Hemophilia, NIH

Hemophilia is the oldest known bleeding disorder that is passed from parent to child. This means that it is *hereditary*. There are two types of hemophilia: A and B (Christmas Disease). About 85 percent of patients have hemophilia A. The remainder have hemophilia B.

The severity of hemophilia (how bad it is) is related to the amount of clotting factor in the blood. Most hemophilia A patients have less than one percent of the normal amount so they have severe hemophilia. A small increase in the blood level of the clotting factor, up to five percent of normal, results in mild hemophilia. With this type, bleeding is rare except after injuries or surgery.

CAUSES

Both types of hemophilia are caused by low levels or absence in the blood of a factor ("an ingredient") which helps clotting. Patients with hemophilia A lack the blood clotting protein, factor VIII. Those with hemophilia B lack factor IX.

SYMPTOMS

- You bleed easily from small cuts.
- Minor bumps can cause bruising.
- There may be sore and swollen joints from bleeding into the joint.
- There may be blood in the urine or stool.
- Any operation or tooth removal can cause bleeding which is excessive.

DIAGNOSIS

Blood tests are used to diagnose this disease. These are done if your caregiver sees bleeding problems.

CHALLENGES

The most important challenges facing the hemophilia patient, health care provider and research community today are:

- Safety of products used for treatment. (See below for more information on this.)
- Management of the disease, including inhibitor formation, irreversible joint damage, and life-threatening *hemorrhage* (heavy bleeding). (See below for more information on these.)

PROGRESS IN TREATMENT

Safety of Products Used for Treatment:

- In the past 10 to 15 years, advances in screening of blood donors, laboratory testing of donated blood, and techniques to inactivate viruses in blood and blood products, have greatly increased the safety of blood products used to treat hemophilia. Although treatment-related infection with the AIDS virus or most of the hepatitis viruses is a thing of the past, these measures do not completely avoid viruses such as hepatitis A and parvo virus. These infections are rare, but they can pose a threat. Researchers are working to improve procedures to destroy these viruses.
- There is a great deal of concern about Creutzfeldt-Jakob disease (CJD), a rare, *transmissible* (passable) nervous system disease that is always fatal, being transmitted (passed) through transfusion. The infection of many hemophilia patients with the AIDS virus before the virus was discovered has created a great deal of concern in the hemophilia community about CJD and its possible transmission through blood-derived treatment products. A disorder related to CJD, bovine spongiforme encephalopathy or "mad cow disease", and its suspected relationship to an especially severe form of CJD, has caused considerable interest recently in Britain. No one has ever detected the transmission of CJD disease through blood or blood products, although a number of CJD victims have been blood donors, even within weeks of coming down with the disease. Studies are underway by the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke to test if the CJD agent(s) can be transmitted by blood.

- To ensure absolute safety from transfusion-transmitted viruses and other agents, hemophiliacs may now be treated with factor VIII that has been produced through biotechnology. This product, recombinant factor VIII, is manufactured by a process entirely free of blood products. It contains only the factor VIII necessary to treat the disease, and none of the other components of blood or other unwanted agents. Although the cost of this product is more than that of the blood-derived product, it is clearly the treatment of choice for those, such as newborns, who have not yet been exposed to blood products. A factor IX product has also been produced in labs and is currently being tested. Once this product is shown to be safe and effective, all hemophiliacs will have available a treatment for bleeding which is totally free of any contaminating agents.

Management of the disease including inhibitor formation, irreversible joint damage and life-threatening hemorrhage:

- While current treatment has greatly improved the outlook for most hemophiliacs, the development of *antibodies* (inhibitors) that block the activity of the clotting factors has made treatment more difficult for some patients. Approximately 15 percent of severe hemophilia A patients and 2.5 percent of hemophilia B patients develop such antibodies after receiving clotting factors in a blood transfusion. When inhibitors are present in large amounts, the patient may require very high and expensive quantities of transfused clotting factors to slow bleeding, and, in some instances, even that may not be effective. The factor VIII products produced through biotechnology have been found to cause inhibitors less often (in only about 5 percent of patients), and are therefore safer in this respect. Still, these inhibiting antibodies will remain a concern for hemophilia patients unless our ability to understand and control the immune system is improved. A number of NHLBI-supported scientists are researching this problem.
- The major cause of disability in hemophilia patients is chronic joint disease, called “arthropathy”, caused by uncontrolled bleeding into the joints. Life-threatening hemorrhage is a constant risk. Traditional treatment of hemophilia has involved “on-demand” treatment, meaning that patients are treated with clotting factor replacement only after bleeding symptoms are recognized. These bleeds ultimately result in severely damaged joints. Several European countries are treating hemophiliacs by regular infusion (*prophylaxis*) regardless of bleeding status. This approach keeps the factor level high enough that bleeding, joint destruction and life-threatening hemorrhage are almost entirely avoided. There are, nevertheless, serious disadvantages such as:
  - The need for frequent infusions.
  - The requirement for almost continuous access to veins by catheters.
  - The considerable cost is a factor. The treatment decisions are not easy ones.

PROGRESS TOWARD A CURE

Although treatment for hemophilia has become safer, *therapeutic* (helpful) products are still not risk free. The ultimate goal is to offer a cure for the disease. Hemophilia is known to be caused by defects in the genes for factor VIII and factor IX. The challenge is to transfer normal genes into a patient so that they will produce the normal clotting protein. A small amount of active factor produced by the patient's own body will correct the disease. Although much remains to be studied before such treatment can be offered to patients, there have been a number of studies done in animals in which a factor VIII or IX gene has been inserted and has produced the proper blood product for periods of more than one year.

Major issues that still must be solved in these attempts include the low level of production of the clotting factor, lessening of immune reactions that stop the production after a period of time, and development of ways to insert the gene directly into the body without manipulating cells outside the body. Until recently, dogs with naturally occurring hemophilia were used for testing of gene therapy techniques; however, the number of such animals is very limited. Recently, a mouse model of hemophilia produced through genetic technology was announced. The availability of this small animal will speed up the development of technologies for use in humans.

SUMMARY

- It is clear that a lot of progress has been made to reduce the exposure of hemophilia patients to transfusion-transmitted disease. This has been done through making the blood supply safer, and by providing

replacement products from sources not involving blood. However, concern remains for hemophiliacs still requiring blood products with the threat of agents that may contaminate the blood supply, where such problems are not avoided or inactivated with currently available techniques.

- It is also known from international studies that crippling joint involvement can be avoided through periodic and regular transfusion. The expense, danger of indwelling catheters, and inconvenience of the treatment regimen are all negative factors.
- All of these issues will become less important, even irrelevant, if the disease can be cured. At the present time, there is sufficient reason to think that that gene therapy will ultimately be this cure. The technology for gene therapy is not simple, but because of special characteristics, hemophilia will likely be among the first genetic diseases to be successfully treated.

SEEK IMMEDIATE MEDICAL ATTENTION IF:

- You develop any bleeding that is not controlled.
- You develop a tender, swollen joint.
- Let your caregiver know if you are considering a pregnancy. You need to be completely aware of the risks and your options.

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