Treatment of Factor VIII Inhibitors
Kasper CK: In Coller BS (ed):
Progress in Hemostasis & Thrombosis
WB Saunders Co., 1989, Vol 9, pp57-86

Carol K. Kasper, MD

Treatment of Factor VIII Inhibitors

Factor VIII inhibitors are pathologic circulating antibodies that specifically neutralize factor VIII (FVIII) procoagulant activity. They may occur in patients with classic hemophilia, in postpartum women, in patients with autoimmune and other disorders, or in older adults without underlying disease. The prevalence is low, with affected persons probably numbering less than 5000 per year in the United States, but management, which often is difficult, consumes an exceptional proportion of available resources.

AFFECTED POPULATIONS

Patients with Classic Hemophilia

Inhibitors to FVIII can arise as alloantibodies in patients with classic hemophilia who have been transfused with blood products containing FVIII. Prevalence rates in severe hemophilia, estimated from studies of patients of all ages alive at the time, which probably were not influenced by selective referral to the observers, are about 6 to 8 per cent (1,2). Bias may have been introduced, however, because of the higher mortality rate of patients with inhibitors (3). Schwarzinger et al. (4) found the cumulative risk of inhibitor development in a cohort of patients followed from birth to be 24 per cent by the age of 25 years.

Characteristics of affected patients have been studied in the hope of identifying predisposing determinants, because if such could be found, preventive measures might be devised (e.g., attempting to induce tolerance in utero by injection of FVIII). In a large survey (5) 80 per cent of 163 inhibitor patients had severe

hemophilia (less than 1 U/dl plasma FVIII) prior to inhibitor development, 15 per cent had moderate hemophilia (1 to 3 U/dl FVIII), and 4 per cent had mild hemophilia (4 U/dl or more FVIII). For comparison, of all 284 male patients with classic hemophilia currently registered at Orthopaedic Hospital, 20 per cent have mild hemophilia. Thus, the presence of some functional FVIII probably decreases the risk of inhibitor development; however, patients with mild hemophilia also have less exposure to exogenous FVIII. In another study, inhibitors developed in 31 patients observed prospectively (6), and two of those with severe hemophilia (less than 1 U/dl FVIII activity) had 5 and 9 U/dl FVIII coagulant antigen (VIII:CAg), respectively, a prevalence of cross-reactive material (CRM) positivity similar to that in the general population of severe hemophiliacs. Thus, the presence of some dysfunctional FVIII molecules does not prevent inhibitor formation.

In classic hemophilia, patients destined to develop inhibitors usually do so at an early age (Table 3-1). The incidence of inhibitor development is maximal in early childhood, then gradually decreases; however, inhibitors have developed as late as the seventh decade of life (6). The number of exposures to exogenous FVIII before inhibitor development tends to be low (Table 3-2), especially in patients who develop high inhibitor levels, but occasional patients develop high-level inhibitors only after hundreds of exposures. Patients may develop minimal inhibitors, often transient, in adulthood after thousands of exposures (Kasper, unpublished data).

The tendency for serious inhibitors to develop early in life, and after limited exposure to FVIII, in a minority of patients, suggests genetic predisposition. The concordance of inhibitors in brother-pairs with hemophilia also supports a genetic susceptibility. Inhibitors are found in both brothers 6 times as often as would be expected from the overall prevalence of inhibitors [summarized by Bloom (8)]. Concordance, however, is imperfect: in half of brother-pairs, only one brother has an inhibitor. In two sets of monozygotic twin hemophiliacs, only one co-twin of each pair had an inhibitor, although both had similar FVIII exposure at similar ages (9). An interesting observation of female mate-specific concordance was seen in a canine pedigree (10) in which inhibitors developed after transfusion of canine cryoprecipitate in all five hemophilic grandsons of a hemophilic Schnauzer mated with a spaniel bitch, but in none of nine hemophilic descendants of the Schnauzer's union with a Schnauzer bitch who was his sibling.

Genetic influences also were suspected on observing inhibitors in 20.9 per cent of black patients but only 13.9 per cent of white patients in a study of 1522 patients with hemophilia A in the United States (5). Although the high overall prevalence of inhibitors in that study probably was biased by selection, black

Table 3-1. Age at Discovery of Inhibitors in Classic Hemophilia

Author(s) (Ref.)	*# Inhibitor Patients*	*Percentage by Age (Years)*					
		0–4	*5–9*	*(0–9)*	*10–19*	*20–29*	*30+*
Brinkhous et al. (1)	93			37	25	19	19
Kasper (2)	29	34	14		21	21	10
Gill (5)	187	28	18		20	19	15

Table 3-2. Days of Exposure to FVIII before Inhibitor Discovery in Classic Hemophilia

Author(s) (Ref.)	*# Inhibitor Patients*	*Age Group Studied*	*Exposure (Days)*	
			Median	*Range*
Strauss (7)	17	Pediatric	About 40	21–260
Kasper (2)	29	General	65	10–900+
McMillan (6)	31	General	48	8–250
Schwarzinger et al. (4)	13	Pediatric	25	12–88

patients with inhibitors were not selected preferentially to white patients with inhibitors.

The search for clues to genetic influences has included examination of the major histocompatibility complex, but results are conflicting. In a study of 26 brother-pairs discordant for inhibitor development and their parents (11), no human lymphocyte antigens (HLAs) were found to be associated with inhibitors. Different results were reported by Shapiro (12), who found HLA-A1 to be underrepresented in inhibitor-forming hemophiliacs. He also found an increased frequency of complement types C4A4 and C4B2 in inhibitor formers.

Since in hemophilia B over 60 per cent of patients with inhibitors to factor IX have gene deletions [summarized by Bloom (8)], investigators have sought a correlation between gene deletion and inhibitors to FVIII in hemophilia A (classic hemophilia). Gitschier et al. (13) reported only one deletion, however, in a series of 14 patients with hemophilia A and inhibitor. We also found only one deletion in a series of 14 of our patients with hemophilia A and inhibitor (unpublished data).

Nonhemophilic Patients

Factor VIII inhibitors sometimes develop as autoantibodies in patients with rheumatoid arthritis, systemic lupus erythematosus, other autoimmune disorders, asthma, severe dermatologic disorders, malignancies, drug reactions (penicillin, ampicillin, diphenylhydantoin), or other serious disorders; older patients with no underlying problems (about 46 per cent of cases) and postpartum women are also at risk (14). The incidence of inhibitors in the named conditions, and the overall incidence in the population, is difficult to estimate because the patients are geographically scattered, as contrasted with hemophiliacs, who tend to be treated at specialized centers. For the same reason, we lack studies of any specific characteristics of patients with autoimmune disorders that may predispose them to develop inhibitors.

CLINICAL COURSE

In hemophiliacs, the presence of an inhibitor does not change the characteristic frequency or location of hemorrhages: bleeding usually occurs in single joints, muscles, or sites of trauma. The adverse effect on survival is modest now-

adays. The pattern of bleeding in nonhemophilic patients with inhibitors to FVIII sometimes differs, with dramatic ecchymoses and hematomas of multiple large soft tissue areas and oozing from superficial puncture sites. Death from hemorrhage occurred in some 22 per cent of the 215 nonhemophilic patients with inhibitors studied by Green and Lechner (14), and in 12 per cent of 16 patients studied by Lottenberg et al. (15), often within months of inhibitor development. Thus, nonhemophilic inhibitor patients are at greater risk of succumbing to uncontrollable hemorrhage than are hemophiliacs with inhibitors.

On the other hand, nonhemophilic patients are more likely than hemophilic patients to have spontaneous remissions of inhibitors. Green and Lechner (14) reported that 38 per cent of those nonhemophilic inhibitor patients who were not treated with immunosuppressive agents had remissions. Those patients with postpartum inhibitors or with no underlying disorders, who had low-level inhibitors, were most likely to have spontaneous remissions. In hemophiliacs, spontaneous remissions with return of normal responsiveness to FVIII may occur with low-level inhibitors (e.g., under 2 Bethesda units, see below); we have seen such a course in 16 heavily treated adults and 2 children (unpublished data). In most, the inhibitor was present briefly. In contrast, we have followed more than two dozen hemophiliacs with inhibitors of 3 Bethesda units or more, and have never seen spontaneous, permanent remission in any of them.

Two patterns of immune response to FVIII infusions are seen. One pattern, the most common in hemophiliacs but rare in nonhemophiliacs, is a brisk increase in inhibitor level beginning about 4 to 7 days after exposure and peaking in 2 to 3 weeks; such patients are called "high responders" (16). Further FVIII given when inhibitor levels already are at a peak may not provoke any more rise in the level, perhaps because a nonimmunogenic FVIII-inhibitor complex is made. If no further FVIII is given, inhibitor levels gradually fall (at rates varying from patient to patient), and may even become undetectable (a condition that does not constitute permanent remission, because another course of FVIII is almost certain to provoke an anamnestic response). The other pattern, that of little or no increase of inhibitor level after infusion of FVIII, no matter how often FVIII is given, is seen in a minority of hemophilia patients; such patients usually have persistently low inhibitor levels. These patients are called "low responders." Nonhemophilic inhibitor patients usually fail to mount an anamnestic response to FVIII infusion, regardless of their inhibitor level; presumably, exogenous FVIII is no more immunogenic that the endogenous FVIII continuously produced by the patient.

CHARACTERISTICS OF INHIBITORS

Antibody Types

Inhibitors are immunoglobulins (Igs) of the IgG heavy chain class in nearly all instances; IgM has been observed in two autoantibodies and one alloantibody [summarized by Hoyer et al. (17)], and IgA in two autoantibodies (18,19). Light chains may be either solely kappa (the most common finding in alloantibodies), solely lambda, or both (8).

Among IgG inhibitors, the IgG4 subclass predominates, and it is equally likely

to be the sole subclass found or to be present together with one other subclass, most often IgG1. IgG3 alone has been demonstrated in four inhibitors, but none have been found consisting only of IgG1 or IgG2 (17,20–22). The predominance of IgG4 antibodies is not surprising because they tend to follow prolonged immunization; IgG1 antibodies are found in the primary immune response (23). The IgG4 subclass does not fix complement (and thus is unlikely to be associated with complement-mediated pathology, an important consideration in choosing to treat a patient with FVIII) and appears to be univalent (thus failing to form the lattice needed for precipitation). Although inhibitors are typically described as nonprecipitating, two highly purified IgG alloantibodies of unspecified subclass did form precipitin lines when studied by immunodiffusion and autoradiography (24). Immune complexes consisting of FVIII and the inhibitor may circulate, with some containing quite small amounts of complement class C1q (25). In one study (26), inhibitor epitopes were localized to either or both of the 72-kilodalton (kD) and 44-kD thrombin fragments of FVIII in 64 patients, and to both the 54-kD and 44-kD thrombin fragments in two patients; in some cases different IgG subclasses in inhibitor plasma from one patient were shown to have different degrees of FVIII polypeptide reactivity. These findings suggest that inhibitors are of restricted polyclonal origin.

Reaction Kinetics

The reaction between FVIII and anti-FVIII antibodies has been shown to be time dependent both in vitro and in vivo, an observation relevant to treatment, because rapidly administered FVIII in high doses might be able to participate in coagulation to some degree in some patients with high-level inhibitors before it is completely inactivated. Two patterns of inactivation are observed in vitro (27–32). In one pattern, with second-order kinetics (also called type I, or "simple"), the amount of antibody is related in a linear fashion to residual FVIII after incubation of FVIII and inhibitor plasma for a fixed period of time. If FVIII is present in excess all inhibitor is bound, and if further FVIII is added it is not inactivated. If inhibitor is present in excess all FVIII is bound. These inhibitors react with FVIII antigenic determinants close to the site responsible for FVIII functional activity, and the reaction is not impeded by the attachment of von Willebrand factor to FVIII (33). Type I kinetics are typical of most inhibitors arising in hemophiliacs, and some arising in nonhemophilic patients.

