MEDICAL GRAND ROUNDS

February 26, 1976

Southwestern Medical School
Dallas, Texas

CLINICAL DISORDERS OF THE FACTOR VIII MOLECULE

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"Strange it is that our bloods
Of colour, weight and heat, pour'd all together
Would quite confound distinction, yet stand off
In differences so mighty."

All's Well That Ends Well
Act II, Scene iii

OUTLINE

I. INTRODUCTION

Factor VIII disorders, in particular classic hemophilia, have fascinated historians and challenged the talents of a variety of disciplines. In recent years the alliance of basic science and clinical medicine has achieved a renaissance in our understanding of the molecular alterations in these disorders and in a spirited growth in the concept of comprehensive care for the hemophiliac as a total person. As a result, hematology, biochemistry, genetics, psychiatry, and orthopedics have come together to offer the hemophiliac an ever-increasing likelihood of leading a reasonably normal life and interacting with society with a sense of autonomy. Unfortunately, many obstacles remain; it is the purpose of this discussion to elucidate how far and how fast we have come and how much more must be done.

II. THE FACTOR VIII MOLECULE

Clearly one of the most exciting areas of current research in hemostasis relates to the biochemical alterations of factor VIII in hemophilia and von Willebrand's disease. The cumulative research experience from several institutions is ultimately aimed at deriving a biochemical model for the normal factor VIII molecule which can account for certain fundamental clinical differences between these two disorders (Figure 1). In classic hemophilia transmission is sex linked, factor VIII activity is usually quite low, and since platelet function is normal the bleeding time (which measures the platelet plug) is normal. In von Willebrand's disease transmission is autosomal dominant with variable penetrance. The factor VIII levels are usually low, but only rarely as low as that seen in hemophilia. Since there is defective platelet adhesion as well, the bleeding time is prolonged. Presumably these patients lack a substance, termed the von Willebrand factor (VWF), which allows normal platelet adhesion and is thus present in hemophilia. In light of these differences it was reasonable to speculate that the common feature, a decreased factor VIII activity, might result from different mechanisms.

CLINICAL COMPARISONS OF FACTOR VIII DISORDERS

	Hemophilia	V.W.D.
Transmission	X-Linked	Aut. Dom.
Factor VIII Activity	↓ ↓	↓
Bleeding Time	Normal	Abnormal
Platelet Adhesion	Normal	↓
V.W. Factor	Normal	↓

Figure 1

It became crucial to purify the normal factor VIII molecule in order to allow comparison of these disorders. Investigations of the factor VIII molecule have been difficult in the past because the protein circulates in trace amounts, is extremely labile, and is difficult to separate from fibrinogen. Recently, however, several investigators have shown that highly purified factor VIII is a very large glycoprotein with a molecular weight greater than one million daltons (1 - 7) (Figure 2). It is composed of an undetermined number of large subunits, joined by disulphide bonds which are identical in size (195,000 molecular weight) and electrical charge (7). Astoundingly, when

these same purification techniques are applied to hemophilic plasma, a protein similar to normal factor VIII but lacking procoagulant activity is recovered in normal amounts (6 - 8). This observation has led to the conclusion that hemophiliacs do not lack the factor VIII molecule, but instead have low factor VIII activity due to synthesis of a functionally aberrant clotting factor. By contrast, plasma from patients with classic von Willebrand's disease contains only small amounts of this protein, indicating that these patients have decreased factor VIII activity due to decreased synthesis of the normal procoagulant protein.

FACTOR VIII: BIOCHEMICAL COMPARISONS

	Normal	Hemophilia	V.W.D.
Native Mol. Wt.	1-2 M	1-2 M	1-2M (?)
Subunit M.W.	195,000	195,000	195,000 (?)
Factor VIII Activity	N	↓ ↓	↓
Factor VIII Protein	N	N	↓
Factor VIII Antigen	N	N	↓

Figure 2

These biochemical determinations confirmed immunologic observations that a rabbit antibody to purified normal factor VIII demonstrated normal amounts of factor VIII-related antigen in hemophilic plasma and reduced antigen in von Willebrand plasma (9-10). It was intriguing, then, that in hemophiliacs the factor VIII antigen was present in normal amounts and that, since their platelet adhesion was normal, they had normal amounts of the von Willebrand factor. In von Willebrand's disease there

was reduced amounts of both factor VIII-related antigen and the von Willebrand factor. This usual (but not foolproof) correlation of factor VIII antigen and von Willebrand factor raised the possibility that they were properties of the same molecule. Indeed, plasma fractions rich in factor VIII corrected the abnormal platelet adhesion in patients with von Willebrand's disease (11). These observations led to the obvious experiment by Bouma et al. in 1972 (12). Highly purified normal human factor VIII, with normal activity and antigen levels, was shown to demonstrate von Willebrand factor activity by correcting <u>in vitro</u> abnormal platelet adhesion of blood from a patient with von Willebrand's disease. Highly purified hemophilic factor VIII, with very low activity but normal antigen levels, also corrected the abnormal platelet adhesion. Subsequent confirmation of the association of activity, antigen, and von Willebrand factor has led to the following conceptual model for the normal factor VIII molecule and its alterations in classic hemophilia and von Willebrand's disease (Figure 3).

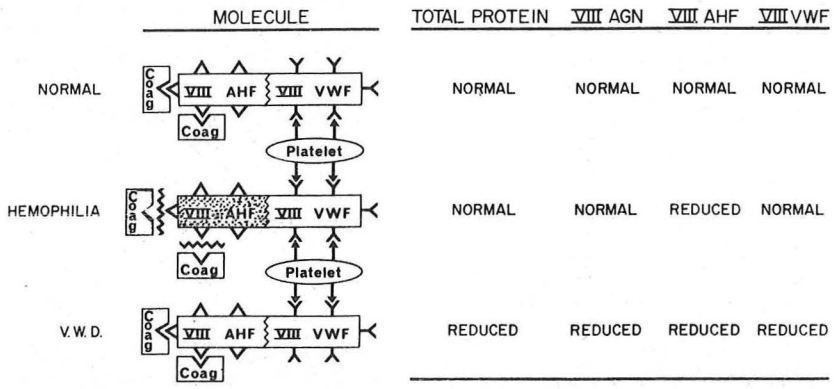


Figure 3. Molecular Model for Factor VIII Disorders

The normal human factor VIII molecule is capable of at least two hemostatic functions. A portion of the molecule is apparently devoted to procoagulant activity within the coagulation cascade and may be termed $VIII_{AHF}$. Another portion of the molecule contains the von Willebrand factor and confers upon the platelet the ability to undergo normal platelet adhesion to vessel walls. This portion is termed $VIII_{VWF}$. Total circulating factor VIII protein is normal, and the rabbit antibody to purified factor VIII recognizes normal factor VIII antigen levels ($VIII_{AGN}$). In classic hemophilia a normal amount of factor VIII protein is present and antigen levels are normal, but the procoagulant portion is deranged, perhaps through an amino acid substitution, leading to decreased coagulation activity. The portion containing the von Willebrand factor is intact and platelet adhesion is normal. In von Willebrand's disease the molecule itself has normal procoagulant and von Willebrand factor portions but total synthesis of the protein is reduced. This results in low procoagulant activity and reduced platelet adhesiveness. This model implies that, although there is a platelet functional defect in von Willebrand's disease, the platelets themselves are normal. This is indeed true, and von Willebrand's platelets, when suspended in normal or hemophilic plasma, which contains normal VWF levels, undergo normal adhesion.

