UNTIL THE ADVENT of components that could more specifically replace specific missing clotting factors, patients with hemophilia were treated with whole blood and then plasma. Such patients had a shortened lifespan and were crippled with severe arthropathy; many died of hemorrhage. With the discovery in 1960 that factor VIII:C was concentrated in cryoprecipitate, more specific replacement concentrates of higher purity, both factor VIII and prothrombin complex concentrates (PCCs), began to be produced.

Lyophilized concentrates revolutionized the care of patients with hemophilia. In home therapy programs, patients were taught to infuse the concentrate in the home setting at the earliest sign of hemorrhage. The long-term effects of hemorrhage were decreased, days lost from work or school and days of hospitalization decreased, and lifespan gradually increased until the AIDS era. Lyophilized concentrate of clotting factors are prepared from plasma obtained from 2,000 to 30,000 donors. Infectious complications from transfusion-transmitted viruses began to be noted in patients with hemophilia in the late 1970s and are still a major concern. Many newer types of factor concentrates are being produced, both to eliminate infectious side effects and increase purity. This review first describes the complications associated with concentrate infusion and then reviews the various factor concentrate products currently available for treatment of hemophilia and their advantages and disadvantages.

The treatment of patients with inhibitors is beyond the scope of this review and is the subject of several recent articles.

COMPLICATIONS OF CONCENTRATE INFUSION

Hepatitis B

The hepatitis B virus (HBV), non-A, non-B hepatitis virus (NANB), and the human immunodeficiency virus (HIV) remain the major agents described to date that are transmitted through concentrate infusions. Acute hepatitis B infection with elevated liver function tests and jaundice is uncommon in hemophilia but ~90% of patients infected before the advent of heat-treated concentrates have developed antibody to hepatitis B (HBsAb), indicating past exposure through factor concentrate. A small percentage of patients (5% to 10%) have become chronic carriers of hepatitis B (HBsAg positive), which may make them more prone to develop chronic liver disease or carcinoma of the liver. Delta hepatitis (HDV), a virus that requires the presence of HBV as a carrier, is also a potential risk to persons with hemophilia since the virulence of HBV infection may be increased. Even with newer methods of viral attenuation (discussed below), infection with hepatitis B still occurs. Thus, we strongly recommend that all newly diagnosed patients with hemophilia receive the hepatitis B vaccine. In a newly diagnosed infant, immunizations should be started soon after birth.

NANB Hepatitis

NANB hepatitis (NANBH) is a common infectious complication associated with factor infusions and may lead to fatal complications. Although it is still a diagnosis of exclusion since no specific serologic test exists, the majority of hemophiliac patients (90% to 100%) who infuse concentrate have either persistently or intermittently elevated liver enzymes which probably represent the consequences of NANBH. In a series of 155 unselected liver biopsies reviewed, 22% of cases had chronic active hepatitis or cirrhosis. This study, however, could not relate the etiology of advanced liver disease solely to NANBH. In another study in 35 patients selected because of abnormal enzymes, 44 liver biopsy samples showed chronic active hepatitis or cirrhosis in 20 samples. Advanced liver disease did not correlate with degree of elevations of aminotransferases. Schimpf et al performed 52 biopsies on 45 patients with hemophilia; 29% had progressive liver disease. Thus, NANBH may represent a potential long-term problem for persons with hemophilia. Studies on NANBH secondary to blood transfusions imply that ~20% of patients with elevated liver function tests will develop chronic liver disease, including cirrhosis.

AIDS

HIV infection is a more recent problem; the virus was introduced into the blood supply in the late 1970s. The first cases of AIDS in hemophiliac patients were reported in 1982. Since then, there have been >800 cases of AIDS in hemophiliac patients. In addition, ~70% of patients with hemophilia have antibody to HIV. They include those patients who received factor concentrates before 1984/1985 and patients treated only with cryoprecipitate or fresh-frozen plasma. By epidemiologic and viral culture data, HIV seropositivity in such persons is consistent with latent infection. Even in the asymptomatic patient, HIV seropositivity has caused immune dysfunction, with decreased CD4 cell levels and decreased helper-suppressor cell ratios. Whether all or most persons infected with HIV will contract AIDS is not yet clear, but hemophiliac patients, especially those infected after age 22 years who have been seropositive for at least 7 years have a >40% probability of contracting AIDS. In vitro evidence shows that exposure to other viruses can activate HIV that has been latent within monocytes.
phocytes already activated by other antigens may be more susceptible to infection by HIV. In addition, HIV in latently infected cells may be activated by multiple cytokines. Thus, theoretically, a concentrate free of all blood-borne viruses might have advantages even to hemophilic patients previously infected with HIV.