In the other pattern of inactivation, with complex reaction kinetics (also called type II), reaction of FVIII with inhibitor begins rapidly, then slows, but does not reach a stable end point. Some FVIII often is still measurable, but if further FVIII is added it also may be partially inactivated. This suggests that the FVIII-inhibitor complex may dissociate, or that the complex may continue to have some FVIII functional activity. Type II inhibitors appear to react with FVIII antigenic determinants that are partially blocked if von Willebrand factor is attached; if von Willebrand factor is not attached these inhibitors have been shown to neutralize FVIII completely, like type I inhibitors. Type II kinetics are typical of most inhibitors found in nonhemophilic patients, and in some hemophilic patients.

Partial inactivation of von Willebrand factor by some FVIII inhibitors (in both hemophiliacs and nonhemophilic patients) has been suggested in a few studies

(34–36). Thomsen and Forbes (37) found that both allo- and autoantibodies to FVIII impaired ristocetin-induced aggregation of normal platelet-rich plasma. It would be attractive to propose that interference with von Willebrand factor causes the widespread ecchymoses and other superficial bleeding seen in some nonhemophilic patients with inhibitors, but current evidence does not support the existence of such a relationship.

Measurement of Inhibitors

The presence of an inhibitor usually is demonstrated with a prolonged activated partial thromboplastin time performed on incubated mixtures of patient and normal plasma. Another, increasingly popular, method of detecting inhibitors is based on measurement of zones of inhibition of fibrin formation in agarose gels containing normal plasma when dilutions of patient plasma are put in wells and the gels are treated with thrombin or calcium chloride (38,39). In nonhemophilic patients, the specificity of the inhibitor for FVIII rather than for another factor or for phospholipid (as in "lupus" inhibitors) can be determined by comparing assays for FVIII (in which FVIII activity should be equally low at all dilutions of patient plasma tested) with assays for factors IX, XI, and XII [which may appear low if only slightly diluted plasma is assayed because of the effect of the inhibitor on FVIII in reagent plasma, but will appear higher if greatly diluted plasma is assayed (40)].

Determination of the potency of a FVIII inhibitor is useful to decide on the method of treatment and to follow the progress of a patient. Quantitative FVIII inhibitor assays are based on specific measurement of the amount of FVIII inactivated by patient plasma under given conditions of temperature (nowadays always 37°C) and time; an inhibitor unit is defined as the reciprocal of the dilution of patient plasma that neutralizes a specified proportion of the FVIII.

There have been three widely accepted quantitative inhibitor assays. The first (27), now known as the "old Oxford" method, used concentrate as the source of FVIII and defined 1 inhibitor unit as the amount that destroyed 0.75 U of FVIII in 1 hour. That test was superceded for most purposes by the "new Oxford" method (41), in which incubation was extended to 4 hours to allow more complete interaction of FVIII and inhibitor, and 1 inhibitor unit was defined as the amount that destroyed 0.5 U of FVIII. In the United States the "Bethesda" method (42) stipulated pooled normal plasma as the source of FVIII and defined 1 inhibitor unit as the amount that destroyed half the FVIII in an equal mixture of normal and patient plasma in 2 hours. On the average, inhibitors measured in Bethesda units (BU) are 1.21 times higher than the results in new Oxford units (43).

Type I inhibitors can be quantitated meaningfully by the above methods since calculations of unitage based on results with various dilutions of patient plasma are similar. With Type II inhibitors, however, only rough estimates of potency can be made. Characteristically, the more the inhibitor is diluted, the higher the calculated unitage. In the Bethesda method, unitage of type II inhibitors is computed by seeking the least dilution of patient plasma (i.e., the highest concentration of patient plasma in buffer) that inactivates precisely half the FVIII in the incubation mixture. Results with greater dilutions of patient plasma are not valid.

MANAGEMENT OF HEMORRHAGES

Principles

The array of treatment modalities and strategies for inhibitors is great, a reflection of the difficulty of management. Therapy should be monitored with assays of FVIII and inhibitor level. Thus, treatment should not be undertaken outside of centers where these techniques are available.

Minor hemorrhages may subside with bed rest and restriction of motion of the affected area, so that weak clots in the damaged vessels are less likely to be disrupted. At least 25 per cent of early joint hemorrhages improve rapidly without clotting factor therapy (44). Patients with autoantibodies sometimes have widespread vivid ecchymoses, alarming to both the patient and the physician; if bleeding is only superficial, however, such patients may recover on bed rest without blood products.

If a hemorrhage requires clotting factor therapy, one can try to raise the plasma FVIII level either by infusion of human or porcine FVIII (preceded by measures to lower the inhibitor level if it is very high) or by infusion of a hemostatic material that bypasses the need for FVIII, such as factor IX (prothrombin complex) concentrate (PCC). In choosing among these alternatives, one should consider the following issues.

First, some patients, including most of those with autoantibodies, have not been infused with blood products previously and have not been exposed to human immunodeficiency virus (HIV), hepatitis B, non-A,non-B hepatitis, or other blood-borne infections. Vaccination against hepatitis B should commence on diagnosis of hemophilia or of an autoantibody to FVIII in case blood product infusion is needed. Because this requires an injection deep into the deltoid muscle, a very small gauge needle is used, and the dose may be divided.

To the extent possible, the blood product infused should be that least likely to transmit such infections. Porcine FVIII concentrate has been favored for patients with autoantibodies because it does not transmit the above infections; those human concentrates treated by the most vigorous viral inactivation measures may now be as safe.

Second, hemophilic patients known to have dramatic anamnestic responses should not be exposed to FVIII needlessly, because treatment options are limited when inhibitor levels are very high. Most clinicians prefer to use PCC for noncritical hemorrhages in high responders because only a few such patients have anamnestic responses to the small amount of contaminating FVIII antigen. Transfusions of whole blood may provoke anamnesis because FVIII is present in the plasma. Laurian et al. (45) reported that washed red blood cells contained no detectable FVIII or FVIII antigen, and caused no anamnesis, in 10 high-responding inhibitor patients.

Third, if a hemorrhage is critical, an attempt should be made to raise the patient's plasma FVIII level to 30 to 50 U/dl or more, because if such a level can be reached bleeding will stop in nearly all instances. Factor VIII infusions resulting in normal plasma FVIII levels are nearly twice as likely to halt bleeding as are PCC infusions (44).

Temporary Reduction of Inhibitor Levels

When an inhibitor level is high, and FVIII infusion is planned for treatment of a critical hemorrhage, the inhibitor level may be reduced by various techniques: 1) exchange plasmapheresis with or without extracorporeal adsorption of antibodies by various agents; or 2) experimentally, by decreasing the affinity between FVIII and FVIII antibody by changing the calcium ion concentration.

Exchange Plasmapheresis

The efficiency of exchange plasmapheresis has improved vastly with the introduction of continuous-flow cell-separation centrifuges. Francesconi et al. (46) monitored exchange plasmapheresis in five inhibitor patients and found that removal of about 40 ml of plasma/kg body weight (about 3 liters in adults, requiring about 3 hours) halved the inhibitor level. Slocombe et al. (47) performed exchange plasmapheresis of 4 liters with as much as a 90 per cent reduction in inhibitor level; using a large-bore central line, 4 liters could be exchanged within as little as 2 hours. The decrease in inhibitor level is maximal at the end of the exchange, before additional antibody enters the circulation from the extravascular space. Therefore, replacement FVIII should be given immediately after the exchange.

Removed patient plasma usually is replaced with albumin and normal plasma, plus calcium as needed. One group (48) used large amounts of FVIII concentrate as part of the initial replacement fluid to hasten inhibitor neutralization.

Exchange plasmapheresis is practical: 1) if the machinery and skilled personnel are available; 2) if the patient has good peripheral vascular access or if central access can be obtained (and justified by the urgency of the patient's condition and reasonable expectation of successful hemostasis at the site); and 3) if the patient's condition allows a delay of a few hours. If delay is not reasonable, one might be able to slow bleeding with other measures (e.g., PCC infusion; see below) while arranging plasmapheresis. Plasma exchange is especially useful in preparing an inhibitor patient for unavoidable surgery. One may perform exchanges 2 or more days in succession to reduce a high inhibitor burden. Plasmapheresis also has been used effectively in patients who first develop inhibitors a few days after a surgical operation. Daily plasma exchange and FVIII infusion then may maintain hemostatic plasma FVIII levels for several more days.

Extracorporeal Inhibitor Absorption

Protein A, a cell wall constituent of certain strains of *Staphylococcus aureus*, selectively binds to the Fc portions of all human IgG subclasses except IgG3 (49). This property makes it useful to absorb human inhibitors, in which IgG4 predominates. Plasma removed during continuous-flow plasmapheresis can be passed through columns in which protein A has been bound to agarose beads. The IgG-depleted plasma is then returned to the patient (50). When one column is saturated, plasma is diverted to a second column while the first is rinsed and the IgG eluted. The columns can absorb IgG when plasma is passed through them at a rate of 10 to 25 ml/minute; treatment may be carried out for 6 or more hours per day, processing about 5 to 9 liters of plasma per day.

Extensive clinical experience has been reported from Sweden, but the technique is still in the stage of experimental trial in the United States. In hemophiliacs,

reduction of IgG ranged from 61 to 78 per cent with a single day's treatment, and reduction of inhibitor level ranged from 66 to 95 per cent. In one patient, a very high inhibitor of 4200 BU was reduced to less than 15 BU in 4.5 days with exchange of 42,500 ml of plasma. In nonhemophiliacs IgG reduction was similar, but inhibitor level reduction was less predictable. A major advantage of extracorporeal adsorption of inhibitors is that the IgG-depleted patient plasma can be returned to the patient, together with normal human intravenous gamma globulin (IVIgG) if desired; therefore, one can avoid transfusion of whole normal plasma, which may transmit viruses. Normal plasma also contains FVIII, which may begin to stimulate an anamnestic response on the first day of administration, an undesired effect if plasma exchange is to take place over several days before FVIII infusion.

Other adsorbents have been used. Nilsson and Freiburghaus (50) have used a partially purified factor IX (FIX) preparation coupled to agarose to adsorb an inhibitor to FIX during extracorporeal circulation of plasma. Factor VIII might be used in a similar fashion, thus removing only anti-FVIII and not other immunoglobulins. Regnault et al. (51) linked highly purified monoclonal anti–human IgG4 antibodies to agarose and removed 54 to 94 per cent of inhibitor in 20 of 21 samples of hemophilic inhibitor plasma tested in vitro; antibodies of other IgG classes were not affected. It is also possible to induce the formation of antibodies reacting against another specific antibody (anti-idiotypic antibodies; ref. 52). Anti-idiotypic antibodies to specific human inhibitors have been raised in animals (53). Such idiotypic antibodies might also be used as immunosorbents, but their use is limited by the necessity to develop an idiotypic antibody to each individual inhibitor, a procedure requiring some weeks and thus not suited for immediate treatment of bleeding in newly diagnosed inhibitor patients. A further possibility is the use of replicas, produced by recombinant DNA techniques (54), of the FVIII epitopes with which inhibitors react. Such FVIII fragments also might be used as adsorbents.

Calcium Infusion

Muhleman et al. (55) reported that in three inhibitor patients, two with autoantibodies and one with alloantibody, carefully monitored intravenous calcium gluconate infusion immediately prior to, and during, FVIII infusion decreased assayed inhibitor potency and improved clinical response. The plasma calcium levels attained did not appear to be relevant; rather, benefit was related to the timing of the calcium infusion with the FVIII infusion. The effect may be due to a change in antigen-antibody affinity.

Elevation of Patient Plasma FVIII Levels

Exogenous Human FVIII

A bolus of FVIII concentrate may be infused directly if the inhibitor level is not too high. Bolus FVIII therapy is usually successful if the inhibitor level is under 5 BU, and it sometimes is successful with levels up to 10 to 20 BU. If inhibitor levels are high, FVIII may be infused after reduction of the level by exchange plasmapheresis or other methods described above. To assure hemostasis, one should try to attain a plasma FVIII level of at least 30 U/dl, and preferably 50 U/dl. The amount of FVIII needed to reach this goal in a given

patient is not as predictable in the presence of an inhibitor as in the absence of an inhibitor, but is roughly correlated with measured inhibitor potency. Our initial dose is about 40 U FVIII/kg plus 20 U FVIII/kg per BU of inhibitor. The patient's plasma FVIII level after concentrate infusion should be monitored with FVIII assays so that, if the FVIII level is not adequate, additional concentrate can be given immediately. Once an inhibitor is neutralized with an initial bolus of FVIII, the amount of FVIII needed on subsequent days to maintain hemostatic plasma levels of FVIII may be little more than the amount a hemophiliac without inhibitor might need, at least until an anamnestic response occurs. In patients with type II inhibitors, response to infusions of FVIII are very difficult to predict from measurements of inhibitor potency.