One must reconcile this model with genetic observations, since the defects and activities in these diseases are inherited by different modes. McKee postulates that the procoagulant portion of the molecule is located in the protein portion of the glycoprotein and that the von Willebrand factor activity is related to the structure or attachment of the carbohydrate portion of the glyco-protein. Hemophilia could be explained by sex-linked synthesis of an altered procoagulant of the protein portion, whereas von Willebrand's disease could be explained by an autosomally controlled post-transcriptional defect related to the carbohydrate moiety (13).

The above factor VIII model places the procoagulant activity and von Willebrand activity on the same molecule. However, recent observations by numerous investigators suggest that these two entities may reside on separate molecules closely

associated in plasma, perhaps by formation of a factor VIII complex. It has been shown that under suitable laboratory conditions, factor VIII can be separated into a high molecular weight fragment, which has the properties of the von Willebrand factor and factor VIII antigen, and a low molecular weight fragment which has procoagulant activity (14 - 22). Also, endothelial cells have been shown to synthesize the von Willebrand factor but not factor VIII procoagulant activity (23). It is tantalizing that the cells in closest proximity to vessel tears synthesize a protein which promotes platelet adhesion. Where the procoagulant portion is synthesized is not clear, but the liver may be a major site (24, 25). Thus, an alternate model for factor VIII suggests sex-linked synthesis of the procoagulant, and that under autosomal control endothelial cells synthesize a separate molecule, the von Willebrand factor. These two molecules then become associated as a factor VIII complex (Figure 4).

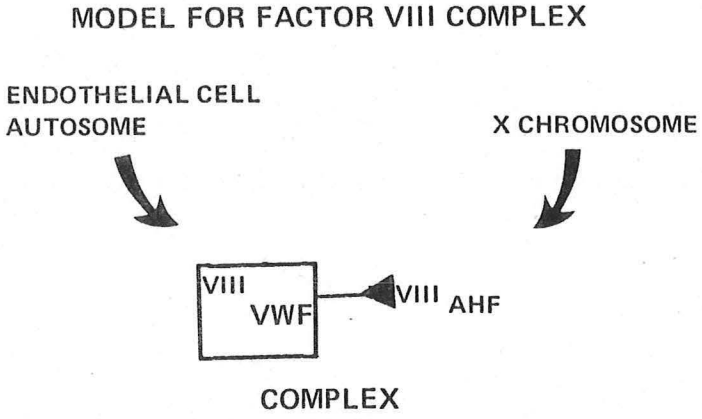


Figure 4

This alternate concept, while provocative, has itself been challenged (13, 26) and at the present time one cannot reconcile the conflicting data to allow an adequate factor VIII model to explain these disorders. It is clear, however, that "factor VIII" is exceedingly more complex than we naively thought in the past, and that it is associated with properties which contribute both to the coagulation cascade and to platelet adhesion to vessel walls.

III. CLASSIC HEMOPHILIA

A. Historical Background

Hemophilia is as old as man's recorded history. In ancient Egypt, a woman whose first son bled to death from a minor wound was not allowed to have further children, and Hebrew law waived the duty of circumcision if two successive males suffered fatal hemorrhages (27). The first significant description of the disease in the medical literature is credited to John Otto in 1803, who collected stories of several New England and Maryland families with hemophilia, some extending back to the early 1700's. Although he apparently saw no patients, he knew much about the disease and wrote that only some males were bleeders. Females were exempt but transmitted the disease to their sons (28). In 1813 Hay wrote, "children of bleeders are never subject to this disposition, but their grandsons by their daughters," (29). These observations on inheritance were formulated by Nasse in 1820 and "Nasse's law" (30) was taught to generations of medical students until sex-linked inheritance was placed in genetic perspective by Mendel in the early 1900's. Nasse, like Otto, did not see a case of hemophilia.

The origin of the word is credited to Schönlein (31). He apparently coined the work in connection with his lectures to medical students in the early 19th century. One of the students, Friedrich Hopff, used the word in the title of his 1828 dissertation (32), attributing the origin to his professor, yet Schönlein never published on the subject. Thus hemophilia and its inheritance were described by physicians who had not seen the disease and it was named by a physician who did not write about it.

B. Genetics

Hemophilia is a sex-linked, recessive defect originally resulting from the mutation of a gene in the X-chromosome of the germ cell - either the sperm of the father or the egg of the mother. If the child is a male, he will be a hemophiliac; if a female, she will be a carrier of the disease and will rarely suffer from it. All sons of the hemophiliac escape the disease, because they derive from their father only the normal Y-chromosome. All daughters of the hemophiliac inevitably receive a defective X-chromosome from their father and thus become obligate carriers of the disease. When female carriers conceive, there is a 50% chance than any son will inherit the defective chromosome, thus becoming hemophilic. There is also a 50% chance that any daughter will inherit the defective chromosome and become a carrier (Figure 5). There are two types of sex-linked hemophilia. The majority of hemophiliacs have hemophilia A, which is characterized by a chromosomal defect causing decreased factor VIII activity. Hemophilia B is the result of decreased factor IX activity.

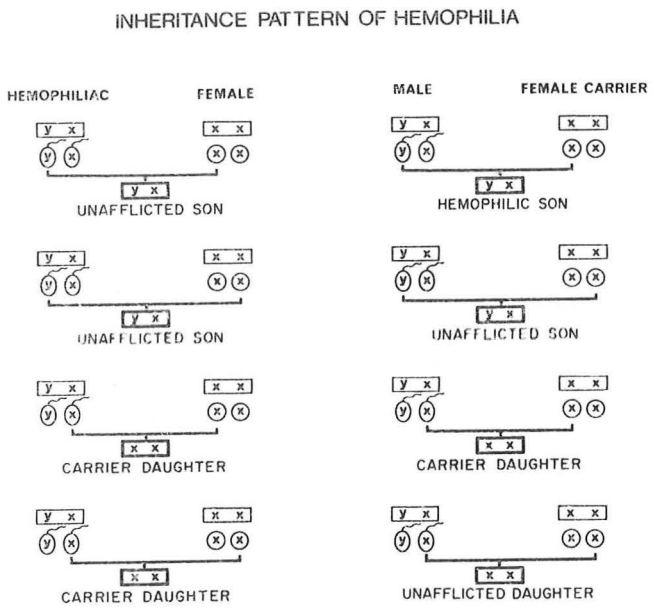


Figure 5 (from Reference 33)

The most famous illustration of the genetics of the disease is demonstrated by the "royal" hemophilia which began with the eighth child of Queen Victoria, Prince Leopold. Victoria, as a result of a spontaneous mutation, was the first carrier of the hemophilic chromosome; besides conceiving Leopold she also conceived two carrier females, Alice and Beatrice, whose descendants developed hemophilia. Since the existence of two different sex-linked hemophilias was not demonstrated until 1952, it is not known whether the royal family was afflicted with classic hemophilia A or hemophilia B (33, 34).

C. Prevalence

Though many hemophiliacs did not, until recently, live into adulthood, hemophilia has maintained itself due to the high incidence of spontaneous mutation which accounts for 40% of all cases. According to The Pilot Study of Hemophilia, there are approximately 25,500 severe and moderate hemophilic patients in the United States (35). Since 80% of hemophiliacs have hemophilia A, one can project that there are 20,000 patients with classic hemophilia.