**Alloantigens in Factor Concentrates**

Factor concentrate itself, perhaps secondary to the large amount of foreign protein present, may cause alterations in the immune systems of hemophilic patients. Since detailed immunologic studies were not done routinely on the hemophilia population before the 1980s when HIV infection became widespread, evidence that immune dysfunction predicted HIV infection is sporadic. In Scotland, Ludlam et al. reported that in a group of HIV antibody-negative patients receiving factor VIII concentrates prepared locally by the Scottish Transfusion Service and not yet contaminated by HIV, 43% of the recipients demonstrated a decreased CD4/CD8 ratio secondary to decreased CD4 levels. These abnormalities appeared to be related to treatment with factor concentrate. They did not correlate with abnormalities in liver function tests, although most of these patients had elevated alanineaminotransferase (ALT). A group of our HIV-seronegative patients have minor immune abnormalities with decreased percentages of CD4 cells and decreased helper-suppressor cells. In addition, in a group of 97 patients with severe/moderate hemophilia A, studied for skin test anergy, anergy correlated more strongly with intensity of factor infusion than with the presence or absence of antibody to HIVs. In vitro studies have also shown that intermediate-purity factor concentrates themselves suppressed a mixed lymphocyte reaction whereas more highly purified preparations did not, although the exact mechanisms have not been defined.

**Additional Complications of Concentrates**

Other complications of factor concentrate include typical allergic reactions of urticaria and temperature elevations which are uncommon. Rarely, anaphylaxis has been reported. Factor concentrates also may contain isoagglutinins (anti-A or anti-B) and when administered to patients with blood types A or B (especially in large amounts as occurs during and after surgery) may cause significant hemolysis. In 1979, decreases in single-breath carbon monoxide diffusion capacity in a group of hemophilic patients was believed to be secondary to lodging of particulate matter from the concentrate in the pulmonary capillary bed. Subsequently, a syndrome of primary pulmonary hypertension was described in five patients with severe hemophilia using large amounts of concentrate. Again, the mechanism was not elaborated but may have resulted from particulate matter or immune complexes being deposited in the lungs or from other immune-mediated reactions.

An additional side effect of prothrombin complex concentrates (PCCs) and activated prothrombin complex concentrates (APCCs) not noted with factor VIII concentrates is that of thrombosis, including deep venous thrombosis, pulmonary embolus, and myocardial infarction. This risk is small but measurable especially in a patient undergoing orthopedic surgery who may require bed rest for prolonged periods of time. The thromboses are believed to be secondary to activated factor VII and X found in PCC preparations, although this has not been proven. Most physicians who treat hemophilia administer prophylactic subcutaneous heparin to the patient receiving large amounts of PCC who will not be ambulatory. Thus, infusion of factor concentrate can be associated with a variety of complications (Table 1).

**VIRUCIDAL TREATMENTS OF CONCENTRATES**

There is now a triple barrier to viral transmission through factor concentrates: (a) self-exclusion for donors, (b) donor screening, and (c) viral inactivation procedures. Self-exclusion includes the asking of detailed questions concerning hepatitis, possible HIV exposure, and general health questions regarding nonspecific symptoms of HIV infection. Donor screening now includes testing for ALT elevations and hepatitis B core antibody (HBcAb) which are surrogate tests for NANBH and which are believed, in tandem, to decrease the incidence of transmission of NANBH by 61%. A serologic test for NANBH is currently under development by Chiron (Emeryville, CA). If proven reliable, it should greatly enhance not only screening of infected units but also diagnosis of NANBH. Testing of the donor for HIV antibody is also done. Any abnormal plasma units with ALT elevation, HIV antibody, or HBcAb are discarded.

Donor screening for HIV does not provide a necessarily safe unit. Experience with blood transfusion shows that HIV may be transmitted by anti-HIV-negative blood if the donor is in the process of seroconversion. The risk of HIV infection from such an HIV-negative unit may be from 1 in 51,000 to 1 in 102,000. Blood, however, is not exposed to any viral-attenuating methods.