Some clinicians use continuous infusion of FVIII to treat patients with inhibitors to FVIII. Blatt et al. (56) described the use of a bolus of roughly 70 to 140 U FVIII/kg followed by continuous infusion of roughly 4 to 14 U FVIII/kg per hour in patients with inhibitor levels of less than 30 BU. Factor VIII levels were monitored and dosage adjusted accordingly.

Some clinicians do not attempt to reach measurable plasma FVIII levels. Rizza (57) described the Oxford policy, begun in 1972, of giving bleeding inhibitor patients a FVIII dose only 2 to 3 times as large as would be given to a noninhibitor hemophilic patient of the same weight, regardless of the inhibitor level; he observed "beneficial clinical effects in many instances despite poor assayed response." Ekert et al. (58) gave 30 U FVIII/kg to four hemophiliacs with inhibitors of 2.6 to 48 new Oxford units for 18 bleeding episodes, and achieved satisfactory control in 15 episodes. Factor VIII levels were not measured, but that dose did not correct the activated partial thromboplastin time, and would not have been expected to raise the plasma FVIII level. Other clinicians (including ourselves) also have observed improvement on a few occasions from FVIII infusions that did not elevate the plasma FVIII level, a benefit that possibly results from rapid involvement of infused FVIII in the coagulation process, before time-dependent inhibition is complete. The frequency of successful clinical response to doses of FVIII that do not provide measurable plasma FVIII levels needs more study. It is not clear whether it exceeds the response expected with nonspecific management.

Protected Forms of FVIII

At one time, platelet infusions were given to bleeding hemophilic patients with some evidence of clinical improvement (59). A rationale for this benefit is suggested by Varadi and Elodi (60), who demonstrated that FVIII complexed with activated FIX and bound to platelet surfaces was inactivated at a much slower rate (half-life 13 minutes) by an inhibitor from a hemophiliac than was free FVIII (half-life 1 minute). An alternative explanation was suggested by the work of Yoshioka et al. (61), who demonstrated that treatment of platelet-FVIII complexes with a phospholipase increased the level of measurable FVIII; perhaps platelets contain some endogenous FVIII bound to phospholipid, which is exposed upon removal of the phospholipid. Barrowcliffe et al. (62) incubated FVIII concentrates with various phospholipids and found that phosphatidylserine protected FVIII from inactivation by an inhibitor in vitro. Littlewood and Barrowcliffe (63) also found that human and, especially, porcine FVIII concentrate incubated with phos-

pholipid was protected against inactivation by some canine type II anti–human FVIII inhibitors. Because porcine concentrate contains little von Willebrand factor, the investigators proposed that an epitope on FVIII involved in both antibody inactivation and phospholipid binding might be exposed by removal of von Willebrand factor. Clinical evaluations of the efficacy of FVIII concentrates containing phospholipids in animals or humans with FVIII inhibitors are planned.

DDAVP (Desmopressin Acetate)

DDAVP, a synthetic analogue of vasopressin, mediates the release of FVIII and von Willebrand factor into the circulation, presumably from storage sites, and is used widely to treat hemorrhages in patients with mild classic hemophilia or von Willebrand disease. Kesteven et al. (64) described the administration of DDAVP to a high-responder inhibitor patient with mild classic hemophilia. He had been treated with human FVIII concentrate (which provoked marked anamnestic responses), porcine FVIII concentrate (which provoked a lesser anamnestic response), and PCC. On two occasions, when the inhibitor was detectable only by sensitive test methods, he was given DDAVP, which stimulated rises of plasma FVIII from 2 U/dl to 13.8 U/dl on one occasion, and from 1.1 U/dl to 24.1 U/dl on another occasion; no anamnestic response followed, suggesting that the patient's endogenous FVIII was less immunogenic than exogenous FVIII. The use of DDAVP in a nonhemophilic patient with a low-level type II inhibitor was described by de la Fuente et al. (65). The patient had been treated previously with cyclophosphamide, with a reduction of inhibitor level from 120 to 1.8 BU, and emergence of detectable plasma FVIII of 13 to 18 U/dl. DDAVP, given on two occasions for dental extractions, provoked a seven- to ninefold increase in plasma FVIII activity (and temporary disappearance of inhibitor activity) during the first hour after infusion. Plasma FVIII levels remained above 35 U/dl for 3 hours after each infusion and then fell to baseline levels. No anamnestic responses ensued.

These two case reports of response to DDAVP have prompted some clinicians to try the drug for patients with more potent inhibitors, without success. Patients likely to respond to DDAVP are those with autoantibodies, low inhibitor levels, and (an associated phenomenon) some measurable plasma FVIII. A trial of DDAVP certainly is appropriate in inhibitor patients who match these characteristics, but is futile in patients with severe classic hemophilia or with high-level inhibitors.

Porcine FVIII

Antibodies to FVIII arising in humans have some degree of species specificity. A desired plasma FVIII level may be easier to achieve in an inhibitor patient with infusions of FVIII concentrate prepared from the plasma of a different mammalian species than with a similar amount of human FVIII. Other primates are not suitable, because their FVIII has a high level of cross-reactivity with anti–human FVIII inhibitors (66). Pigs and cows are suitable, because their FVIII has a low level of cross-reactivity, and porcine or bovine FVIII interacts well in the human coagulation system. Early FVIII concentrates prepared from those species were used for life-threatening hemorrhages in patients with classic hemophilia,

without inhibitors, before human FVIII concentrates were developed (67) and later they were used for patients with inhibitors (27,41).

Problems were encountered with the early preparations because they were crudely purified, poorly soluble, and allergenic. Some patients developed thrombocytopenia, attributed to a substance in animal plasma, "platelet-aggregating factor" (PAF; ref. 68), which later was shown to be von Willebrand factor. After using animal FVIII for several days, the level of FVIII recovered in the patient's plasma with standard doses often fell. This "resistance" might or might not be associated with a demonstrable increase in the level of inhibitor against the animal FVIII. These problems limited the use of early animal concentrates to critical problems, and the number of courses of therapy per patient was restricted.

A more highly purified porcine FVIII concentrate (Hyate-C; Speywood Laboratories, England), containing about 25 U FVIII/mg protein, was prepared in the early 1980s. Factor VIII was adsorbed on ethylene maleic anhydride polyelectrolytes, which attract little von Willebrand factor (69). This preparation has been used extensively in recent years in the United Kingdom (70), in Italy (71,72), in the United States (73), and elsewhere.

Studies of the cross-reactivity of anti–human FVIII inhibitors with porcine FVIII help predict patient response. The degree of inhibition of porcine FVIII was studied in England (70) with the old Oxford inhibitor test, substituting porcine concentrate for human FVIII concentrate. Elsewhere, the Bethesda test was used, replacing pooled normal human plasma with porcine concentrate diluted in human hemophilic plasma to contain 1 U FVIII/ml. Inhibitor neutralizing ability against porcine FVIII is positively correlated with that against human FVIII, but it is invariably lower than that against human FVIII in patients never exposed to porcine FVIII. The range of cross-reactivity is wide (Table 3-3), but on the average, anti–human FVIII inhibitors neutralize only one fourth to one fifth as much porcine FVIII as human FVIII. The range of cross-reactivity with autoantibodies is similar to that with alloantibodies. After treatment with porcine FVIII, the level of anti–human and anti–porcine FVIII inhibition and degree of cross-reactivity usually rise, but the degree of elevation of anti–human FVIII inhibitor usually is less than after use of human FVIII in the same patient. Occasional patients have no anamnesis despite frequent, repeated use of porcine FVIII; most patients have moderate anamnestic responses, and in a few patients anamnestic responses are high, even spectacular (74).

Table 3-3. Cross-reactivity of Anti–Human FVIII against Porcine FVIII in Patients Previously Not Exposed to Porcine FVIII

Author (Ref.)	*Assay Method*	*Antibody Type, #*		*Inhibition of Porcine FVIII as Percentage of Inhibition of Human FVIII*	
		Allo	*Auto*	*Mean*	*Range*
Kernoff (69)	Old Oxford	6	9	21	0–75
Gatti & Mannucci (72)	Bethesda	16	1	28	0–74
Kasper, 1987[a]	Bethesda	35	7	19	0–68

[a] Unpublished results.

Response is monitored by measuring plasma FVIII levels. A good clinical result usually depends on attaining a hemostatic plasma FVIII level of 30 U/dl or more. In patients with no inhibitor to porcine FVIII, or in whom the inhibitor had been neutralized, the average rise in plasma FVIII was 1.22 U/dl (72) to 1.29 U/dl (70) for every unit of porcine FVIII infused per kilogram of body weight. Brettler et al. (73) evaluated data from 38 inhibitor patients treated at 25 hemophilia centers in the United States and found that some patients responded well clinically, although postinfusion plasma FVIII levels were low or unmeasurable.

Anti-porcine FVIII inhibitor measurements often are not available in emergencies. Kernoff (69) reported that his policy in such circumstances is to decide dosage according to the anti–human FVIII inhibitor level, using 20 to 50 U porcine FVIII/kg as an initial dose in patients with less than 5 BU inhibitor, 50 to 100 U/kg in patients with 5 to 50 BU inhibitor, and 100 U/kg in patients with more than 50 BU inhibitor. Response is monitored with FVIII assays.

The "resistance" sometimes encountered with the old animal concentrates, that is, diminishing recovery of FVIII after infusions without demonstrable increase in measurable inhibitor levels, has been seen in rare instances in patients given the new highly purified porcine FVIII, and is associated with thrombocytopenia. The agent responsible for platelet aggregation in these instances probably is porcine von Willebrand factor. Altieri et al. (75) showed that aggregation of human platelet-rich plasma by porcine FVIII concentrate could be suppressed by addition of anti–porcine von Willebrand factor antibodies.

Reactions to the new polyelectrolyte-fractionated porcine FVIII have been far fewer, and, in general, less severe than with the old concentrates. Mild to moderate febrile reactions have been reported in about 10 per cent of infusions and may be controlled with antihistamines and corticosteroids. Severe allergic reactions or anaphylaxis are possible, but rare (76,77). Because of the possibility of such reactions, few patients have been allowed to use porcine FVIII on home self-infusion programs.

There have been no reports of transmission of blood-borne infections with porcine FVIII concentrate; therefore, it has been popular for use in patients not previously exposed to blood products, such as patients with autoantibodies.

Prothrombin Complex Concentrate (PCC)

If the use of FVIII to treat a hemorrhage is not practical because the inhibitor level is too high, or if FVIII is being reserved for more critical hemorrhages in high responders, PCC (factor IX complex) may be given in an attempt to bypass the need for FVIII. In plasma fractionation, prothrombin, factor IX, factor X, and, to varying degrees, factor VII, are concentrated together. Some activation of these factors may take place during fractionation, and activation can be enhanced deliberately to create activated PCC (APCC), also called anti-inhibitor coagulant complex (AICC), for use specifically in inhibitor patients.

Prothrombin complex concentrate was developed originally for use in patients with hemophilia B, and that remains its primary indication. Several brands of PCC were introduced in the late 1960s and the 1970s. During early studies (78), PCC was given to a patient with classic hemophilia. It shortened his whole blood clotting time and promptly slowed oozing from a wound. A few years later, a PCC

(an early version of the APCC Autoplex; Hyland, United States) was first given to patients with inhibitors and critical hemorrhages, with success (79). One other APCC, known as FEIBA (Immuno, Austria), was introduced in the late 1970s.

The identity of the component(s) responsible for the so-called FVIII bypassing activity or factor eight inhibitor bypassing activity (FEIBA) has been studied extensively, but no definite conclusion has been reached. The debate was reviewed by Aronson (80). Candidate entities for the essential component have included activated factor X, with or without phospholipid; activated factor VII; elevated levels of all the factors present; or even FVIII in a protected form (81; see above).