D. Clinical Features

Deficiency of factor VIII activity is the most common inherited coagulopathy associated with severe bleeding. The bleeding history dates back to early childhood, often with circumcision, but the hemorrhagic diathesis may not be obvious until several months after birth, especially when the child begins to crawl. The clinical severity varies considerably from family to family, but among afflicted members of the same family the severity is approximately the same. The degree of abnormal bleeding is best related to the level of factor VIII activity which tends to remain constant throughout life (Figure 6). A patient with less than 1% activity has a severe hemostatic defect; spontaneous hemorrhages are frequent and are often preceded by periods of anxiety. Even small quantities of factor VIII offer some protection, and patients with greater than 3 to 5% activity are little troubled by spontaneous bleeding. Mild hemophiliacs may lead fairly normal lives, and diagnosis is often made when bleeding occurs under the stress of dental extraction or other surgery (36).

RELATION OF FACTOR VIII ACTIVITY TO CLINICAL SEVERITY IN HEMOPHILIA A

Factor VIII Activity (% normal)	Clinical Features
<1	Severe, crippling form of the disease. Bleeding into joints common. Deep tissue hemorrhage, urinary tract bleeding. Frequent hospitalization necessary.
1 – 3	Gross bleeding after minor injuries. Occasional bleeding into joints and other spontaneous bleeding manifestations.
3 – 15	Severe bleeding after minor trauma and surgery. Spontaneous bleeding rare. Often diagnosed only after an episode of postoperative bleeding.
15 – 40	Increased bleeding only after major trauma and surgery. Often not diagnosed.

Figure 6
(Modified from Biggs and Macfarlane, Reference 36)

Patients with platelet disorders tend to have bleeding which is manifested by petechiae, ecchymoses, and oozing from mucous membranes. Superficial bleeding responds to local pressure. In contrast, patients with hemophilia or other plasma coagulation deficiencies tend to have bleeding which is delayed and affects deeper structures (Figure 7).

CLINICAL MANIFESTATIONS OF HEMOPHILIA

Hemarthroses
Hematomata
Neurologic Complications
Hematuria
Bleeding from Mucous Membranes
Hemophilic Cysts (Pseudotumors)

Figure 7

Hemarthrosis is the most frequent indication for admission to a hospital. Although any joint may be involved, the knee is most frequently involved, followed in frequency by ankle, hip, elbow, wrist and shoulder. Over time there is extensive destruction to the joint, with associated muscle wasting and soft tissue contraction. Prior to the use of factor VIII concentrate, 80% of severe hemophiliacs had impairment of at least one knee joint by the age of ten (37).

Hematomata are usually subcutaneous or intramuscular. Bleeding may occur in any muscle but the lower part of the body is most vulnerable (calves, thighs, buttocks), and such bleeding may be followed by permanent deformity. Hematomata notoriously dissect down facial planes, and bleeding into the neck or the mouth may lead to acute air way obstruction. Retroperitoneal bleeding is fairly common and occasionally bleeding into the abdominal cavity occurs.

The most common neurologic complication arises from an intramuscular hemorrhage, and compression of peripheral nerves may result in excruciating pain, paresthesias, and muscle atrophy. Because of the frequency of bleeding into the iliopsoas muscle, the most frequently involved nerve is the femoral. A major cause of death is intracranial bleeding, which occurs in 10% of all hemophiliacs. Antecedent trauma, which would allow expectant therapy, is present in only half the cases and mortality is high. Subarachnoid hemorrhage carries the best prognosis, intracerebral the worst (38, 39).

Hematuria occurs in 20% of moderate and severe hemophiliacs. While trauma is often a factor, the cause usually cannot be determined. While some feel urologic investigation is not necessarily warranted, intravenous pyelography is safe provided compression of the ureters is not attempted (40).

Certain features are noteworthy regarding bleeding from mucous membranes. In hemophilia, epistaxis is common, hematemesis is uncommon, and hemoptysis is quite unusual. Hematemesis warrants careful investigation since the incidence of bleeding from structural abnormalities, notably peptic ulcer disease,

runs high. Bronchitis, tuberculosis, or other lesions of the lung should always be considered in a patient with hemoptysis. Hemoptysis should be differentiated from bleeding from the epithelium of the mouth, usually caused by tongue biting.

Hemophilic cysts are rare but dangerous complications. These may be simple cysts within muscle as a sequela of a hematoma. They may also cause pressure necrosis of adjacent bone. The most classic variety arises from a subperiosteal hemorrhage which strips the periosteum from the cortex, often compressing it and destroying adjacent muscle. They tend to expand over years, are frequently very large, are difficult to remove, and often resemble malignant bone tumors (41).

Symptoms of hemophilia are frequently cyclical, with a series of bleeding episodes followed by an asymptomatic period. Remissions may last months, even in severe types. When a hemophiliac reaches puberty he usually experiences a decrease in bleeding, and from this point moderate or mild hemophiliacs may lead almost normal lives.

E. Diagnosis

If a male has had repeated joint hemorrhages and a clear-cut sex-linked history, the diagnosis of hemophilia A or B is certain. In the case of a female with factor VIII activity deficiency, von Willebrand's disease must be ruled out. Occasionally a female carrier may have low enough factor VIII levels to cause symptoms (42). Rarely, a female may be truly hemophilic if the mother is a carrier and the father a hemophiliac, and several such instances have been reported (43 - 44). Also, phenotytic females with hemophilia should alert the physician to XY, XO, and XX/XO mosaic karyotypes (45, 46). Lastly, Graham, et al. have described a kindred of hemophilia A inherited by females in autosomal dominant fashion (47).

Laboratory diagnosis is suggested by initial screening tests and confirmed by specific factor VIII assay (Figure 8).

The Lee White clotting time is a poor screening test for hemophilia and is abnormal only in the severe and moderate cases. Factor VIII activity as low as 5% may not prolong the test. The

partial thromboplastin time (P.T.T.) is usually prolonged, but may be normal in mild cases. Since the prothrombin time does not require the presence of factor VIII, it is normal. The factor VIII assay specifically demonstrates the inability of the patient's plasma to correct the P.T.T. of another hemophiliac's plasma. The factor VIII assay is of particular help in clinically mild cases with a normal P.T.T. If the factor VIII is normal, a factor IX assay is performed. Despite the fact that hemophiliacs are called "bleeders", their bleeding time is normal, since their platelets aggregate normally and since normal amounts of von Willebrand factor allow for normal platelet adhesion.

HEMOSTASIS TESTS IN HEMOPHILIA A

Lee White Clotting Time	Abn. or Normal
P.T.T.	Usually Abn.
P.T.	Normal
Platelet Function	Normal
Factor VIII Assay	Abnormal

Figure 8

F. Management

Perhaps no other disease carries as much emotional impact as classic hemophilia. The vision of a child in pain; the sense of helplessness by child and parent; the social and financial strain on the family unit - all underscore the mandatory need to treat the hemophiliac as a whole individual whose own life and the lives of his family members have been dramatically and irrevocably changed. The purpose of this section is to characterize the spectrum of difficulties which the hemophiliac and his family face, and to describe the extent to which these difficulties have been met by the medical and non-medical community.

1. Psycho-social problems: Psycho-social happiness relates directly to the attainment of a sense of autonomy, power, and positive self-image. In our highly competitive society, where many without physical impairment never reach this goal, the task for the hemophiliac (and for his family members who must take on added burdens) becomes even greater in magnitude. From infancy the chronically disabled hemophiliac, shackled to his disease, faces many obstacles to his adult autonomy. (Figure 9).