Multiple methodologies for inactivating viruses during processing of factor concentrate have been devised. Heat treatment is currently the most commonly used procedure. Efficacy of this method is dependent on (a) temperature; (b) duration of heat treatment; (c) presence of clotting factor stabilizers which may also stabilize virus; and (d) the method of heat treatment [whether the concentrate is heated when lyophilized ("dry heat treated") or heated while in suspension or solution ("wet heat treated") which appears to be more effective]. Dry heat methods include heating for 30 to 72 hours at temperatures from 60 to 68°C. Recently, a

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**Table 1. Complications of Factor Concentrate**

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Hepatitis B/delta hepatitis</th>
<th>Non-A, non-B hepatitis</th>
<th>HIV</th>
<th>Parvovirus</th>
<th>HTLV-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild immunosuppression</td>
<td>Allergic reactions</td>
<td>Hemolysis secondary to isoagglutinins</td>
<td>Primary pulmonary hypertension</td>
<td>Thromboses (only with PCCs and APCCs)</td>
<td></td>
</tr>
</tbody>
</table>
“super dry heat” method has been used in which heating occurs at 80°C for 72 hours. Wet heating methods include suspension of the concentrate in n-heptane followed by heating at 60°C for 20 hours (Alpha, S Pasadena, CA), vapor suspension followed by heating at 60°C for 10 hours at 190 mbar plus a one-hour 80°C treatment at 370 mbar (Immuno, Vienna), and heating in solution for 10 hours at 60°C (“pasteurized,” Behringwerke [Marburg, W Germany], Cutter [Berkeley, CA]).

In addition to heat-treatment methods chemical methods are used to inactivate virus. Use of solvent/detergent combinations which disrupt lipid-coated viruses such as HIV and hepatitis virus is being studied by the New York Blood Center and the American Red Cross. The New York Blood Center is using 0.3% tri-n-butyl phosphate (TNBP) as the solvent and 0.2% sodium cholate as the detergent; the American Red Cross/Hyland is using 0.3% TNBP and 1% Triton X-100. In Europe, for PCC products, β-propiolactone and ultraviolet (UV) light are used to kill virus. This method has not been licensed in the United States.

A third method for eliminating virus from concentrate involves affinity chromatography with a mouse monoclonal antibody (MoAb) to either FVIII:VWF or FVIII:C attached to solid-phase agarose support. Cryoprecipitate is used as the starting material, and several purification steps are performed. A much higher purity factor VIII:C concentrate results (specific activity >3,000 U/mg protein before addition of albumin stabilizer). Moreover, when model viruses such as Sindbis virus and pseudorabies are placed in the starting material, a significant log kill occurs with the chromatography procedure itself. HIV is also reduced significantly by this process. The product is either heat-treated in the final dry state at 60°C for 30 hours (Monoclate, Armour, Horsham, PA) or is initially treated with TNBP/Triton X-100 (Hemophil M, Hyland, Glendale, CA). A third product, now in phase 2 trials, is pasteurized after MoAb affinity chromatography. The various types of viral inactivation procedures, the pharmaceutical company producing them, and the brand names are shown in Table 2.

Because animal models, especially for NANBH, are not available, human trials with concentrates are needed to prove viral safety. To show whether a specific concentrate is free of hepatitis B, NANB, or HIV, studies using previously untransfused patients, mostly newly diagnosed infants, are undertaken.

The International Committee on Thrombosis and Hemostasis (ICTH) has set forth criteria for constructing clinical trials to evaluate the viral safety of new concentrates. Subjects must have had no previous blood transfusions including cryoprecipitate and must have normal baseline values for ALT. They must be serologically negative for HIV and hepatitis B unless they have been vaccinated; if they have, HBsAb positivity is acceptable. Testing for ALT must be performed at 2-week intervals so that elevations are not missed and sampling should continue at this interval for 4 months. Multiple lots of the new concentrate should be tested, and at least 20 patients should be enrolled so that the probability that a concentrate carries NANBH even with a completely negative study is decreased.