The potency of PCC is described in FIX units. That of APCC is described in FVIII correctional or bypassing units, which are peculiar to each brand. Dosage is determined arbitrarily, based on clinical experience and unrelated to inhibitor level. There is no laboratory test that specifically monitors response. Although some shortening of prothrombin times, partial thromboplastin times, and whole blood clotting times may be seen, these are not useful guides to therapy (although excessive shortening is to be avoided).

Early Reports

During the 1970s, PCC and APCC came to be used widely for hemorrhages in patients with inhibitors. Hemostasis was achieved in a majority of instances (Tables 3-4 and 3-5), sometimes with the first dose and sometimes after several doses. Dramatic control of bleeding from open wounds was reported in several instances (e.g., refs. 89,92,93). The confidence in Autoplex was so great in some quarters that it was even used to prepare patients for surgical operations and maintain hemostasis thereafter (94–96). FEIBA provided excellent hemostasis during several surgical procedures in one child, although postoperative hemostatic control was not always satisfactory (97).

Problems with Clinical Evaluation

In the late 1970s, some dissatisfaction with the efficacy of PCC and APCC was expressed. Parry and Bloom (98) described continuing bleeding in 6 of 14 hemorrhages treated with FEIBA, and slow response in the remaining episodes. Blatt et al. (99) surveyed 12 hematologists who treated 170 hemorrhages in 52 patients with PCC or APCC; according to the subjective judgment of the physi-

Table 3-4. Early Reports of Efficacy of Prothrombin Complex Concentrates for Hemostasis in Patients with Inhibitors to Factor VIII

Author (Ref.)	*Brand*	*Dose FIX (U/kg)*	*# Episodes*	*# Infusions*	*Clinically Effective Responses (%)*	
					1st Dose	*Total*
Abildgaard et al. (82)	Konyne	15–100	64	130	—	100
Kelly & Penner (83)	Proplex	50–100+	90	171	42	81
Price et al. (84)	Prothrombinex	10–50	12	38	8	100
Yolken & Hilgartner (85)	Proplex	40	54	92	61	100
Buchanan & Levy (86)	Proplex & Konyne	50–75	156	503	—	60
Ekert et al. (58)	Prothrombinex	30	18	23	—	100

Table 3-5. Early Reports of Efficacy of Activated Prothrombin Complex Concentrates for Hemostasis in Patients with Inhibitors to Factor VIII

Author (Ref.)	*Brand*	*Dose (U/kg)*	*# Episodes*	*# Infusions*	*Clinically Effective Responses (%)*	
					1st Dose	*Total*
Kurczynski & Penner (87)	Autoplex	—	~12	60	~50	100
Mannucci et al. (88)	FEIBA	50–70	5	16	40	60
Buchanan & Kevy (86)	Autoplex	—	31	44	—	65
Abildgaard et al. (89)	Autoplex	~40–100	25[a]	34	68	88
Aronstam et al. (90)	Autoplex	35–50	18	—	72	—
Hilgartner & Knatterud (91)	FEIBA	50–70	165	—	36	93

[a] Critical hemorrhages were excluded.

cians, the concentrate was effective in 33 per cent of episodes, ineffective in 39 per cent, and of uncertain usefulness in 28 per cent.

More carefully controlled trials clearly were needed. Subjective judgments about control of hemostasis were questioned, because most hemorrhages are internal and, therefore, not observed directly. The problems of accurate assessment of the effect of concentrates on internal hemorrhages were summarized by Lusher (100). Joint swelling decreases too slowly to serve as a useful index of response. Range of motion in a joint can be measured objectively, but it may not return to baseline values for several days even in noninhibitor patients successfully treated with FVIII. It is difficult to choose the optimal time to evaluate the effect of a given infusion on a hemorrhage; if the time chosen is too short, the effects of cessation of bleeding may not yet be obvious, whereas if the time chosen is too long, the apparent response rate may be spuriously high, since most untreated hemarthroses eventually resolve. In recent years, the use of canine hemophiliacs for objective study of the efficacy of concentrates has been proposed, using standardized incisions such as the gingival biopsies described by Kingdon and Hassel (101).

Controlled Trials

Because objective clinical evaluation is difficult, several double-blind, randomized controlled trials of the efficacy of PCC and APCC for joint hemorrhages have been performed in recent years (Table 3-6). Efficacy of the initial dose of concentrate within the first day after its infusion has been evaluated by measuring joint range of motion and assessing the patient's symptoms. In all three studies, one dose of PCC or APCC was effective in about half of instances. Lusher et al. (44) included an uncontrolled study of 20 hemophiliacs without inhibitors whose joint hemorrhages were treated with FVIII and found that all had subjective improvement within 6 hours of infusion, 65 per cent had improvement in joint mobility, and none had a decrease in joint circumference. Thus, one dose of FVIII was judged to be close to 100 per cent effective for acute hemarthroses in patients with classic hemophilia and no inhibitor, whereas one dose of PCC was about 50 per cent effective in patients with classic hemophilia with inhibitor.

Table 3-6. Controlled Studies of Efficacy of PCC and APCC for Hemostasis in Patients with Inhibitors to Factor VIII

Author (Ref.)	*Brand*	*Dose (U/kg)*	*Episodes Halted with First Dose (%)*
Lusher et al. (44)	Konyne	75	48
	Proplex	75	53
	Albumin placebo	—	29
Sjamsoedin et al. (102)	Prothromblex	~48	52
	FEIBA	~48	64
Lusher et al. (103)	Proplex	75	50
	Autoplex	75	52
	Autoplex	50	56

At the present time, PCC and APCC have a definite role in the management of bleeding in inhibitor patients, but are not panaceas. Regardless of product used, joint hemorrhages improve with the first dose about half the time. Increased dosage and use of two or three doses in the first day of treatment might improve response. Instances of dramatic response in critical hemorrhages are reported on occasion.

Side Effects

One of the major advantages of the use of PCC or APCC for bleeding in the presence of inhibitors is that anamnesis is not provoked in the large majority of patients. A few patients, however, have developed increased levels of inhibitor to FVIII (104). In one large series (105), the inhibitor level rose to at least twice the pretreatment value in 13.5 per cent of 261 episodes of treatment with PCC or APCC in 75 patients. Conditions predisposing to such a response appeared to include patient idiosyncrasy, low pretreatment inhibitor levels, and repeated exposure to the material over several days. In another study, the effect of Autoplex infusions on inhibitor levels after 102 infusions in 18 hemophilic patients was reviewed (106). An anamnestic response was observed on only one of 95 occasions when a single dose of Autoplex was given, but occurred in five of seven instances when multiple doses were given. The authors measured levels of FVIII coagulant antigen in 26 lots of Autoplex, and found an average of 20 U/vial (range 10 to 36); they wondered if this level of contamination might be responsible for provoking anamnesis. Onder and Hoyer (107) found 0.87 to 1.54 U of FVIII coagulant antigen/ml in five lots of Konyne, and 0.12 to 0.15 U/ml in three lots of Proplex. Those patients who have had marked anamnesis after PCC or APCC often are then treated with FVIII concentrates, porcine or human, because anamnesis seems inevitable regardless of product choice.

On rare occasions, inhibitors to FIX have developed after use of PCC or APCC for patients with inhibitors to FVIII (108,109).

Thrombotic problems also are encountered occasionally. Such events are well known as possible side effects of intense use of PCC in patients with hemophilia B undergoing surgery, or in patients with inadequate liver function (110). Disseminated intravascular coagulation (DIC) has been reported after use of APCC

in a few patients (111–113), usually after several doses had been given for the same hemorrhage.

Myocardial infarction, often fatal, has been reported in several inhibitor patients, ages 15 to 40, treated intensively for hemorrhages over 4 to 8 days with PCC or APCC (114–119). Autopsies were performed on four patients and revealed myocardial infarcts but patent coronary arteries. The normal condition of these vessels has led to the hypothesis that the critical event was coronary spasm, or perhaps a direct toxic effect on the myocardium.

The occurrence of DIC or myocardial infarction in some intensively treated patients has led to caution in use of high or frequently repeated doses of PCC or APCC, or prolonged courses of therapy. If two or three standard doses are ineffective within the first couple of days of treatment, then another therapeutic modality should be considered.

Activated Factor VII

Some attempts have been made to isolate an active component of PCC to bypass FVIII. In Sweden, a highly purified preparation of factor VII in its activated form successfully controlled bleeding in two patients with inhibitors to FVIII, without side effects or anamnesis (120). Investigation of the efficacy of that concentrate is continuing.

IMMUNOSUPPRESSION OF INHIBITORS

Immunosuppressive Drugs

Autoantibodies

Autoantibodies in nonhemophilic patients often can be diminished or eradicated by the use of such immunosuppressive drugs as corticosteroids, cyclophosphamide, or azathioprine (Table 3-7). In a series of 16 patients receiving corticosteroids as the primary mode of therapy (in a dose equivalent to 1 to 1.5 mg prednisone/kg per day), 7 had a complete and 4 a partial remission (69 per cent response) within 14 days (121). In the large multicenter survey of 215 nonhemophilic patients conducted by Green and Lechner (14), corticosteroids alone were

Table 3-7. Full or Partial Remissions in Patients with Autoantibodies to FVIII After Treatment with Immunosuppressive Drugs

Authors (Ref.)	*Drugs*	*Remissions (%)*
Spero et al. (121)	Corticosteroids	11/16 (69)
Green & Lechner (14)	Corticosteroids	22/45 (49)
	Azathioprine, with or without corticosteroids	19/28 (68)
	Cyclophosphamide, with or without corticosteroids	37/72 (51)
	No drug	11/39 (28)
Green et al. (122)	Cyclophosphamide with or without corticosteroids	8/11 (73)
Herbst et al. (123)	Cyclophosphamide and prednisone	6/6 (100)

used in 45 patients, and in 22 of them (49 per cent) the inhibitor disappeared or declined. The efficacy of other immunosuppressive drugs is difficult to assess, because they rarely have been used alone, and usually have been given together with corticosteroids. In the same survey, inhibitors declined or disappeared in 19 of 28 (68 per cent) patients treatd with azathioprine, usually given with prednisone, and in 37 of 72 (51 per cent) patients treated with cyclophosphamide, usually also given with prednisone. Overall, they found that 58 per cent of patients treated with some immunosuppressive drug improved, whereas only 38 per cent of untreated patients improved. Green et al. (122) reported that 8 of 11 (73 per cent) patients with autoantibodies had a remission after treatment with cyclophosphamide, with or without prednisone; all 7 with inhibitor levels less than 10 BU responded, but only 1 of 4 with levels greater than 10 BU responded. Herbst et al. (123) reported remission in all six patients treated with cyclophosphamide and prednisone; one patient, however, soon relapsed. Green (124) reported an interesting patient who failed to respond to a course of cyclophosphamide, azathioprine, and methotrexate. Months later, when treated for a critical hemorrhage with concurrent bolus doses of 10,000 U of FVIII and 1.5 g of cyclophosphamide, her inhibitor fell and eventually disappeared. Green hypothesized that the large dose of exogenous FVIII stimulated the patient's antibody-producing cells so that they were in a state peculiarly susceptible to the effects of the cytotoxic agent.

Dosages of immunosuppressive drugs used for autoantibody patients vary; however, in adults, initial doses of 40 to 80 mg prednisone/day are common, as are initial doses of about 1 g of cyclophosphamide intravenously as a bolus, or orally at 100 to 150 mg/day. Most clinicians choose to treat patients with autoantibodies with immunosuppressive drugs as soon as the diagnosis is made. Although spontaneous remission is possible, serious hemorrhage occurs in some 87 per cent of patients and a fatal outcome in 22 per cent. These risks outweigh those of a course of immunosuppressive drugs.