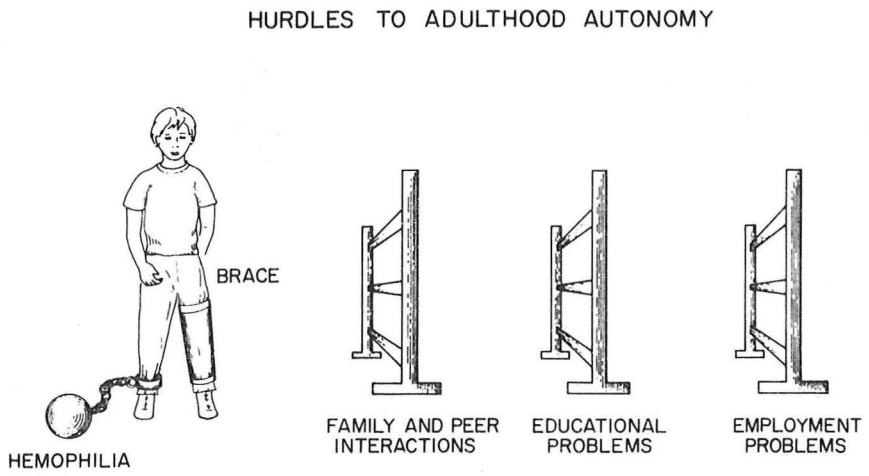


Figure 9

The physical influence of the illness upon the child's ability to adapt is always present. From the outset the disease limits the child's desires to participate in normal aggressive activities. He develops a fear of aggressive drives, since they often produce bleeding, pain, immobilization, and separation from his family. Hospitals and physicians seem to usurp control of his destiny. As a result, passivity is the direction often taken; as will be discussed later, home programs are helping the hemophiliac to attain realistic self-care.

Hemophilia produces a tremendous strain on the family unit. The financial burden is awesome; the mother frequently is guilt-ridden about her role in the genetic transmission and may over-protect the child, encouraging either passivity or maladaptive dare-devil reactions. Such over-protection may force the father into the role of an outsider, denying the child an important influence toward his own sense of masculinity (48). Katz has pointed out that these early experiences related to a self-image of inadequacy carry into later years as an inability to assume adult social and employment responsibilities (49). The psychologic burden on family members promotes divorce, and delinquency is high among the attention-deprived siblings. Because of the physical disability and associated lack of school attendance, it is difficult to form adequate peer relationships.

There is a stunning discrepancy between measured intelligence and educational achievement in the hemophiliac. Dietrich, reporting on the hemophiliacs in the Los Angeles area, found that the average I. Q. among youngsters of a representative sample was 117. However, their academic achievement in junior high school was two years below the national average. While reading levels were commensurate with their I. Q.'s, spelling and arithmetic were significantly below normal (50).

The reasons for this discrepancy are numerous. Hemophiliacs often enter school emotionally tied to Mother and have not reached the degree of autonomy and adequacy necessary for competition. They tend to fall behind in school because of frequent absences due to their disease. Teachers may become part of a "self-fulfilling prophecy". Since the child is disabled, they might feel he should not be overtaxed.

In recent years educational opportunities for the hemophiliac have begun. New national legislative emphasis is being placed on pre-school education. Attendance in classes with their non-disabled peers is desirable, but additional special programs are being initiated to provide continuing education for the child when he is hospitalized or recuperating at home.

The vocational adaptation of hemophiliacs has been recently reviewed by Katz (52). His 1965 study found that 20% of hemophiliacs of working age were unemployed, a rate four times that of the general population. Another 15% of hemophiliacs had never worked and were passive and apathetic. Within

the 65% who were working there was no direct correlation between the severity of physical symptoms and occupational status (53). More recent surveys continue to show high unemployment, job difficulties due to the disease, and work in inappropriate jobs (54 - 57). These findings are logical end points considering the educational under-achievement and lack of self-confidence. Indeed, Katz has concluded that the hemophiliacs' employment status is as much dependent on the individual's self-perception as upon the degree of disability (52). The problem is compounded by inadequate career counseling and employer prejudice against hiring hemophiliacs. Through the efforts of the National Hemophilia Foundation, vocational guidance and employer awareness are being offered by the Federal-State Vocational Rehabilitation Program and the Department of Health, Education, and Welfare.

In summary, the hurdles to adult autonomy can only be overcome by measures, largely generated by the community, which are designed to give the hemophiliac the chance to develop a special view of himself despite his disease.

2. Replacement therapy:

a. Demand on blood resources. Modern treatment of hemophilia is obviously dependent upon the avilability of an adequate supply of blood from which factor VIII activity can be recovered. Unfortunately, treatment of hemophilia is only one of the several demands placed on the nation's limited blood supply. Other demands call for increasing use of red cells, albumin, and concentrates of platelets and granulocytes. These increasing demands for blood products are being met, in part, by the use of component therapy. By separating red cells, plasma, platelets, and white cells, a single unit of blood can serve the specialized needs of many patients. Still, the blood needs of the hemophilic population are staggering and have been summarized by Stengle in Table 1. This is a tabulation of the equivalents of units of whole blood calculated to be required in three alternate programs, based on calculations from the Hemophilia Pilot Study. The first column assumes that all patients would be treated on an episodic basis and that cryoprecipitate would be used. The second column displays episodic treatment with dry concentrates. The difference between the 3,150,000 total in the first column and 8,751,000 in the second

is solely the result of the difference in percentage yield using the different products. The third column assumes that all moderates remain on episodic care and severe patients are on a prophylactic program, all factor VIII being given as cryoprecipitate. The 13,550,000 total exceeds by more than 4 1/2 million units the total blood collected in 1970 in U. S. blood banks. The use of dry concentrates instead of cryoprecipitate for prophylaxis results in a multiplication of the total units required by a factor of 3 (58). Also, these figures are based on a presumed 50% yield of factor VIII in cryoprecipitation, yet recent figures suggest an average yield of only 40% (59).

In summary, the needs of the hemophiliac are great, and prophylactic care for the hemophiliac, the ideal therapy, is impossible considering the blood resources of the nation.

ESTIMATED POTENTIAL DEMAND BY HEMOPHILIA FOR BLOOD PRODUCTS

	Equivalents of Units of Whole Blood		
	Episodic Infusion		Prophylaxis for severe patients
	Cryoppt.	Dry Conc.	
Severe pts.	2,331,500	6,475,000	12,736,000
Moderate pts.	819,000	2,276,000	819,000
Total Units Whole Blood	3,150,500	8,751,000	13,555,000

Table 1
(Modified from Stengle, Reference 58)

b. Factor VIII concentrates. It is incredible that reasonable factor VIII concentrates were not developed for

clinical use until the 1960s. Prior to that time transfusion therapy for hemophiliacs had evolved little since its beginning in 1840 (60). The use of citrated plasma rather than whole blood began in 1923 (61), and with the advent of blood banking in the 1930's transfusions became an integral part of hemophilic therapy. Yet it was obvious that with catastrophic bleeding hypervolemia and congestive heart failure prevented adequate factor VIII replacement by plasma.

While Blomback's purification techniques in the late 50's represented the beginning of concentrate therapy (62), the advent of a concentrate with reasonable potency began with a fortuitous observation by Pool and Robinson. They described how "it was by chance observed that the AHG content of the last few drops of plasma left in a bottle after a transfusion was greater than that of the freshly transfused unit" (63). From this sprang the discovery of cryoprecipitate in 1965, whereby the cold precipitate could be recovered from fresh-frozen plasma thawed at refrigerator temperature (64).