### Table 2. Commercial Factor VIII Concentrates and Viral Inactivation Method Used

<table>
<thead>
<tr>
<th>Viral Inactivation Method</th>
<th>Name of Concentrate</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heating in lyophilized state—dry heat</td>
<td>Factor VIII-HT</td>
<td>Armour*</td>
</tr>
<tr>
<td>60°C for 32 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60°C for 72 h</td>
<td>Hemophil-T</td>
<td>Hyland*</td>
</tr>
<tr>
<td>68°C for 72 h</td>
<td>Koate HT</td>
<td>Cutter</td>
</tr>
<tr>
<td>Super dry heat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80°C for 72 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vapor heating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heating in suspension with heparin 60°C for 20 h</td>
<td>Profilate-HT</td>
<td>Alpha</td>
</tr>
<tr>
<td>Heating in aqueous solution (pasteurization)</td>
<td>Koate-HS</td>
<td>Cutter</td>
</tr>
<tr>
<td>60°C for 10 h</td>
<td>Hurnate-P</td>
<td>Behringwerke</td>
</tr>
<tr>
<td>Solvent/detergent TNBP/cholate</td>
<td>Factor VIII-SD</td>
<td>NY Blood Center</td>
</tr>
<tr>
<td>Purification by affinity chromatography</td>
<td>Monoclate</td>
<td>Armour</td>
</tr>
<tr>
<td>60°C for 30 h in lyophilized state</td>
<td>Monoclate</td>
<td>Armour</td>
</tr>
<tr>
<td>TNBP/Triton X-100 in &quot;wet&quot; state</td>
<td>Hemophil M</td>
<td>Hyland</td>
</tr>
<tr>
<td>60°C for 10 h in aqueous solution (pasteurization)</td>
<td>Monoclate M</td>
<td>Armour†</td>
</tr>
</tbody>
</table>

*Product no longer available. †Available in Europe only. ‡Now in therapeutic trials.

New onset of infection with hepatitis B or HIV after a concentrate is infused can be demonstrated with serologic assays. Documenting infection with NANB virus is more difficult since no serologic tests yet exist; thus, infection is still a diagnosis of exclusion. NANBH is inferred if a subject’s ALT levels rise to greater than two and one-half times normal after a concentrate infusion and remain elevated for at least 2 weeks after the initial abnormal measurement. New serologic tests for NANB virus may make diagnosis of NANBH no longer one of exclusion.

### EVALUATION OF VIRAL SAFETY TRIALS

**Hepatitis**

Most presently available products have been in clinical trials using previously untransfused hemophiliac patients as described above. However, although it is beyond the scope of this review to analyze each trial individually, certain trials have used patients treated previously with cryoprecipitate or other single-donor blood fractions, have small numbers, or have not obtained ALT levels at regular close intervals. Each clinical trial should be evaluated critically by the persons treating hemophilia before they make decisions on safety. One of the results of the trials to date is to confirm that the NANB virus as well as the hepatitis B virus is difficult to inactivate. In three trials using “dry heat” concentrate
heated from 60 to 68°C for 30 to 72 hours,16–18 16 of 21 subjects developed NANBH as defined by the ICTH. However, in one trial using concentrate dry heated at 80°C for 72 hours, none of 32 subjects developed NANBH.34 Thus, heating the concentrate in the lyophilized state does not appear to kill NANBH virus uniformly unless, perhaps, heating is done at high temperatures. No hepatitis B occurred in these studies.

"Wet-heated" concentrates are products heated either in suspension or in solution (pasteurized). In one trial of 18 subjects using factor VIII concentrate suspended in heptane, four contracted NANBH.35 In another trial with vapor-treated concentrate, none of 24 subjects contracted NANBH.36 With use of the pasteurization method, no cases of NANBH were reported in 26 patients.37 Thus, treatment of concentrate with vapor or in solution appears to have decreased the incidence of NANBH. However, with the vapor-treated concentrate, four patients developed markers consistent with hepatitis B infection. Several cases of HBV were also reported "off study" in patients using the pasteurized product, which emphasizes once more that all newly diagnosed patients with hemophilia should be vaccinated against HBV.