Alloantibodies

Hemophiliacs with inhibitors have not responded well to immunosuppressive drugs given alone. If such patients could be identified and treated at the time of the primary immune response, results might be better. Dormandy et al. (125) gave human cryoprecipitate to patas monkeys to induce formation of anti–human FVIII antibodies. After the inhibitor level had become undetectable, a second course of cryoprecipitate was given. If azathioprine was given before and during the second course of cryoprecipitate, inhibitors did not recur. In two patients with mild classic hemophilia whose initial inhibitor development was noted during close postoperative monitoring of therapy with animal FVIII (126), immediate administration of prednisone was associated with rapid disappearance of the inhibitors. Stein and Colman (127) reported the successful suppression and permanent eradication of a newly discovered inhibitor in a bleeding hemophiliac given a bolus of cyclophosphamide, 3 weeks of oral prednisone, and daily FVIII for 36 days. It is not clear whether their success should be attributed to the use of immunosuppressive drugs, to prolonged administration of FVIII, or to the combination (see below).

Dormandy (128) performed an international survey of the use of immuno-

suppressive drugs in 54 hemophiliacs with inhibitors. The most commonly used drug, cyclophosphamide, was administered in various doses without other immunosuppressive drugs at the time of FVIII infusion on 97 occasions in 45 patients; it prevented anamnesis in 64 per cent of episodes. Other agents given to other patients in various combinations were unhelpful in the majority of instances. Dormandy and Sultan (129) examined further some cases in which cyclophosphamide had suppressed anamnesis, and concluded that success was most likely if the patient had received little or no FVIII since development of the inhibitor, that is, if the drug was given during or soon after the primary immune response. Hultin et al. (130) treated seven hemophiliac inhibitor patients with various immunosuppressive drugs. Three were treated with FVIII and cyclophosphamide (together with prednisone in two instances) soon after the initial appearance of the inhibitor; anamnesis was blunted in one case and prevented in two patients, with the inhibitor then disappearing in both. Three of their four patients in whom immunosuppressive drugs were unhelpful had long-standing inhibitors with multiple exposures to FVIII. Despite the above reports of occasional suppression of anamnesis by administration of immunosuppressive drugs at the time of FVIII infusion, such treatment did not become popular. The drugs must be given with each course of FVIII to prevent anamnesis, and, in some patients, hemorrhages occur frequently (e.g., several times a month). Thus, in many patients immunosuppressive therapy would be nearly continuous if given with every infusion of FVIII.

Prolonged FVIII Administration

In 1974 in Bonn, Brackmann treated a hemophiliac with a high inhibitor level and a serious hemorrhage over a prolonged period of time with both FVIII and PCC, and observed that the level of inhibitor fell. After several similar observations in other patients, a treatment regimen, nicknamed the "Bonn protocol," was instituted to try to eradicate high-responding inhibitors in hemophiliacs (131,132). In "Phase One," the patient was given 100 U FVIII/kg and 40 to 60 U FEIBA/kg (the latter to try to prevent intercurrent hemorrhages) every 12 hours. The inhibitor level peaked within the first month or two, and then fell abruptly. When the inhibitor level reached 1 unit, treatment was reduced ("Phase Two") to 150 U FVIII/kg once daily, without FEIBA. When the inhibitor could no longer be detected and the plasma half-disappearance time of infused FVIII was normal, most patients continued to use FVIII in low doses several times a week as prophylaxis against hemorrhages, as was the usual regimen for patients with classic hemophilia at Bonn. Of 21 patients begun on the protocol, two died of traumatic injuries while inhibitor levels were still high, four discontinued treatment, and the remainder achieved either complete suppression of the inhibitor or reduction of the inhibitor to less than 1 unit (with no anamnesis on further exposure to FVIII).

The Bonn patients were grouped according to the interval between their last anamnestic response and commencement of the protocol. Group I (six patients) had had anamnestic responses to FVIII several weeks before starting the Bonn protocol. Group II (nine patients) had had no recent exposure to FVIII. Group II patients required far less therapy, spending an average of 7.6 months in Phase

One and 8.9 in Phase Two, whereas group I patients spent an average of 23.5 months in Phase One and 14.5 in Phase Two. Thus, therapy took longer to be effective in recently stimulated patients.

Similar high-dose protocols were tried with success in a few other centers (e.g., refs. 133–136). The status of 18 patients treated by the Bonn protocol (12 patients from Bonn and 6 from other centers) was evaluated some years later (137) and all patients showed a "sustained alteration in the behavior of their antibody." All had undetectable or very low inhibitor levels and infusion of FVIII did not provoke increases in inhibitor levels. All but two were using FVIII for prophylaxis. Continuing FVIII use probably is important for maintenance of immune tolerance.

The Bonn protocol, using large doses of FVIII plus FEIBA, was expensive (at current prices in the United States, at least $1.5 million per treatment regimen for a 60-kg patient in Group II). Lesser doses have also been reported to be effective. Aznar et al. (138) used 50 U FVIII/kg once daily together with a brief (21-day) initial course of fluprednisolone (0.5 mg/kg per day), to induce immune tolerance in four of five high-responding inhibitor patients in Spain. In the United States we induced immune tolerance in 9 of 12 patients given 50 U FVIII/kg per day, without immunosuppressive drugs (139). Initial anamnestic responses occurred in only six patients, all within the first month. Tolerance was induced within 4 months in eight of nine successful cases. In the Netherlands, 25 U FVIII/kg were given every other day without immunosuppressive drugs to 18 patients (140). One patient discontinued the protocol himself and 5 patients were terminated because their initial inhibitor peak exceeded 80 BU, but immune tolerance was induced in the 11 remaining patients. Wensley et al. (141), in Manchester, reported that 9 of 10 inhibitor patients achieved tolerance when treated with a total of 250 U FVIII every other day.

Rizza and Matthews (142) reported a related experience. Before 1972, they used FVIII in inhibitor patients only for critical hemorrhages. Since 1972 they have used FVIII in their 24 inhibitor patients for treatment of all hemorrhages (i.e., fairly often, but at unpredictable intervals), with improvement in inhibitor levels in 13 patients. Levels eventually became undetectable in seven patients who had had low to moderate inhibitors. Inhibitor levels and anamnestic responses showed downward trends over the years in six more patients who had been high responders. Thus, frequent but irregular FVIII therapy slowly induced some degree of tolerance in a few patients.

Intravenous Gamma Globulin (IVIgG)

In the early 1980s, Nilsson et al. (143) treated a patient with hemophilia B and an anti–factor IX inhibitor with extracorporeal adsorption of his gamma globulin followed by FIX infusion and cyclophosphamide; anamnesis was not suppressed. The next time the patient required FIX replacement therapy, he was given cyclophosphamide again, but this time in combination with 5 g of IVIgG. He had no anamnesis, and only gradual recurrence of his inhibitor. Nilsson et al. (144) reported on the current status of four patients with hemophilia B and inhibitors to FIX treated with a combination of FIX, cyclophosphamide, and large doses of IVIgG for bleeding episodes. In three of the patients no evidence of an inhibitor remains, and the fourth has been converted to a low responder. Since

three of the four patients previously had been treated with FIX and cyclophosphamide without IVIgG, and one with FIX and IVIgG without cyclophosphamide, they attributed the successful immune suppression to the combination of agents.

Recently, the same investigators (145) reported induction of immune tolerance in 7 of 10 patients with hemophilia A and high-responding inhibitors to FVIII by 1) removing inhibitors by extracorporeal absorption, 2) infusing high doses of FVIII twice daily to maintain measurable plasma levels, 3) infusing high-dose IVIgG, and 4) administering cyclophosphamide. The relative importance of each element of this complex protocol is difficult to evaluate, but the combination of agents may be responsible for the very rapid induction of tolerance, within 2 weeks in most instances.

The influence on inhibitors of infusions of IVIgG alone have been mixed. Sultan et al. (146) reported that high-dose IVIgG (400 mg/kg per day for 5 days) caused a rapid and prolonged, although incomplete, suppression of two autoantibodies but had little or no effect on two alloantibodies. A few other reports have appeared of successful suppression of autoantibodies by infusion of IVIgG alone (147–149) and failure to suppress alloantibodies (150).

The reason for the immunosuppressive effect of IVIgG on inhibitors has been debated. Sultan et al. (146) believed the effect could be attributed to the presence of anti-idiotypic antibodies to inhibitors. Frommel (151) described a fascinating pair of brothers with classic hemophilia, of whom one (A) had a persistent inhibitor and the other of whom (B) developed a transient inhibitor. Serum taken from brother B after the disappearance of his transient inhibitor partly neutralized brother A's persistent inhibitor, suggesting that brother B had developed anti-idiotypic antibodies that suppressed his own inhibitor completely and could neutralize those of brother A. Sultan et al. (152) studied IgG from individual normal blood donors and found that some had suppressive activity against autoantibodies to FVIII, and others had no such activity at all. They suggested that donors with high anti-idiotypic activity might be identified to produce a particularly effective IVIgG preparation, and later reported (153) that infusion of large doses of polyspecific IVIgG in patients with either allo- or autoantibodies to FVIII resulted in a rapid decrease in antibody level in most cases. Anti-idiotypic activity of IVIgG in vitro correlated with in vivo efficacy. Anti-idiotypic antibodies also have been prepared in animals immunized with inhibitors (53,154).

Anti-idiotypic antibodies in IVIgG, or prepared from immunized animals, might neutralize inhibitors in vivo, but this action would not explain the prolonged immunosuppressive effect of IVIgG described by several investigators. Perhaps anti-idiotypic antibodies modify the immune response by an effect on specific suppressor cells, as suggested by Hoyer (155), or IVIgG has another, as yet undefined, effect on the immune response.

RECOMMENDATIONS

Upon considering the information described in this chapter, together with personal experience, as of the beginning of 1988, the author makes the following recommendations for management of patients with inhibitors utilizing currently licensed and reasonably available products. It should be pointed out, however,

that if various experienced clinicians were polled, disagreement about the most favored treatment strategy in a given situation would be inevitable.

Action Taken When FVIII Inhibitor Is Identified

Autoantibody

1. Institute immunosuppressive therapy, for example, cyclophosphamide (100 to 150 mg/day) and prednisone (40 to 80 mg/day); consider high-dose IVIgG (400 mg/kg per day for 5 days). IVIgG is not yet licensed as indicated treatment for inhibitors, but its status may soon change.
2. Identify resources, local or other, for patient monitoring with FVIII assays and measurement of inhibitor levels against human and porcine FVIII, and obtain baseline measurements.
3. Identify resources, local or other, for treatment in case of hemorrhage. Can exchange plasmapheresis be performed? How is porcine FVIII procured? Which human FVIII and PCC concentrates currently marketed have undergone the most stringent viral inactivation measures?

Alloantibody

1. Identify resources for laboratory monitoring, as above, and treatment for hemorrhages, as above. Most patients with hemophilia are allied with expert centers, and only in a few instances will such resources be unavailable. Obtain baseline measurement of inhibitor levels against human and porcine FVIII. If patient has not been exposed to HIV and hepatitis viruses, identify those FVIII and PCC concentrates currently marketed that have undergone the most stringent viral inactivation measures.
2. Consider immediate induction of immune tolerance. Patients may be most responsive when the inhibitor has developed recently. Many protocols have been tried, and the success rate is high with all. Other variants of the described protocols doubtless will be tried, and the ideal program is not yet known. All programs, however, include frequent (usually daily) administration of human FVIII concentrate. For HIV-negative patients, the FVIII concentrate should be the safest available, a choice that may entail exceptional costs. Addition of immunosuppressive drugs (brief courses of corticosteroids or cyclophosphamide) or IVIgG may hasten immune tolerance, and reduce total costs.

Treatment of Hemorrhage

Autoantibody, Low Level

1. Desmopressin (DDAVP) is the treatment of choice (because the synthetic drug transmits no infections), if some circulating plasma FVIII can be detected preinfusion. Postinfusion plasma FVIII levels should be measured; if the level reaches 30 U FVIII/dl and the clinical response is good, the drug may be used again. Note that DDAVP depletes stored FVIII, and stores may not be replenished for 24 to 48 hours. The drug is useful primarily for management of isolated hemorrhages, or for preparation for minor surgical procedures such

as tooth extraction. One cannot rely upon it for maintenance of FVIII levels in the hemostatic range over several days, as after a major surgical procedure.

