperitoneal hemorrhage from the usual acute abdominal conditions. In this regard, Traum72 reported a patient who was operated upon with a mistaken diagnosis of peritonitis from a ruptured appendix. An hematoma the size of a child’s head was found around the right kidney which was evacuated and packed. The patient subsequently died. Scherkin99 has discussed the differential diagnosis of abdominal symptoms in hemophilia and described a 47-year old hemophiliac in whom a diagnosis of acute appendicitis was made. He was treated without operation in spite of the development of a sausage-shaped tumor in the right lower quadrant which disappeared in eight days. A gangrenous appendix, however, was successfully removed by Prima94 complicated by a fist-sized hematoma in the wound. Cioran95 likewise reported the removal of a perforated gangrenous appendix with a good result.

It is impossible to be didactic concerning operative intervention on patients with hemophilia in whom an acute abdomen is suspected. Two important facts may be reiterated, however. Intra-abdominal or retroperitoneal bleeding is far more common in hemophiliacs than are the usual abdominal emergencies. Secondly, major surgery has a very high mortality rate in hemophilia. With these facts in mind an unnecessary operation usually may be avoided. A case in point is that of Platou and Platou6 concerning an eight-year old hemophiliac who was very ill with signs of intestinal obstruction. He improved following the institution of continuous gastric aspiration. Blood transfusions were administered and operation was delayed from day to day and finally avoided. A diagnosis of bleeding into the bowel wall was made. In our experience this set of circumstances has occurred a number of times and operation has not yet been necessary. Likewise, in patients with pain in the right lower quadrant resembling appendicitis, operation has not been done although their number has been large. An ileopsoas hemorrhage was suspected in each. In view of the work of Crile110 with the use of massive doses of penicillin in peritonitis resulting from appendicitis, the danger of not removing an acutely inflamed appendix may not be as great as it was formerly considered to be. It is probable that occasionally an acute appendix will be missed by this conservative treatment, but again, the operative risk may be as great or greater than that of an unoperated, acutely inflamed appendix.

14. Social, economic and psychiatric implications. An hereditary disease with an outlook of life-long partial disability inevitably brings with it a multitude of social, economic and psychiatric problems. It is the physician’s duty not only to care for
the hemorrhagic episodes, but, in addition, to consider and advise on such matters as vocation, marriage and children.

Rightfully, preventive therapy must begin in childhood as soon as the diagnosis of hemophilia is established. The nature of the disease must be clearly explained to the parents so that they will not only endeavor to prevent hemorrhages but will so orient, care for, and instruct the child that he will grow into as useful and productive a citizen as possible, for only in this way will he be well adjusted, and thus happy. More than most children he must be taught independence and self-reliance and must not depend too much upon his parents. This is often difficult for the rest of the family for the hemophiliac is, of course, subject to frequent bouts of pain which automatically make him the center of attention.

Early in life a vocation must be carefully planned. Too often hemophiliacs grow to adult life with little formal schooling because of frequent illness. Vocational training is likewise scanty so that they are capable only of manual labor for which they are quite unfit. A little consideration of the individual and his bent will indicate whether he is to work chiefly with his brain or his hands. In the latter category, art, architecture, mechanical drawing, watch repairing, electrical and radio work offer opportunities. In some communities vocational training of the kind required by hemophiliacs is available.

Ten of the 28 hemophiliacs over 20 years of age in our series are married and have a total of 13 children. To advise against marriage simply adds another probably unnecessary burden to an already troubled life. However, one can ensure that both partners understand fully the nature of the disease and their responsibility both as to its hereditary implications and to the prognosis for future morbidity. The decision is then left to the individuals concerned. It is certainly well for the prospective bride to have a possible gainful vocation in case of prolonged illness of her husband, but many of our hemophiliacs have been able by careful planning to provide an adequate home.

The hemophiliac is continually exposed from an early age to those who feel sorry for him, want to help him, or even consider him an inferior. In addition, he has frequent illnesses and must bear considerable pain. It requires a strong mental constitution to become adjusted to such a life. Fortunately, most hemophiliacs accept their additional burdens as they come and in this way each period of stress builds a better adjusted individual. The physician by frequent discussions is in a position to aid greatly the individual’s own effort to learn to live with his disease.

REFERENCES

HEMOPHILIA

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