The viral safety trials with concentrates using the solvent/detergent method and the affinity chromatography method are still ongoing. With New York Blood Center concentrate (TNBP/sodium cholate), none of 15 subjects have developed NANBH,37 although the trial did not adhere to the ICTH criteria.38 With MoAb affinity chromatography techniques, none of 35 previously untransfused subjects have yet developed NANBH.38,39

HIV

HIV is heat labile. No seroconversions have occurred in any of the viral safety trials in which HIV antibody status has been studied. However, 18 cases of HIV seroconversion have occurred with dry-heat–treated factor VIII concentrate infused between 1985 and 1987.40 No case was involved in viral safety trials. Twelve seroconversions were associated with a single brand of concentrate using dry heating at 60°C for 30 hours. This product was subsequently withdrawn from the market. Some of the above cases also involved use of concentrate for which plasma unscreened for HIV had been used. In four of the remaining cases, dry-heat–treated concentrate of other manufacturers was also used; some lots were HIV antibody screened and others were not. One of these four patients, however, received dry-heated concentrate for which all plasma had been screened. In one case, the patient received both concentrate heated in the lyophilized state and in suspension, and in the remaining case the patient received only concentrate heated in suspension with n-heptane using plasma from unscreened donors.

Although the above cases are anecdotal reports, either dry heat at higher temperatures for longer periods of time or concentrates vapor treated or heat treated in solution (pasteurized) appear to be the most efficacious in killing HIV. The solvent-detergent methods as well as purification by affinity chromatography also appear to be safe with regard to HIV infection, although data are still being collected. As for the HIV seroconversions described above, most pharmaceutical companies have (a) discarded concentrate previously produced with HIV-unscreened plasma, and (b) stopped production of dry-heat–treated concentrate. Both actions, especially the latter, have begun to create an international shortage of factor concentrates, especially factor VIII.

In summary the newer products appear to have increased viral safety, especially those heat treated in solution or purified with MoAbs. Table 3 summarizes the trials. With the ability to clone the factor VIII gene, two companies (Genentech[S San Francisco]/Cutter, Genetics Institute[Cambridge, MA]/Hyland) are now producing recombinant factor VIII concentrate for limited human trials. The advent of this technology may, we hope, eliminate transmission of human blood-borne viruses.

**HIGHLY PURIFIED CONCENTRATES**

Concentrates purified using MoAb affinity chromatography have a final specific activity of factor VIII:C of ~3,000 U/mg protein. Even after albumin is added as a stabilizer, the purity is still significantly higher than previously available products, and many extraneous human proteins have been removed. These products are clearly efficacious. In a group of seven patients treated with a highly purified product for >24 months, clinical efficacy was excellent, as was half-life (T1/2) and recovery.41 No inhibitors against factor VIII:C developed in these patients and no allergic reactions were noted. In a larger study involving 33 previously untransfused patients, three patients developed factor VIII inhibitors,42 a percentage in the expected range. Whether increased purity of concentrate may lead to increased development of inhibitors is unknown.

Since large amounts of extraneous proteins such as immune complexes, aggregated immunoglobulins and the living or killed viruses may be additionally suppressive to the immune system of a hemophilic patient, concentrates that have only factor VIII:C and albumin may be less immunosuppressive.43 Theoretically this would be beneficial not only to previously untransfused patients but also to HIV-seropositive patients. In vitro experiments have shown that at a standard milligram-per-milliiliter concentration (either in terms of protein concentration or units of factor VIII), factor

| Table 3. Summary of Viral Safety Trials With Factor VIII Concentrates |
|-----------------|-----------------|-----------------|-----------------|
| **Viral Inactivation Process** | **No. of Patients Who Acquire Viral Infection** | **NANBH** | **HBV** | **HIV** |
| Dry heat | 16/21 | 0/21 |
| Super dry heat | 0/32 | 0/32 | 0/32 |
| Pasteurized | 0/26 | 0/10 | 0/26 |
| Suspension/heptane | 4/18 | 0/18 | 0/18 |
| Vapor treated | 0/24 | 4/14 | 0/28 |
| Solvent/detergent | 0/16 | 0/17 |
| Affinity chromatography dry heat* | 0/18 | 0/18 |
| Affinity chromatography solvent detergent* | 0/17 | 0/17 |

*Published in abstract form.
CONCENTRATES FOR TREATMENT OF HEMOPHILIA

VIII concentrate made with affinity chromatography methods did not inhibit lectin-induced lymphocyte proliferation whereas conventional AHF concentrates did. Similar experiments have shown decreased mixed lymphocyte reactions as well, using conventional concentrates rather than highly purified concentrates. Other experiments have shown that intermediate purity factor VIII concentrates may suppress monocyte function by downregulating Fc receptors.