2. Porcine FVIII should be considered next. The concentrate has not been known to transmit any infection. The amount of expensive porcine FVIII concentrate needed to raise the plasma FVIII level to, say, 30 U/dl, is almost invariably less than the amount of the expensive, safest human FVIII concentrate (for example, the "pasteurized" human FVIII, heated in solution to 60°C.) Postinfusion plasma FVIII levels should be measured immediately. If the first dose of FVIII is ineffective, another dose may be effective. Thus, repeated plasma FVIII assays are needed as treatment is initiated. The inhibitor level to human and porcine FVIII should be reassayed after a few days.
3. Human FVIII concentrate that has undergone stringent viral attenuation measures is considered next. Postinfusion plasma FVIII levels should be measured immediately, and the inhibitor level reassayed after a few days.
4. Prothrombin complex concentrate can be given if FVIII is ineffective. A single dose of PCC is likely to be much less expensive but also less effective than the dose of porcine FVIII or the safest human FVIII large enough to raise the circulating plasma FVIII level into the hemostatic range. No currently licensed, widely available PCC is treated with viral attenuation methods as stringent as the most vigorous ones used in the production of some FVIII concentrate. One brand is heat treated in *n*-heptane suspension, a process probably more effective than heating dry lyophilized concentrate.
5. Activated PCC can be given if all else fails. It is more expensive than PCC, and controlled studies did not demonstrate that it was more advantageous than PCC for hemarthroses. We and other clinicians have noted superior efficacy on some occasions or in specific patients; therefore, its trial seems justified.

Autoantibody, High Level

1. The level of inhibition of porcine FVIII sometimes is remarkably lower than that of human FVIII, that is, the degree of cross-reactivity may be very low. If the inhibitor level to porcine FVIII is under 5 to 10 BU, then immediate infusion of porcine FVIII may be tried and plasma FVIII levels monitored.
2. Reduction of inhibitor level by exchange plasmapheresis should be considered. The inhibitor level above which infusions of porcine or human FVIII are likely to be ineffective has not been defined well. The lower the inhibitor level, the better the chance of attaining a measurable plasma FVIII level, and, perhaps, the better the chance of infused FVIII interacting beneficially in local coagulation even if none remains in the plasma to be measured. Some clinicians will not infuse FVIII preparations if the inhibitor level is over 5 to 10 BU, but others will try such infusions when inhibitor levels are higher.

   Experimental procedures to lower inhibitor level include: 1) adsorption of patient gamma globulin on protein A, requiring machinery currently becoming available in more centers, including the University of Massachusetts and Mt. Sinai Hospital in New York (156); 2) manipulation of calcium levels; and 3) infusion of IVIgG in the hope that it contains neutralizing anti-idiotypic antibodies. Future experimental procedures may include infusion of tailored anti-idiotype antibodies or synthesized specific FVIII epitopes.
3. After sufficient reduction of inhibitor levels, immediate infusion of porcine

FVIII may be attempted while plasma FVIII levels are monitored. If porcine FVIII is not available or advisable, then the safest human FVIII can be used.
4. If inhibitor levels cannot be reduced (because machinery is not available, or delay would be prejudicial), then PCC, APCC, or large doses of FVIII may be administered in the hope of some clinical benefit.

Alloantibody, Low Responder

Such patients typically have low inhibitor levels and are easily managed with administration of human FVIII at doses some 2 to 4 times higher than those given to hemophiliacs of the same weight who do not have inhibitors. The clinician should be aware that occasional patients have a low-responding pattern early in the course of the inhibitor, but gradually become high responders.

Alloantibody, High Responder, Current Low Inhibitor Level

1. For *minor hemorrhage,* use PCC or APCC to avoid needless anamnesis.
2. For *serious hemorrhage,* use sufficient FVIII to attain a hemostatic plasma FVIII level. Porcine FVIII is useful in patients who tend not to have anamnesis with it, who have low cross-reactivity, or who have not acquired blood-borne viral infections. Patients already infected with HIV usually are treated with less expensive human FVIII concentrate that has undergone standard viral attenuation measures (e.g., heating at 68°C in the lyophilized state).

   If FVIII is ineffective, PCC or APCC can be tried.

Alloantibody, High Responder, Current High Inhibitor Level

1. For *minor hemorrhage,* use PCC or APCC.
2. For *serious hemorrhage:*
   a. If anti–porcine FVIII inhibitor level is low enough (low cross-reactivity) infuse porcine FVIII immediately.
   b. If above is not feasible, reduce inhibitor level by exchange plasmapheresis or experimental means.
   c. After inhibitor reduction, infuse porcine FVIII (if cross-reactivity is favorably low) or human FVIII in large doses, attempting to attain a hemostatic plasma FVIII level.
   d. If above measures are unsuccessful, or if initiation of treatment is advisable while awaiting exchange plasmapheresis, infuse PCC or APCC.

CONCLUSION

The management of patients with inhibitors is ever-challenging and ever-changing. New products and techniques are introduced so frequently that no essay on treatment can be trusted to be thoroughly up-to-date once it leaves the author's hands. In recent years, increasing numbers of hemophiliacs with alloantibodies have undergone induction of immune tolerance, leaving fewer patients requiring elaborate, exotic, or chancy treatment techniques. These remaining patients may best be served by soliciting the current advice or assistance of an expert center, which usually is a center treating many hemophiliacs.

REFERENCES

1. Brinkhous KM, Roberts HR, Weiss AE: Prevalence of inhibitors in hemophilia A and B. In Brinkhous KM, Owren PA, Hinnom S, Surgenor DM, Sherry S, Stengle JM (eds): Thrombosis: Risk Factors and Diagnostic Approaches. New York, FK Schattauer Verlag, 1972, 315–320
2. Kasper CK: Incidence and course of inhibitors among patients with classic hemophilia. Thromb Diath Haemorrhag 30:263–271, 1973
3. Rizza CR, Spooner RJD: Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976–1980. Br Med J 286:929–933, 1983
4. Schwarzinger I, Pabinger I, Korninger C, Haschke F, Kundi M, Niessner H, Lechner K: Incidence of inhibitors in patients with severe and moderate hemophilia A treated with factor VIII concentrates. Am J Hematol 24:241–245, 1987
5. Gill FM: The natural history of factor VIII inhibitors in patients with hemophilia A. Prog Clin Biol Res 150:19–29, 1984
6. McMillan CW: Clinical patterns of hemophilic patients who develop inhibitors. Prog Clin Biol Res 150:31–44, 1984
7. Strauss HS: Acquired circulating anticoagulants in hemophilia A. N Engl J Med 281:866–873, 1969
8. Bloom AL: The treatment of factor VIII inhibitors. In Verstraete M, Vermylen J, Lijnen HR, Arnout J (eds): Thrombosis and Haemostasis. Leuven, Leuven University Press, 1987, 447–471
9. European Study Group of Factor VIII Antibody: Development of factor VIII antibody in haemophilic monozygotic twins. Scand J Haematol 23:64–68, 1979
10. Giles AR, Tinlin S, Hoogendoorn P, Greenwood P, Greenwood R: Development of factor VIII:C antibodies in dogs with hemophilia A (factor VIII:C deficiency). Blood 63:451–456, 1984
11. Frommel D, Allain JP, Saint-Paul E, Bosser C, Noel B, Mannucci PM, Pannicucci F, Blomback M, Prou-Wartelle O, Muller JY: HLA antigens and factor VIII antibody in classic hemophilia. Thromb Haemost 46:687–689, 1981
12. Shapiro SS: Markers for the factor VIII antibody response in hemophilia A. Scand J Haematol 33(Suppl 40):181–185, 1984
13. Gitschier J, Wood WI, Tuddenham EGD, Shuman MA, Goralka TM, Chen EY, Lawn RM: Detection and sequence of mutations in the factor VIII gene of haemophiliacs. Nature 315:427–430, 1985
14. Green D, Lechner K: A survey of 215 nonhemophilic patients with inhibitors to factor VIII. Thromb Haemost 45:200–203, 1981
15. Lottenberg R, Kentro TB, Kitchens CS: Acquired hemophilia: A natural history study of 16 patients with factor VIII inhibitors receiving little or no therapy. Arch Intern Med 147:1077–1081, 1987
16. Allain JP, Frommel D: Antibodies to factor VIII. V. Patterns of immune response to factor VIII in hemophilia A. Blood 47:973–982, 1976
17. Hoyer LW, Gawryl MS, de la Fuente B: Immunochemical characterization of factor VIII inhibitors. Prog Clin Biol Res 150:73–85, 1984
18. Glueck H, Coots M, Benson M, Dwulet F, Hurtubise P: A unique factor VIII:C monoclonal IgA (kappa) inhibitor in a patient with primary amyloidosis. Thromb Haemost 58:521, 1987 (Abstr)
19. Gralnick H, Flamm MA, Kessler CM, Zimbler H, Coller BS: IgA inhibitor to factor VIII von Willebrand factor. Br J Haem 59:149–158, 1985
20. Hultin MB, London FS, Shapiro SS, Yount WJ: Heterogeneity of factor VIII antibodies: Further immunochemical and biologic studies. Blood 49:807–817, 1977
21. Kavanagh ML, Wood CN, Davidson JF: The immunological characterization of human antibodies to factor VIII isolated by immuno-affinity chromatography. Thromb Haemost 45:60–64, 1981
22. Allain JP, Gaillandre A, Lee H: Immunochemical characterization of antibodies to factor VIII in hemophilic and nonhemophilic patients. J Lab Clin Med 97:791–800, 1981
23. Aalberse RC, van der Gaag R, van Leeuwen J: Serologic aspects of IgG4 antibodies. I. Prolonged immunization results in an IgG4-restricted response. J Immunol 130:722–726, 1983
24. Lavergne J-M, Meyer D, Girma J-P, Larrieu M-J: Precipitating anti-VIII:C antibodies in two patients with haemophilia A. Br J Haematol 50:135–146, 1982
25. Kazatchkine MD, Sultan Y, Burton-Kee EJ, Mowbray JF: Circulating immune complexes containing anti-VIII antibodies in multi-transfused patients with haemophilia A. Clin Exp Immunol 39:315–320, 1980
26. Fulcher CA, Mahoney SdeG, Zimmerman TS: FVIII inhibitor IgG subclass and FVIII polypeptide specificity determined by immunoblotting. Blood 69:1475–1480, 1987
27. Biggs R, Bidwell E: A method for the study of antihaemophilic globulin inhibitors with reference to six cases. Br J Haematol 5:379–395, 1959
28. Biggs R, Denson KWE, Nossell HL: A patient with an unusual circulating anticoagulant. Thromb Diath Haemorrhag 12:1–11, 1964