The discovery of cryoprecipitate has been the single most important advance in hemophilic care. Recently, concentrates with even greater potency have been developed, usually available as lyophilized concentrates. Their cost is greater than that of cryoprecipitate, chiefly due to lower yields from plasma. Because of the availability of these concentrates, severe bleeding episodes and virtually any surgical procedure (open heart surgery, craniotomy) can be managed, since high factor VIII activity is achieved with small volume infusions. Table 2 lists the available concentrates.

Side effects of factor VIII concentrates are noteworthy (Figure 10). Anaphylactic or febrile reactions are common, usually occurring within an hour but sometimes up to 24 hours after administration. These reactions are often controlled by antihistamines, but epinephrine is required in severe reactions with bronchospasm. Hepatitis has been a serious problem which is being reduced by the use of volunteer rather than commercial (paid) donors and by careful screening for the hepatitis B antigen (65). Hemolysis is a rare event but may occur with infusions of concentrates containing anti-A or anti-B isoantibodies (66, 67). Thrombocytopenia, a common sequel to the use of animal concentrates and seen as a washout phenomena following

massive whole plasma infusion, is apparently not seen with human concentrate therapy, but alterations of platelet function are known to occur (68, 69). Protein antigenicity has been implicated in the 25% incidence of increased IgG and IgM in hemophiliacs, and amyloidosis has been rarely noted in multiply-transfused bleeders (70 - 72). Although it was feared that the use of concentrates might cause an increased incidence in circulating antibodies to factor VIII, recent data have not shown this to be true (73).

FACTOR VIII CONCENTRATES

Cryoprecipitate

Dry Concentrates

- **AHF (Abbott)**
- **Factorate (Armour)**
- **Hemofil (Hyland)**
- **Humafac (Parke Davis)**
- **Koate (Cutter)**

Table 2

FACTOR VIII CONCENTRATES: SIDE EFFECTS

Anaphylactic or febrile reaction

Hepatitis

Hemolysis

Platelet dysfunction

? Amyloid

Figure 10

c. Specific management. The successful management of hemophilia depends largely on the infusion of factor VIII in amounts sufficient to arrest spontaneous or traumatic bleeding and to prevent abnormal bleeding at the time of surgery. Guidelines have been established for the level and duration of factor VIII activity desired, dependent upon the clinical situation. Calculation of factor VIII dosage required to achieve a desired level of activity is based on the premise that the blood volume

represents approximately 70 ml per kg body weight. Plasma volume is calculated knowing the estimated blood volume and the patient's hematocrit. Since one unit of factor VIII activity is arbitrarily designated as that present in 1 ml fresh plasma, one can calculate the amount of factor VIII units required to achieve the desired plasma activity. For example (Figure 11), a 50 kg patient has a blood volume of 3500 ml. If his hematocrit is 40, his plasma volume is 60% of 3500 or 2100 ml. To raise his factor VIII level from less than 1% to 100% would require 2100 units, and to raise his level to 40% would require 840 units, etc. Each bag of cryoprecipitate averages approximately 100 factor VIII units, while dry concentrates contain a fairly precise number of units as designated on each vial.

CALCULATION OF FACTOR VIII DOSAGE

Example:

Patient Wt. = 50 kg.

Patient Hct. = 40

Blood Volume = .07 x 50 = 3.5 L. (3500 ml)

Plasma Volume = $\frac{100 - 40}{100}$ x 3500 = 2100 ml.

If desired Factor VIII level 100% —

100% of 2100 = 2100 units

If desired level 40% —

40% of 2100 = 840 units

Figure 11

Crucial to sustained therapeutic levels are an initial loading dose and knowledgeable use of the 12 hour half life of infused factor VIII. Thus, if sustained minimal levels of 40% activity are desired, one must administer a loading dose twice the

amount required (Figure 12). In 12 hours, when the factor VIII activity has fallen to 40%, one then administers half the loading dose, keeping the activity at least 40% by successive q12h infusions. It is often desirable, especially when using cryoprecipitate, to check the response to infusion by specific factor VIII assay.

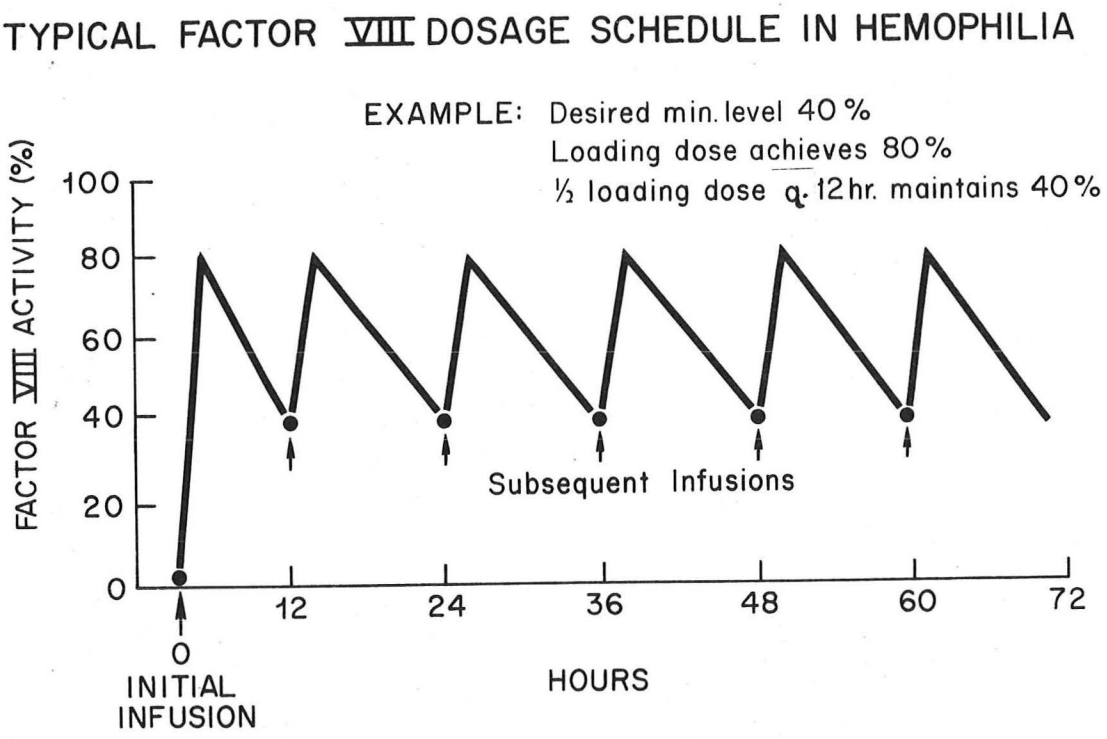


Figure 12

Specific therapy may be largely categorized into 1) treatment of hemorrhages into joints, muscle, and urinary tract, 2) management of surgery and major bleeding, and 3) management of the patient with an acquired inhibitor to factor VIII (Figure 13)

The treatment of a hemarthrosis may be accomplished by a large single infusion of factor VIII on an outpatient basis if the bleed is minimal or moderate and the patient is reliable. A minimal bleed is usually early and subjective to the patient,

with no known trauma and few objective signs. This may be controlled by a single factor VIII dose that achieves a 20% activity (74). For a moderate hemarthrosis or soft-tissue hemorrhage, a larger single infusion achieving 50 to 60% activity is usually successful. However, the patient should be followed, and if no improvement is noted in 12 to 24 hours, a second infusion should be given and hospitalization considered (75 - 77). It must be stressed that factor VIII therapy alone is not total care; non-aspirin analgesics and ice are helpful and immobilization during the acute phase in the position of function helps prevent flexion contraction.