Whether high-purity concentrates affect the immune system in vivo is not known. In the seven HIV-seropositive patients described above who have received a high-purity concentrate for >2 years, CD4 levels have stabilized, and in three of seven patients skin test anergy has been reversed. These three patients initially had no positive skin test reactions and at the end of 2 years reacted to at least two antigens. However, no controlled study comparing the effects over time on the immune system of the newer purer concentrates to the more conventional intermediate-purity concentrates has been completed; two such studies are now ongoing. This is of great importance since stabilization of the immune system would be of significant benefit to HIV-infected individuals.

With regard to factor IX concentrates, a plasma-derived preparation devoid of factors II, VII, and X, and viral attenuated, is currently being used in clinical trials. Complications of thrombosis that occasionally occur in postoperative hemophilia B patients may be eliminated with these types of products.

Pharmaceutical companies are beginning to use conventional chromatographic techniques to produce purer concentrates from plasma without using MoAbs. Thus, production of virus-free concentrates with less extraneous protein may be possible at lower cost.

WHICH CONCENTRATE TO CHOOSE

All concentrates now available in the United States are viral inactivated. Most pharmaceutical companies in the United States have withdrawn dry-heat–treated concentrates. Thus, the current choices involve use of either concentrates heat treated in suspension or solution, concentrates viral-attenuated using solvent/detergent methods, or concentrates more highly purified with MoAbs plus viral inactivated. Although data suggest that the more highly purified products may produce stabilization of the immune system in individuals who are already HIV infected, conclusive evidence does not exist. However, because interaction with other viruses such as herpes virus or hepatitis viruses may at least in in vitro systems activate latent intracellular HIV, the best viral-attenuated products perhaps should be administered to all persons with hemophilia, especially those who are HIV infected. This is controversial because some physicians believe that individuals who are already HIV infected should receive concentrates less intensively heat treated and therefore less costly.

We believe that a pasteurized or monoclonally purified product can be used for previously untreated and infrequently treated hemophilic persons and persons who are free of HIV infection. More data on the solvent/detergent concentrates with respect to transmission of NANBH needs to be accumulated, but they also appear to be safe. For HIV-seropositive patients, concentrates that are viral inactivated and highly purified offer theoretical benefits. Unfortunately, factors other than scientific are also now involved in such a choice. The first is supply. There is now a national shortage of factor VIII concentrates which may last for many months. The reasons for this are multifactorial and include withdrawal of most dry-heat–treated products from the market, decreased yields of factor obtained with the more intense viral inactivation and purification procedures, and collapse of the albumin market which had helped defray the cost of factor VIII concentrates. First, even if a physician or a patient requests a specific product, it may not be available. Second, expense is an issue. Because of the more sophisticated extraction methods, the lower final yields, and the loss of profit from albumin, concentrates currently are four to ten times more expensive than in previous years. How third-party insurers will deal with these new price increases is unclear, although early experience is remarkably encouraging. Both the National Hemophilia Foundation and individual physicians are attempting to find solutions to these complex supply and financial problems.

NEW APPROACHES

Cloning of the factor VIII:C and IX gene provides many possibilities for treatment and perhaps eventual cure of hemophilia. Two factor VIII concentrates using recombinant technology and thus eliminating the need for collection of human plasma are available for experimental purposes. Both products are now undergoing human clinical trials. Data suggest that in two patients who have been using one such product for at least 1 year, T1/2 and recovery are excellent, and no adverse effects have been noted. Because the VIII:C is expressed from a hamster-derived cell line, we must be concerned about traces of animal protein in the material even though affinity chromatography with mouse MoAb has apparently removed most such contaminants. We must also be concerned with the stability of the gene in the fermentation system. However, freedom from human virus, eventual large supply, and ultimate low cost are all probable future benefits. Although this material is currently technologically difficult to produce in large amounts, it as well as a recombinant factor IX concentrate may be widely available in 2 to 3 years.

Currently, liver transplantation offers a cure for hemophilia, albeit a somewhat impractical one. In a series of four patients with hemophilia reported from Pittsburgh, who required liver transplantation because of end-stage liver disease, three survived the initial surgery and then normalized their factor VIII:C levels and required no further replacement. Cloning of the genes for factor VIII and IX and recombinant genetic technology may allow "gene therapy" and eventually cure of this disease.

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Factor concentrates for treatment of hemophilia: which one to choose? [see comments]

DB Brettler and PH Levine