29. Biggs R, Austen DEG, Denson KWE, Rizza CR, Borrett R: The mode of action of antibodies which destroy factor VIII. I. Antibodies which have second-order concentration graphs. Br J Haematol 23:125–135, 1972
30. Biggs R, Austen DEG, Denson KWE, Borrett R, Rizza CR: The mode of action of antibodies which destroy factor VIII. II. Antibodies which give complex concentration graphs. Br J Haematol 23:137–155, 1972
31. Green D: Spontaneous inhibitors of factor VIII. Br J Haematol 15:57–75, 1968
32. Allain JP, Frommel D: Antibodies to factor VIII: Specificity and kinetics of iso- and hetero-antibodies in hemophilia A. Blood 44:313–322, 1974
33. Gawryl MS, Hoyer LW: Inactivation of factor VIII coagulant activity by two different types of human antibodies. Blood 60:1103–1109, 1982
34. Koutts J, Meyer D, Rickard K, Stott L, Firkin BG: Heterogeneity in biological activity of human factor VIII antibodies. Br J Haematol 29:99–107, 1975
35. Allain JP, Gaillandre A, Frommel D: Acquired haemophilia: Functional study of antibodies to factor VIII. Thromb Haemost 45:285–289, 1981
36. Moroose R, Hoyer LW: Anti-VWF reactivity in the plasmas of patients with factor VIII inhibitors. Thromb Haemost 54:77, 1985 (Abstr)
37. Thomsen C, Forbes CD, Prentice CRM: Relationship of factor VIII to ristocetin-induced platelet aggregation: Effect of heterologous and acquired factor VIII antibodies. Thromb Res 3:363–372, 1973
38. Bird P: Coagulation in an agarose gel and its application to the detection and measurement of factor VIII antibodies. Br J Haematol 29:329–340, 1975
39. Coots MC, Glueck HI, Miller MA: Agarose gel method: Its usefulness in assaying factor VIII inhibitors, evaluating treatment and suggesting a mechanism of action for factor IX concentrates. Br J Haematol 60:735–750, 1985
40. Kasper CK, Ewing NP: Acquired inhibitors of plasma coagulation factors. J Med Technol 3:431–439, 1986
41. Rizza CR, Biggs R: The treatment of patients who have factor VIII antibodies. Br J Haematol 24:65–82, 1973
42. Kasper CK, Aledort LM, Counts RB, Edson JR, Fratantoni J, Green D, Hampton JW, Hilgartner MW, Lazerson J, Levine PH, McMillan CW, Pool JG, Shapiro SS, Shulman NR, Van Eys J: A more uniform measurement of factor VIII inhibitors. Thromb Diath Haemorrhag 34:875–876, 1975
43. Austen DEG, Lechner K, Rizza CR, Rhymes IL: A comparison of the Bethesda and new Oxford methods of factor VIII antibody assay. Thromb Haemost 47:72–75, 1982
44. Lusher JM, Shapiro SS, Palascak JE, Rao AV, Levine PH, Blatt PM, Hemophilia Study Group: Efficacy of prothrombin-complex concentrates in hemophiliacs with antibodies to factor VIII: A multicenter therapeutic trial. N Engl J Med 303:421–425, 1980
45. Laurian Y, Girma JP, Allain JP, Verroust F, Larrieu MJ: Absence of anamnestic response after transfusion of washed red blood cells in haemophilia A patients with antibody to factor VIII. Scand J Haematol 28:233–237, 1982
46. Francesconi M, Korniger C, Thaler E, Niessner H, Hocker P, Lechner K: Plasmapheresis: Its value in the management of patients with antibodies to factor VIII. Haemostasis 11:79–86, 1982
47. Slocombe GW, Newland AC, Colvin MP, Colvin BT: The role of intensive plasma exchange in the prevention and management of haemorrhage in patients with inhibitors to factor VIII. Br J Haematol 47:577–585, 1981
48. Apter B, McCarthy V, Shapiro SS, Ballas SK: Successful preoperative apheresis of factor VIII antibody using factor VIII concentrate as a replacement fluid. J Clin Apheresis 3:140, 1986
49. Lee H, Tucker D, Allain JP: Rapid isolation and purification of antibody to factor VIII by protein A. Thromb Res 14:925–930, 1979
50. Nilsson IM, Freiburghaus C: Removal of inhibitors. In Ciavarella NL, Ruggeri ZM, Zimmerman TS (eds): Factor VIII/von Willebrand Factor: Biological and Clinical Advances. Milan, Wichtig Editore, 1986, 253–263
51. Regnault V, Rivat C, Vallet J-P, Francois-Gerard C, Brochier G, Allain J-P: A potential new procedure for removing anti-factor VIII antibodies from hemophilic plasma. Thromb Res 45:51–57, 1987
52. Kennedy RC, Melnick JL, Dreesman GR: Anti-idiotypes and immunity. Sci Am 255:48–56, 1986
53. de la Fuente B, Hoyer LW: The idiotypic characteristics of human antibodies to factor VIII. Blood 64:672–678, 1984
54. Scandella D, Fulcher CA: Human factor VIII inhibitors: Further epitope localization and neutralization using bacterially produced factor VIII fragments. Blood 70(Suppl 1), 1987 (Abstr)
55. Muhleman AF, Glueck HE, Miller MA, Coots M: Factor VIII inhibitors: In vivo decrease of inhibitory activity during calcium infusion. Am J Hematol 20:107–117, 1985
56. Blatt PM, White GC II, McMillan CW, Roberts HR: Treatment of anti-factor VIII antibodies. Thromb Haemost 38:514–523, 1977
57. Rizza CR: The management of haemophi-

liacs who have antibodies to factor VIII. Scand J Haematol 33(Suppl 40):187–193, 1984
58. Ekert H, Price DA, Lane JL, Dean FL: A randomized study of factor VIII or prothrombin complex concentrate infusions in children with haemophilia and antibodies to factor VIII. Aust N Z J Med 9:241–244, 1979
59. Bloom AL, Hutton D: Fresh platelet transfusions in haemophilic patients with factor VIII antibodies. Lancet 2:239, 1975
60. Varadi K, Elodi S: Protection of platelet surface bound factors IXa and VIII against specific inhibitors. Thromb Haemost 47:32–35, 1982
61. Yoshioka A, Peake IR, Furlong BL, Furlong RA, Giddings JC, Bloom AL: The interaction between factor VIII clotting antigen (VIIICAg) and phospholipid. Br J Haematol 55:27–36, 1983
62. Barrowcliffe TW, Kemball-Cook G, Gray E: Overcoming factor VIII inhibitors: A possible new approach. Scand J Haematol 33(Suppl 40):207–212, 1984
63. Littlewood JD, Barrowcliffe TW: The development and characterization of antibodies to human factor VIII in haemophilic dogs. Thromb Haemost 57:314–321, 1987
64. Kesteven PJ, Holland LJ, Lawrie AS, Savidge GF: Inhibitor to factor VIII in mild haemophilia. Thromb Haemost 52:50–52, 1984
65. de la Fuente B, Panek S, Hoyer LW: The effect of 1-deamino-8 D-arginine vasopressin (DDAVP) in a nonhemophilic patient with an acquired type II factor VIII inhibitor. Br J Haematol 59:127–131, 1985
66. Coppola R, Lombardi R, Hawkey C, Ruggeri ZM, Mannucci PM: Varied immunological reactivity of factor VIII from animal plasmas. Thromb Res 17:473–480, 1980
67. Macfarlane RG, Mallam PC, Witts LJ, Bidwell E, Biggs R, Fraenkel GJ, Honey GE, Taylor KB: Surgery in haemophilia: The use of animal antihaemophilic globulin and human plasma in thirteen cases. Lancet 2:251–259, 1957
68. Evans RJ, Austen DEG: Assay and characterization of the factor in porcine and bovine plasma which aggregates human platelets. Br J Haematol 36:117–126, 1977
69. Kernoff PBA: Porcine factor VIII: Preparation and use in treatment of inhibitor patients. Prog Clin Biol Res 150:207–224, 1984
70. Kernoff PBA, Thomas ND, Lilley PA, Matthews KB, Goldman E, Tuddenham EGD: Clinical experience with polyelectrolyte-fractionated porcine factor VIII concentrate in the treatment of hemophiliacs with antibodies to factor VIII. Blood 63:31–41, 1984
71. Ciavarella N, Antonecchi S, Ranieri P: Efficacy of porcine factor VIII in the management of haemophiliacs with inhibitors. Br J Haematol 58:641–648, 1984
72. Gatti L, Mannucci PM: Use of porcine factor VIII in the management of seventeen patients with factor VIII antibodies. Thromb Haemost 51:379–384, 1984
73. Brettler D, Forsberg A, Levine P, Aledort L, Hilgartner M, Kasper C, Lusher J, McMillan C, Roberts H: The use of porcine factor VIII concentrate (Hyate:C) in the treatment of patients with inhibitor antibodies: A multicenter US trial. Blood 70(Suppl. 1):327a, 1987 (Abstr)
74. Exner T, Rickard KA: Anamnestic response to high purity porcine AHF. Thromb Haemost 50:623, 1983
75. Altieri DC, Capitanio AM, Mannucci PM: Von Willebrand factor contaminating porcine factor VIII concentrate (Hyate:C) causes platelet aggregation. Br J Haematol 63:703–711, 1986
76. Erskine JG, Davidson JF: Anaphylactic reaction to low-molecular-weight porcine factor VIII concentrates. Br Med J 282:2011–2012, 1981
77. Colvin BT, Ainsworth M, Buckley CE: Experience with highly purified porcine factor VIII in a patient with haemophilia A and a factor VIII inhibitor. Clin Lab Haematol 5:55–59, 1983
78. Breen FA Jr, Tullis JL: Prothrombin complex concentrates in treatment of Christmas disease and allied disorders. JAMA 208:1848–1852, 1969
79. Fekete LF, Holst SL, Peetoom F, DeVeber LL: Auto-factor IX concentrate: A new therapeutic approach to treatment of hemophilia A patients with inhibitors. Abstract 295, 14th Congress of International Society of Hematology, Sao Paolo, July 16–22, 1972
80. Aronson DL: There is no correlation between vitamin K dependent coagulant content and clinical effectiveness of activated and standard factor IX complex concentrates. Prog Clin Biol Res 150:243–250, 1984
81. Barrowcliffe TW, Kemball-Cook G, Gray E: Factor VIII inhibitor bypassing activity: A suggested mechanism of action. Thromb Res 21:181–186, 1981
82. Abildgaard CF, Britton M, Harrison J: Prothrombin complex concentrate (Konyne) in the treatment of hemophilic patients with factor VIII inhibitors. J Pediatr 88:200–205, 1976
83. Kelly P, Penner JA: Antihemophilic factor inhibitors: Management with prothrombin complex concentrates. JAMA 236:2061–2064, 1976
84. Price DA, d'Souza S, Ekert H: The use of non-activated prothrombin concentrate in the management of haemophilia A with factor VIII antibodies. Aust NZ J Med 7:286–290, 1977
85. Yolken RH, Hilgartner MW: Prothrombin complex concentrates: Use in treatment of

hemophiliacs with factor VIII inhibitors. Am J Dis Child 132:291–293, 1978
86. Buchanan GR, Kevy SV: Use of prothrombin complex concentrates in hemophiliacs with inhibitors: Clinical and laboratory studies. Pediatrics 62:767–774, 1978
87. Kurcznski E, Penner JA: Activated prothrombin concentrate for patients with factor VIII inhibitors. N Engl J Med 291:164–167, 1974
88. Mannucci PM, Ruggeri ZM, Capitanio A, Pareti F: Clinical experience with a prothrombin-complex concentrate in the management of factor VIII inhibitors. In: Workshop on Inhibitors of Factors VIII and IX. Vienna, Facultas-Verlag, 1976, 136–140
89. Abildgaard CF, Penner JA, Watson-Williams EJ: Anti-inhibitor coagulant complex (Autoplex) for treatment of factor VIII inhibitors in hemophilia. Blood 56:978–984, 1980
90. Aronstam A, McLellan DS, Wassef M: The use of an activated factor IX complex (Autoplex) in the management of haemarthroses in haemophiliacs with antibodies to factor VIII. Clin Lab Haematol 4:231–238, 1982
91. Hilgartner MW, Knatterud GL, FEIBA Study Group: The use of factor eight inhibitor by-passing activity (FEIBA Immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. Blood 61:36–40, 1983
92. DeWitt RT, Feinstein DI: Prothrombin complex concentrate: Use in a hemophiliac with a factor VIII inhibitor. Arch Intern Med 137:1211–1213, 1977
93. Rickard KA, Exner T, Campbell J, Hodgson J: Life threatening haemorrhage in a haemophiliac with an inhibitor controlled with Autoplex. Abstract, XVth Congress of World Federation of Hemophilia, Stockholm, June 27–July 1, 1983
94. Penner JA, Hassouna HI: Inhibitor disorders with comments on management. In: Proceedings of the Second International Symposium on Hemophilia Treatment, Tokyo, Japan, 1981. Tokyo, Kyoritsu Printings, 1981, 241–248
95. Hanna WT, Madigan RR, Miles MA, Lange RD: Activated factor IX complex in treatment of surgical cases of hemophilia A with inhibitors. Thromb Haemost 46:638–641, 1981
96. Hutchinson RJ, Penner JA, Hensinger RN: Anti-inhibitor coagulant complex (Autoplex) in hemophilia inhibitor patients undergoing synovectomy. Pediatrics 71: 631–633, 1983
97. Heisel MA, Gomperts ED, McComb JG, Hilgartner M: Use of activated prothrombin complex concentrate over multiple surgical episodes in a hemophilic child with an inhibitor. J Pediatr 102:951–954, 1983
98. Parry DH, Bloom AL: Failure of factor VIII inhibitor bypassing activity (FEIBA) to secure haemostasis in haemophilic patients with antibodies. J Clin Pathol 31:1102–1105, 1978
99. Blatt PM, Menache D, Roberts HR: A survey of the effectiveness of prothrombin complex concentrates in controlling hemorrhage in patients with hemophilia and anti-factor VIII antibodies. Thromb Haemost 44:39–42, 1980
100. Lusher JM: Assessment of response to treatment and design of clinical trials. Prog Clin Biol Res 150:167–179, 1984
101. Kingdon HS, Hassell TM: Hemophilic dog model for evaluating therapeutic effectiveness of plasma protein fractions. Blood 58:868–872, 1981
102. Sjamsoedin LJM, Heijnen L, Mauser-Bunschoten EP, van Geijlswijk JL, van Houwelingen H, van Asten P, Sixma JJ: The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII: A double-blind clinical trial. N Engl J Med 305:717–721, 1981
103. Lusher JM, Blatt PM, Penner JA, Aledort LM, Levine PH, White GC, Warrier AI, Whitehurst DA: Autoplex versus Proplex: A controlled, double-blind study of effectiveness in hemophiliacs with inhibitors to factor VIII. Blood 62:1135–1138, 1983
104. Kasper CK, Feinstein DI: Rising factor VIII inhibitor titers after Konyne factor IX complex. N Engl J Med 295:505, 1976
105. Kasper CK, Hemophilia Study Group: Effect of prothrombin complex concentrates on factor VIII inhibitor levels. Blood 54:1358–1368, 1979
106. Laurian Y, Girma JP, Lambert T, Meyer D, Larrieu MJ: Incidence of immune responses following 102 infusions of Autoplex in 18 hemophilic patients with antibody to factor VIII. Blood 63:457–462, 1984
107. Onder O, Hoyer LW: Factor VIII coagulant antigen in factor IX concentrate. Thromb Res 15:569–572, 1979
108. Panicucci F, Sagripanti A, Conte B, Pinori E, Vispi M: Inhibitor to factor IX following activated prothrombin-complex concentrate treatment. Thromb Haemost 45:96, 1981
109. Pollmann H, Sutor AH: Anti-factor IX-antibody after treatment with FEIBA. Abstract, XVth Congress, World Federation of Hemophilia, Stockholm June 27–July 1, 1983
110. Kasper CK: Blood—Its derivatives and its problems: Factor IX. Ann NY Acad Sci 240:172–180, 1975
111. Stenbjerg S, Jorgensen J: Activated F IX concentrate (FEIBA) used in the treatment of haemophilic patients with antibody to F VIII. Acta Med Scand 203:471–476, 1978