The exact role of therapeutic aspiration in hemarthrosis has not been resolved (78). While orthopedic opinion varies, the general trend is against aspiration except under special circumstances such as 1) failure to relieve unremitting pain, 2) failure to decrease a massively distended joint with adequate replacement therapy, and 3) imminent neurovascular or skin compromise. Aspiration is performed only after factor VIII infusion. The value of aspiration in a chronically swollen joint is questionable. Contraindications to aspiration include: 1) the presence of a factor VIII inhibitor, 2) surrounding skin infection, 3) lack of expertise, and 4) an uncooperative patient (79).

The use of steroids in hemarthroses is also unsettled. Intra-articular injection is not felt to be beneficial. Oral prednisone has been shown in one double blind study to decrease the amount of factor VIII required (80); however, its use has not been generally employed.

Repeated frequent hemarthroses often necessitate prophylactic factor VIII infusions and prophylaxis may also be required during rehabilitation of the joint (81).

Hematuria is generally treated with factor VIII although it may cease spontaneously. While replacement therapy may rarely cause renal tract clots with colic (62), the use of fibrinolysis inhibitors, such as epsilon-aminocaproic acid (EACA, Amicar), is associated with a significant incidence of renal tract obstruction and is to be deprecated (82 - 85). Hematuria is often refractory to factor VIII replacement, and short-term high dose steroids may be of benefit (77).

The replacement management for surgery and major bleeding is outlined in Figure 13; a few areas deserve special clarification.

The classic therapy for dental procedures is shown in the figure. This approach is not applicable to the removal of primary teeth; they usually are safely removed without replacement therapy unless the surrounding tissue is chronically irritated and fragile (86). There have also been recent strides toward reducing replacement therapy in removal of permanent teeth. Walsh and his workers have shown that a single, large infusion of factor VIII and EACA, followed only by 10 days of oral EACA was effective in controlling bleeding and reducing by almost two-thirds the amount of factor VIII required (87, 88). It should again be stressed that ancillary measures are exceedingly important. A vigorous dental hygiene program ultimately saves hospitalization time and dollars. Also, hypnosis is being increasingly employed to help control operative bleeding as well as other bleeding situations (89, 90).

After replacement therapy has been initiated, gastrointestinal bleeding should be thoroughly evaluated, since a structural source is highly likely. Carron, et al., found that of 14 hemophiliacs with this complication, 12 were shown to have a duodenal ulcer (91). Gastrointestinal bleeding in hemophiliacs shows a striking increase as they enter their third decade (92).

Hemophiliacs may also hemorrhage into the retroperitoneal space, notoriously within the iliopsoas muscle sheath, simulating an "acute abdomen." Hematomas may also occur in the gut wall or mesentery, occasionally resulting in an obstruction which necessitates surgery. However, the majority of these patients respond to conservative therapy with factor VIII. Britten and Salzman have pointed out in an extensive surgical review that "more hemophiliacs have died from unnecessary surgical interference than from neglected appendicitis." (93)

Intracranial bleeding is a frequent cause of death in hemophilia (39, 94), and vigorous therapy is required. If there is head injury without apparent bleed, therapy is still required. In the face of suspected bleeding with neurologic deficit,

vigorous replacement therapy may arrest the process, but subdural bleeding appears the most resistant to conservative measures and may be successfully managed surgically under cover of replacement therapy (95). With the available factor VIII concentrates there is little justification for avoiding neurologic or neurosurgical procedures which are deemed necessary.

FACTOR VIII THERAPY IN HEMOPHILIA

Type of Hemorrhage	Initial Dose	Maintenance Dose
Surgically induced Major Surgery Dental Surgery**	1 PV* 1 to 2 hr pre-operatively	½ PV every 8 hr for 24 hr, then ½ PV every 12 hr for 7 to 10 days; then ¼ PV every 12 hr for 5-7 days
Major Retroperitoneal hematoma Neck, thigh, wrist, foot bleeding Hemophilic pseudocyst Gastrointestinal bleeding Intra-abdominal bleeding Head injury	1 PV	½ PV every 8 hr for 24 hr, then ½ PV every 12 hr until 3-5 days after cessation of bleeding
Minor Early minimal hemarthrosis (no trauma; few signs)	1/5 PV	Usually none required
Moderate hemarthrosis (usual) Simple soft tissue bleed (non-vital area)	½ PV	Repeat dose may be required at 12-24 hr
Hematuria	½ PV	½ PV q. 12 hr. until at least 24 hr. after cessation of bleeding

*PV = Plasma volume; the number of milliliters in the PV fraction corresponds with the number of factor VIII units to be administered.
** Dental surgery usually requires only 7 days of therapy.

Figure 13

Management of the patient with an acquired inhibitor to factor VIII is exceedingly difficult (Figure 14). Inhibitors of clinical significance arise in 5 - 10% of hemophiliacs (96). Acquired hemophilia can also result from the appearance of an inhibitor post-partum, in association with other diseases, or in otherwise healthy individuals. A factor VIII inhibitor in classic hemophilia is clinically suspected when a patient fails to respond to factor VIII infusion. Diagnosis is confirmed in the laboratory by demonstrating that patient's plasma specifically inactivates factor VIII within 30 to 60 minutes at 37° C. The process of inactivation is by direct antigen-antibody interaction, and the majority of these inhibitors have been shown to be IgG4 antibodies (97, 98). There is no relation between the development of an inhibitor and the frequency of factor VIII infusions. However, once the inhibitor is identified, subsequent factor VIII therapy may result in an anamnestic rise in the inhibitor titer. Thus one should avoid administration of factor VIII whenever possible. Management of a superficial bleed should be attempted with local measures, such as ice and pressure. When red cells are required they should be washed with saline. Elective surgery is contraindicated. The major problem arises when severe hemorrhage occurs. Treatment with corticosteroids is usually of no benefit. Exchange transfusion occasionally permits successful factor VIII therapy. Animal concentrates may be successful but their antigenicity is extremely high. Frenkel and Stastny were the first to demonstrate a response with administration of 6-MP (99), and this generated an enthusiasm for trials with several immunosuppressive agents. The most promising regimen consists of administering very large amounts of factor VIII as a single bolus with Cytoxan to inhibit the anamnestic response (100). Unfortunately, immunosuppressive therapy is far less successful with classic hemophiliacs than in acquired hemophiliacs (101, 102). Furthermore, inhibitors may spontaneously decrease in titer or disappear entirely, making interpretation of immunosuppressive therapy difficult. Most recently, prothrombin complex concentrates have been used successfully, possibly acting by bypassing the coagulation block and allowing thrombin formation (103). However, these concentrates may be thrombogenic (104), and insufficient data has been gathered on their relative safety and efficacy in this situation (105).

FACTOR VIII INHIBITORS

1) Arise in 5% - 10% of hemophiliacs

2) Are usually IgG 4 antibodies which inactivate factor VIII

3) Unrelated to frequency of factor VIII infusions

4) Treatment is difficult and often unsatisfactory

   a) Minor hemorrhage - local measures

   b) Severe hemorrhage - single large factor VIII bolus plus Cytoxan
      animal concentrates (highly antigenic)
      ? prothrombin complex concentrates

Figure 14

G. Important Areas of Health Care Delivery

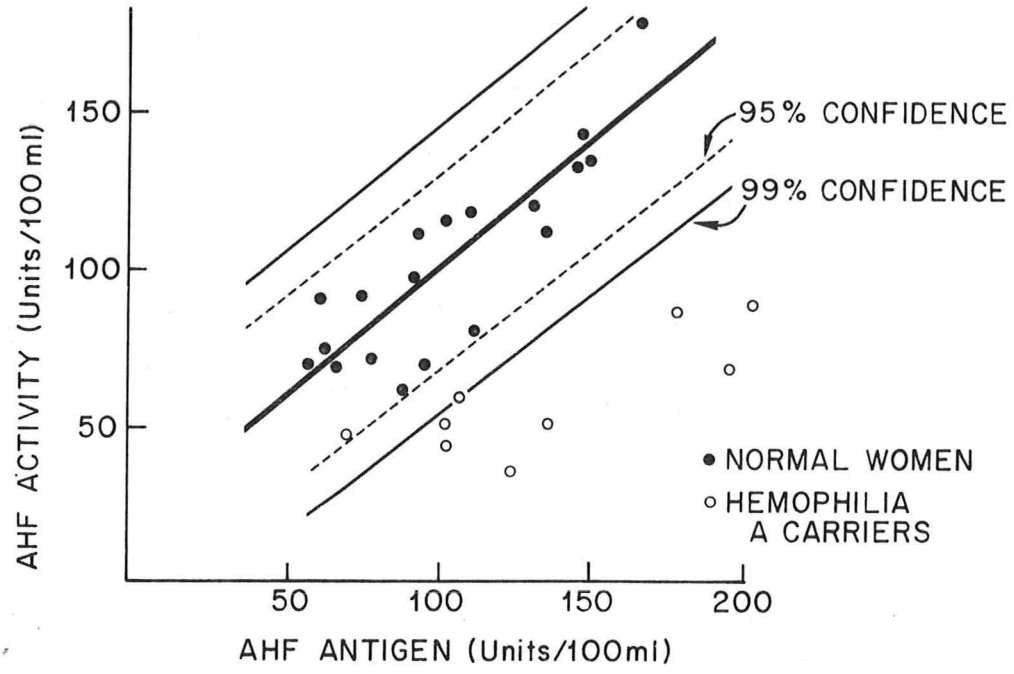
1. Home Therapy. Home therapy for hemophilia is now being offered by a number of medical centers (81, 106, 107). The success of these programs supports the contention that many aspects of a chronic illness can be handled at home by the patient and his family with proper instruction. This concept has been well utilized with insulin therapy and home dialysis. Work by Levine and others has demonstrated many advantages to home infusions, including reduction in hospitalization, absenteeism, factor VIII usage, arthropathy, and total health care costs (107). The overall advantage of this realistic self-care is to free the hemophiliac from the physician and hospital except when necessary, thus allowing a more powerful self-image and sense of autonomy. While potential dangers exist, such as delay in therapy of serious hemorrhage, transmission of hepatitis, and further alienation of the father or siblings (108, 109), these occurrences are uncommon with proper prior instruction.

2. The National Hemophilia Foundation. This organization is a prime force in the development and coordination of medical and social services for hemophiliacs. The Foundation coordinates blood drives, educational meetings, home infusion classes, contributes to research in hemophilia, and promotes legislation for aid to the hemophiliac.

3. Orthopedic management. The orthopedic management of hemophilia is complicated and wrought with controversy. Its discussion is beyond the scope of this text, but several recent reviews are available (78, 79, 110 - 115).

4. Detection of the carrier state and genetic counseling. Since the lyonization phenomenon applies to classic hemophilia, one would predict that random inactivation of either X chromosome in a female carrier would result in an average 50% factor VIII activity. While this is true for large carrier populations, wide variations in activity of carriers and in the normal population limits the predictability of the carrier state in an individual by activity assay alone. However, recent immunologic work has shown that comparison of factor VIII activity with actual factor VIII protein, measured as antigen, allows a high degree of predictability for carriers (116 - 119). According to this method, over 90% of carriers have a significantly lower activity level than antigen level when compared to normal women (Figure 15). These procedures can only be performed reliably on fresh samples. Although these results are exciting, a small percentage of false positive and false negative results occur, and some laboratories have had considerably less success with the method (120). Genetic counseling should be an integral part of the education of hemophiliacs, their parents, and their siblings. Hopefully, immunologic methods for carrier detection will be increasingly refined and employed in this area.

DETECTION OF HEMOPHILIA A CARRIERS



From Hoyer and Rick, Ann. N.Y. Acad. Sci. 240:97-108. 1975

Figure 15

IV. VON WILLEBRAND'S DISEASE

A. Historical Background

In 1926 Erik von Willebrand was a middle-aged physician practicing internal medicine in Helsinki, when one day a five year old girl was brought to him from the Aland islands, which lie in the Gulf of Bothnia between Finland and Sweden. The girl had had a history of severe bleeding, and she told Dr. von Willebrand that four of her seven sisters had died of intractable hemorrhage. Von Willebrand subsequently went to the islands and studied 66 of the inhabitants, 23 of whom had the disorder. Von Willebrand postulated that although their platelet counts were normal, their platelets and blood vessels were functionally abnormal (121 - 123). Over a generation later investigators made the additional discovery that factor VIII activity was reduced in this disease (124 - 127).

B. Prevalence.

The actual incidence and prevalence of von Willebrand's disease is not known. That many patients have very mild symptoms and may not be diagnosed until surgical challenge probably plays a role. Also, some patients have in the past been diagnosed as having mild hemophilia. Despite these uncertainties, von Willebrand's disease may be one of the most common inherited bleeding disorders.

C. Acquired von Willebrand's Disease.

A disease similar to von Willebrand's disease may rarely arise in apparently normal individuals. It has also been described in the course of another disease, usually of immunologic origin, and may disappear with successful treatment of the associated condition (128 - 131).

D. The Stimulating Factor.

As early studies focused on differentiating patients with von Willebrand's disease from patients with classic hemophilia, some astounding results were obtained. When fresh, normal plasma or a factor VIII concentrate is administered to a hemophiliac, his factor VIII rise is immediate and one can predict the rise in activity knowing how many factor VIII units were infused. When one infuses factor VIII into a patient with typical von Willebrand's disease, the peak concentration is not reached immediately but usually 4 to 24 hours later, and the level of factor VIII achieved is far greater than can be accounted for by the number of factor VIII units infused (Figure 16). Most astounding is the fact that the infusion of hemophilic plasma, containing little or no factor VIII activity, into a patient with von Willebrand's disease evokes an even greater response than normal plasma (132 - 135). Cryoprecipitate evokes the greatest response. This characteristic response has been attributed to a substance called the "von Willebrand stimulating factor", and this stimulating factor increases proportionately in plasma or plasma fractions with increasing concentrations of the factor VIII molecule. It appears from the transfusion experiments that actual factor VIII procoagulant activity is not necessary; however, the correlation of stimulating activity and factor VIII protein is unmistakable. The normal factor VIII molecule or complex also contains the von Wille-

brand factor, which shortens the bleeding time in these patients, and fractions progressively rich in factor VIII (and thus $VIII_{VWF}$) are more potent in shortening the bleeding time. Actual proof that the stimulating factor is a property of the factor VIII molecule awaits further studies.