112. Rodeghiero F, Castronovo S, Dini E: Disseminated intravascular coagulation after infusion of FEIBA (factor VIII inhibitor bypassing activity) in a patient with acquired haemophilia. Thromb Haemost 48:339–340, 1982
113. Hasegawa DK, Edson JR: Thrombocytopenia and hypofibrinogenemia following activated prothrombin complex concentrate therapy in a patient with hemophilia A and factor VIII inhibitor. Prog Clin Biol Res 150:386, 1984
114. Fuerth JH, Mahrer P: Myocardial infarction after factor IX therapy. JAMA 245:1455–1466, 1981
115. Agrawal BL, Zelkowitz L, Hletco P: Acute myocardial infarction in a young hemophiliac patient during therapy with factor IX concentrate and epsilon aminocaproic acid. J Pediatr 98:931–933, 1981
116. Schimpf K, Zeltsch C, Zeltsch P: Myocardial infarction complicating activated prothrombin complex concentrate substitution in patient with haemophiliac A. Lancet 2:1043, 1982
117. Tabor DC, Votaw ML: Fatal myocardial hemorrhagic infarction in hemophilia A after factor IX and Autoplex therapy. Blood 62(Suppl 1):278a, 1983 (Abstr)
118. Gruppo RA, Bove KE, Donaldson VH: Fatal myocardial necrosis associated with prothrombin-complex-concentrate therapy in hemophilia A. N Engl J Med 309:242–243, 1983
119. Sullivan DW, Purdy LJ, Billingham M, Glader BE: Fatal myocardial infarction following therapy with prothrombin complex concentrates in a young man with hemophilia A. Pediatrics 74:279–281, 1984
120. Hedner U, Kisiel W: Use of human factor VIIa in the treatment of two hemophilia A patients with high-titer inhibitors. J Clin Invest 71:1836–1841, 1983
121. Spero JA, Lewis JH, Hasiba U: Corticosteroid therapy for acquired F VIII:C inhibitors. Br J Haematol 48:635–642, 1981
122. Green D, Schuette PT, Wallace WH: Factor VIII antibodies in rhematoid arthritis: Effect of cyclophosphamide. Arch Intern Med 140:1232–1235, 1980
123. Herbst KD, Rapaport SI, Kenoyer DG, Stanton W, Feinstein DI: Syndrome of an acquired inhibitor of factor VIII responsive to cyclophosphamide and prednisone. Annal Intern Med 95:575–578, 1981
124. Green D: Suppression of an antibody to factor VIII by a combination of factor VIII and cyclophosphamide. Blood 37:381–387, 1971
125. Dormandy KM, Hawkey C, Churchill WGL, Cowley J: Immunosuppression of inhibitors to human factor VIII in the patas monkey. Thromb Diath Haemorrhag Suppl 43:355–364, 1971
126. Beck P, Giddings JC, Bloom AL: Inhibitor of factor VIII in mild haemophilia. Br J Haematol 17:283–288, 1969
127. Stein RS, Colman RW: Hemophilia with factor VIII inhibitor: Elimination of anamnestic response. Ann Intern Med 79:84–87, 1973
128. Dormandy KM: Immunosuppression in the treatment of hemophiliacs with antibodies to factor VIII. In Proceedings of the IXth Congress, World Federation of Hemophilia, Istanbul. (International Congress Series # 356.) Amsterdam, Excerpta Medica, 1975, 225–239
129. Dormandy KM, Sultan Y: The suppression of factor VIII antibodies in haemophilia. Pathol Biol (Paris) 23:17–23, 1975
130. Hultin MB, Shapiro SS, Bowman HS, Gill FM, Andrews AT, Martinez J, Eyster ME, Sherwood WC: Immunosuppressive therapy of factor VIII inhibitors. Blood 48:95–108, 1976
131. Brackmann HH, Gormsen J: Massive factor-VIII infusion in haemophiliac with factor-VIII inhibitor, high responder. Lancet 2:933, 1977
132. Brackmann H-H: Induced immunotolerance in factor VIII inhibitor patients. Prog Clin Biol Res 150:181–195, 1984
133. Lechner K, Korninger C, Niessner H, Thaler E, Francesconi M: Suppression of hemophilic antibodies by continuous treatment with factor VIII concentrate and prothrombin complex preparation. Abstr, 18th Congress of International Society of Hematology, Montreal, August 16–22, 1980
134. White GC II, Taylor RE, Blatt PM, Roberts HR: Treatment of a high titer anti-factor VIII antibody by continuous factor VIII administration: Report of a case. Blood 62:141–145, 1983
135. Stenbjerg S, Ingerslev J, Zachariae E: Factor VIII inhibitor treatment with high doses of F VIII. Thromb Res 34:533–539, 1984
136. Scheibel E, Feddersen C, Hertz H: Long-term high dose factor VIII treatment of 3 haemophiliacs with factor VIII inhibitor. Scand J Haematol 34:378–384, 1985
137. Sultan Y, White GC, Aronstam A, Bosser C, Brackmann HH, Brochier G, Gormsen J, Mariani G, Roberts HR, Scarabin Y, Scharrer I, Scheibel E: Hemophilic patients with an inhibitor to factor VIII treated with high dose factor VIII concentrate: Results of a collaborative study for the evaluation of factor VIII inhibitor titer, recovery and half life of infused factor VIII. Nouv Rev Fr Hematol 28:85–89, 1986
138. Aznar JA, Jorquera JI, Peiro A, Garcia I: The importance of corticoids added to continued treatment with factor VIII concentrates in the suppression of inhibitors in haemophilia A. Thromb Haemost 51:217–221, 1984

139. Ewing NP, Sanders NL, Dietrich SL, Kasper CK: Induction of immune tolerance to factor VIII in hemophiliacs with inhibitors. JAMA 259:65–68, 1988
140. Van Leeuwen EF, Mauser-Bunschoten EP, van Dijken PJ, Kok AJ, Sjamsoedin-Visser EJM, Sixma JJ: Disappearance of factor VIII:C antibodies in patients with haemophilia A upon frequent administration of factor VIII in intermediate or low dose. Br J Haematol 64:291–297, 1986
141. Wensley RT, Burn AM, Reading OM: Induction of tolerance to factor VIII in haemophilia A with inhibitors using low doses of human factor VIII. Thromb Haemost 54:227, 1985 (Abstr)
142. Rizza CR, Matthews JM: Effect of frequent factor VIII replacement on the level of factor VIII antibodies in haemophiliacs. Br J Haematol 52:13–24, 1982
143. Nilsson IM, Sundqvist S-B, Ljung R, Holmberg L, Freiburghaus C, Bjorlin G: Suppression of secondary antibody response by intravenous immunoglobulin and development of tolerance in a patient with haemophilia B and antibodies. Scand J Haematol 30:458–464, 1983
144. Nilsson IM, Berntorp E, Zettervall O: Induction of split tolerance and clinical cure in high-responding hemophiliacs with factor IX antibodies. Proc Nat Acad Sci USA 83:9169–9173, 1986
145. Nilsson IM, Berntorp E, Zettervall O: Tolerance induction in high-responding hemophiliacs with F VIII antibodies by means of combined treatment with IgG, cyclophosphamide and F VIII. Thromb Haemost 58:519, 1987 (Abstr)
146. Sultan Y, Maisonneuve P, Kazatchkine MD, Nydegger UE: Anti-idiotypic suppression of autoantibodies to factor VIII (antihaemophilic factor) by high-dose intravenous gammaglobulin. Lancet 2:765–768, 1984
147. Gianelli-Borradori A, Hirt A, Luthy A, Wagner HP, Imbach P: Haemophilia due to factor VIII inhibitors in a patient suffering from an autoimmune disease: Treatment with intravenous immunoglobulin. Blut 48:403–407, 1984
148. Zimmermann R, Kommerell B, Harenberg J, Eich W, Rother K, Schimpf K: Intravenous IgG for patients with spontaneous inhibitor to factor VIII. Lancet 1:273–274, 1985
149. Green D, Kwaan HC: An acquired factor VIII inhibitor responsive to high-dose gamma globulin. Thromb Haemost 58:521, 1987 (Abstr)
150. Seifried E, Gaedicke G, Pindur G, Rasche H: The treatment of haemophilia A inhibitor with high dose intravenous immunoglobulin. Blut 48:397–401, 1984
151. Frommel D: Anti-idiotypic suppression of antibodies to factor VIIIc. Lancet 2:1210–1211, 1984
152. Sultan Y, Rossi F, Kazatchkine M: Therapeutic immunoglobulins (i.v.Ig) in anti-factor VIII (VIII:C) suppression. La Ricerca 16:104–105, 1986 (Abstr)
153. Rossi F, Sultan Y, Kazatchkine M: Auto and Allo anti-FVIII:C antibodies are recognized by anti-idiotypic antibodies contained in normal immunoglobulins. Thromb Haemost 58:521, 1987
154. Moffat EH, Furlong RA, Bloom AL, Peake IR: Anti-idiotype reagents in haemophilia: In vitro studies. Thromb Haemost 58:520, 1987 (Abstr)
155. Hoyer LW: New alternatives and strategies in the treatment of inhibitors. Prog Clin Biol Res 150:367–372, 1984
156. Uehlinger J, Watt R, Aledort L: Extracorporeal immunoadsorption: An alternative treatment for hemophiliacs with high-responding inhibitors. Blood 70(Suppl 1), 1987 (Abstr)
157. Zettervall O, Sundqvist S-B, Nilsson IM: Characterisation of the tolerant state in a patient with haemophilia B after removal of high-titre factor IX antibodies. Scand J Haematol 34:446–454, 1985