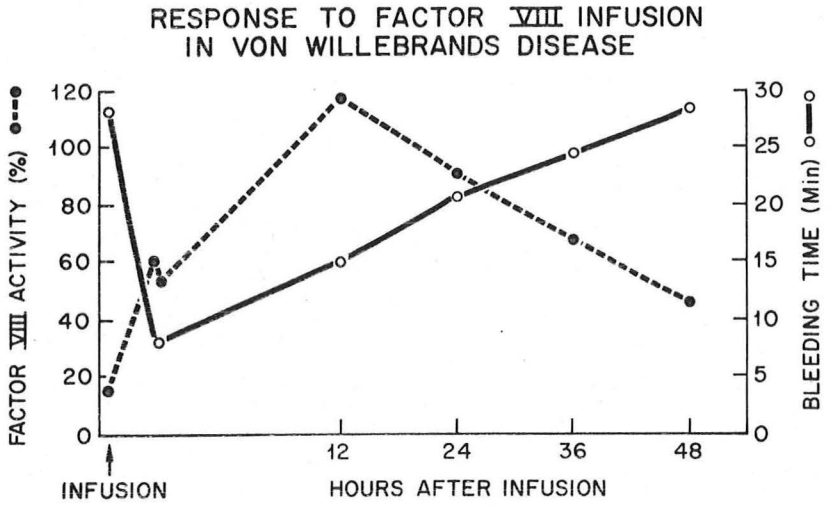


Figure 16

E. Clinical Features (Figure 17).

Since inheritance is autosomal dominant, both sexes are equally affected. However, the severity may vary in a family due to variable pentrance. Symptoms may begin in infancy but more commonly appear later in childhood. Bleeding is usually from the skin and the mucuous membranes, and epistaxis is probably the most common symptom, particularly early in life. Bleeding from the gums and from the shedding of deciduous teeth may be troublesome. Menorrhagia is also common and usually replaces epistaxis as the primary bleeding source at menarche. However, pregnancy often lessens the severity of the disease,

perhaps due to the associated rise in factor VIII (136). The more severe the disease, the more likely the patient is to develop gastrointestinal bleeding, hematuria, and hemarthroses. Although there are many exceptions, the severity of the disease seems to lessen with age. In many patients the diagnosis is considered only after surgical challenge causes prolonged bleeding.

Clinical Features of von Willebrand's Disease

Common	Uncommon
Bleeding from skin	Gastrointestinal bleeding
Epistaxis	Hematuria
Gum bleeding	Hemarthroses
Menorrhagia	

Figure 17

F. Laboratory Diagnosis.

The laboratory diagnosis of von Willebrand's disease has been hampered due to the variability of the disease itself and to the difficulty of the diagnostic tests employed. Perhaps most disconcerting is the long established observation that laboratory abnormalities in any individual may vary considerably from time to time, further confounding interpretation and necessitating repeated testing. Much has been written about the spectrum of von Willebrand's disease, and "von Willebrand's syndrome" is probably more appropriate (135, 137). While the classic patient with low factor VIII levels and a long bleeding time may be easily characterized, a battery of tests are often necessary for proper elucidation of "variants" of the disease.

The observations that these variants may have selective or non-concordant decreases of the various components of the factor VIII molecule or complex has amplified the complicated molecular heterogeneity of this condition. Hoyer has recently summarized the dilemma (138) (Figure 18).

von Willebrand's Syndrome

	Classic V.W.D.	Variant					
		A	A′	B	C	D	E
VIII AHF	↓	nl	↓	↓	↓	nl	↓
VIII AGN	↓	nl	↓	nl	nl	↓	↓
VIII VWF	↓	↓	↓↓	nl	↓	↓	sl↓
Bleeding Time	long	long	long	nl	long	long	nl/long
Transfusion Resp.	V.W.D.	V.W.D.	V.W.D.	brief	var.	—	V.W.D.
Molecular Charge	nl	abn.	abn.	—	abn.	—	nl

Figure 18
(from reference 138, with permission from Dr. L. W. Hoyer)

The partial thromboplastin time may or may not be abnormal since it is often relatively insensitive to mild decreases in factor VIII activity (Figure 19). If the P.T.T. is normal but the disease is suspected, a factor VIII assay is justified. The factor VIII assay reveals reduced activity except in some variants. The actual factor VIII activity is rarely as low as in most classic hemophiliacs, and activities usually range from 2 to 40% (139).

The bleeding time (preferably template method) is usually prolonged, but further testing of platelet function isolates the exact defect, namely abnormal platelet adhesiveness. The effect of reduced von Willebrand factor on platelet adhesion may be demonstrated by filtering blood through a column of glass beads, a technique first described by Hellem (140). Platelets normally adhere to the beads, and the platelet count of the filtered blood is low. In von Willebrand's disease, the blood platelet count approaches the platelet count before filtering, demonstrating a reduced adhesiveness which can be calculated. Since electron microscopy has shown that platelets both adhere and aggregate to the beads, platelet "retention" is now the preferred term. Despite numerous attempts at refinement of this method (141, 142), it is unfortunately difficult to standardize and is subject to a number of variables, limiting its utility in diagnosis (143). Furthermore, abnormal platelet retention to glass beads is not specific for von Willebrand's disease (144).

While platelet aggregation to usual aggregating agents shows no alteration in the vast majority of patients, platelet aggregation in the presence of ristocetin is impaired. This antibiotic was removed from human use due to a high incidence of thrombocytopenia. It was subsequently found that ristocetin aggregates platelets from normal individuals but fails to aggregate platelets in the majority of patients with von Willebrand's disease (145). It has been shown that ristocetin can aggregate platelets only in the presence of adequate von Willebrand factor (146, 147). While this test is rapidly replacing the glass bead retention tests, it also is not totally satisfactory. It may not detect some mildly affected patients (148, 149). Also, it may be abnormal in certain intrinsic platelet disorders; however, the addition of normal plasma fails to correct the defect, in contrast to von Willebrand's disease (149).

A useful clinical tool in classic patients is the effect of transfused factor VIII. Many patients achieve the characteristic hyper-response of factor VIII levels and a shortened bleeding time. Unfortunately, for reasons which are unclear, the bleeding time remains long in some patients, despite adequate levels of von Willebrand factor (139, 150 - 153).

Laboratory Diagnosis of von Willebrand's Disease

P.T.T.	Abnormal or normal
P.T.	Normal
Factor VIII assay	Usually abnormal
Bleeding time	Usually abnormal
Platelet adhesion	Usually abnormal
Routine platelet aggregation	Normal
Ristocetin aggregation	Usually abnormal

Figure 19

G. Treatment.

Treatment of von Willebrand's disease has not been standardized to any extent approaching that of hemophilia. Aspirin and other drugs affecting platelet function are scrupulously avoided as in hemophilia. Fortunately the disease is not severe in most patients and is usually controlled by less vigorous infusion regimens.

The mainstay of therapy for bleeding or surgical coverage is cryoprecipitate, which raises the factor VIII activity and provides von Willebrand factor for platelet adhesion. Adequate factor VIII activity levels are usually achieved without difficulty because of the secondary rise which occurs. A dosage schedule of one bag of cryoprecipitate per ten kg per day has successfully maintained a minimal factor VIII level of 25% (154). Patients undergoing surgery should probably be given a loading dose to raise their factor VIII activity levels to that required for hemophiliacs. Because of the variability of response, each maintenance level should be tailored to the individual by monitoring factor VIII activity and bleeding time.

While other concentrates have also been used, what little work has been done in this area suggests that they may not shorten the bleeding time as consistently as cryoprecipitate (11).

V. SUMMARY

Our understanding of the molecular alterations in factor VIII disorders has been broadened in recent years. These discoveries have led to even more questions, and hopefully the exact biochemical nature of factor VIII will be elucidated in the near future. Therapy for hemophilia and von Willebrand's disease has reached increasing heights of sophistication, yet more work is needed in educational, legislative, and psychosocial areas. With increasing awareness by the physician and the community, these persons may be enabled to fulfill their own needs and to actively contribute to society.

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